Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

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NIH Pragmatic Trials Collaboratory Rethinking Clinical Trials

About the FNIH

- The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people's lives.

- The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.

- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in marketplace
- Disseminate knowledge
- Enhance credibility
- Reduce costs
- Support training & education
- Manage complexity

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By the Numbers

$1.2B raised to date

$0.90 of every dollar spent directly supports programs

600+ programs supported since inception

117 *active* research partnerships, scientific education/training, conferences/events, capital programs

18 years of outstanding Charity Navigator ratings

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Select FNIH Partnerships

- **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)** — **$1+ billion**
  NIH (OD), NIAID, NCATS, NHLBI, NINDS, 8 government agencies, 20+ companies, 4 not-for-profit organizations
- **Accelerating Medicines Partnership (AMP)** — **$776 million**
  NIH OD, 15 NIH ICs, 28 companies, 23 not-for-profit organizations
- **Partnership for Accelerating Cancer Therapies (PACT)** — **$220 million**
  NCI, PhRMA, 12 pharmaceutical companies
- **Grand Challenges in Global Health (GCGH)** — **$201 million**
  Bill & Melinda Gates Foundation
- **Alzheimer's Disease Neuroimaging Initiative (ADNI)** — **$206 million**
  NIA, NIBIB, 25+ companies, 3 not-for-profit organizations
- **The Biomarkers Consortium** — **$107 million**
  FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations
- **LungMAP: Master Lung Protocol Trial** — **$163 million**
  NCI (SWOG), FDA, Friends of Cancer Research, 10 companies to date
- **Helping End Addiction Long-Term (HEAL) Partnership Committee** — **$0.4 million**
  NIH contract

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FNIH Partnerships Cover a Spectrum of Designs

Funded exclusively by public organizations

ACTIV

Funded by both public and private organizations

LUNG-MAP

ADNI

Funded exclusively by private organizations

BIOMARKERS CONSORTIUM

IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

Grand Challenges in Global Health

LAUNCH

On April 17, 2020, 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**

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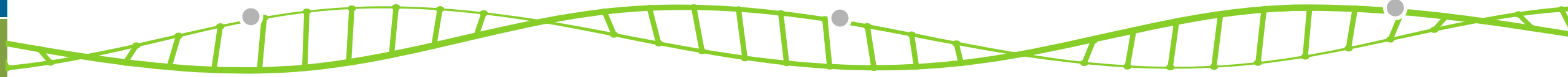
ACTIV Stakeholders

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



BARDA
CDC
Department of Defense
European Medicines Agency
U.S. Food & Drug Administration
Operation Warp Speed
NIH
Department of Veterans Affairs
FNIH

abbvie
AMGEN
AstraZeneca
Bristol-Myers Squibb
dewpoint therapeutics
Eisai
Lilly
gsk
Johnson & Johnson
MERCK
moderna
NOVARTIS
RHYTHM THERAPEUTICS
Roche Genentech
Pfizer
SANOFI
Takeda
NOVAVAX
VIR

Bill & Melinda Gates foundation
Fred Hutch Cures Start Here
RTI International
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ACTIV Governance

ACTIV Governance includes representation from key stakeholders in both the private and public sector.

ACTIV Executive Committee

Co-Chairs

Original:
Francis Collins, NIH
Paul Stoffels, J&J

Current:
William Pao, Pfizer
Lawrence Tabak, NIH

Members

Anthony Fauci, NIAID
Gary Gibbons, NHLBI
Janet Woodcock, OWS
Mikael Dolsten, Pfizer
Gary Disbrow, BARDA
Peter Marks, FDA
Andrew Plump, Takeda

ACTIV Leadership Team

Scientific leaders from all participating organizations

Preclinical Working Group
**Mission accomplished in 2021*

TRACE Working Group

Therapeutics Clinical Working Group

Clinical Trial Capacity Working Group
**Mission accomplished in 2021*

Vaccines Working Group
**Mission accomplished in 2021*

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ACTIV Fast-Track Focus Areas | Objectives & Composition

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 :

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

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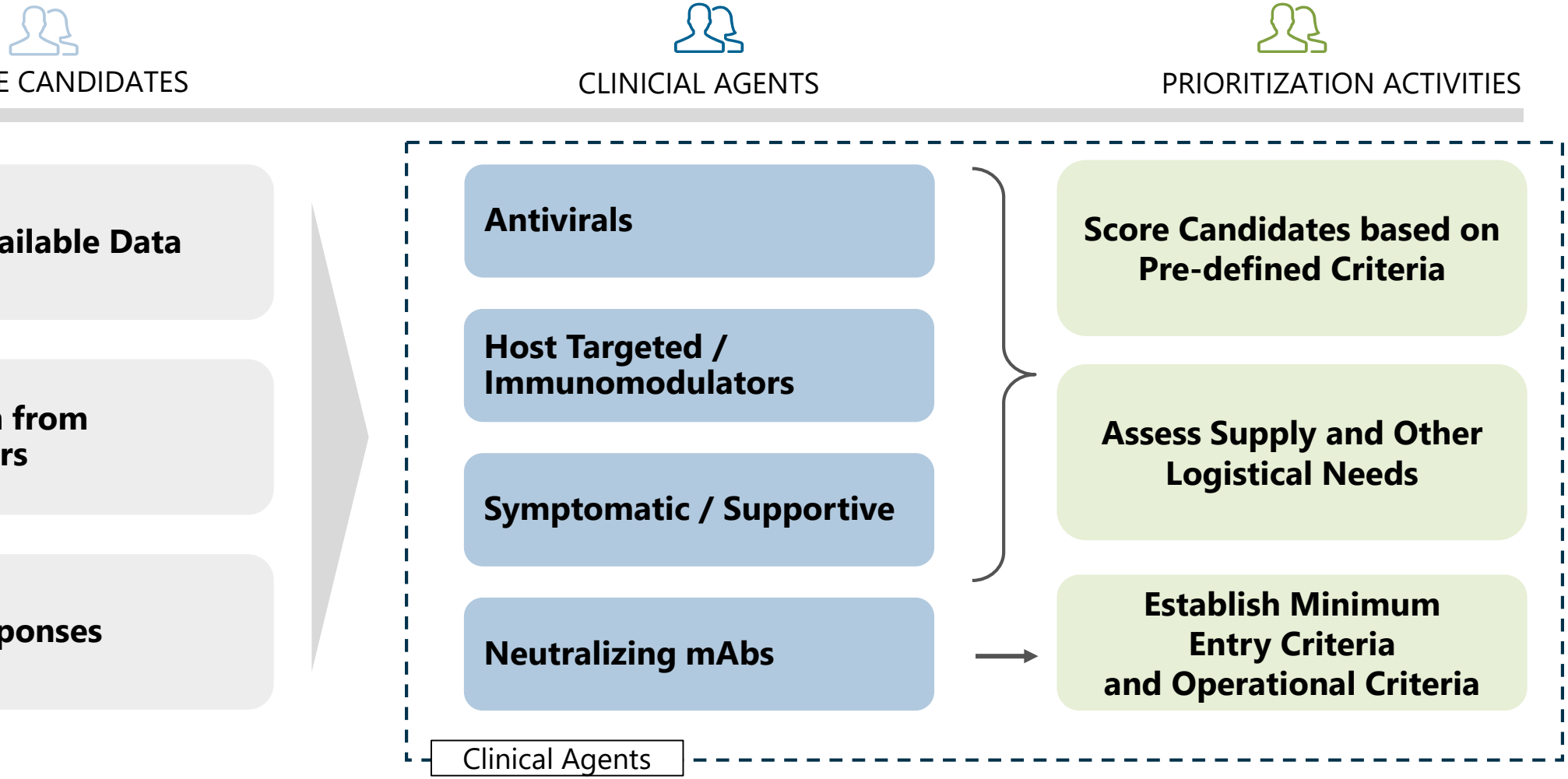
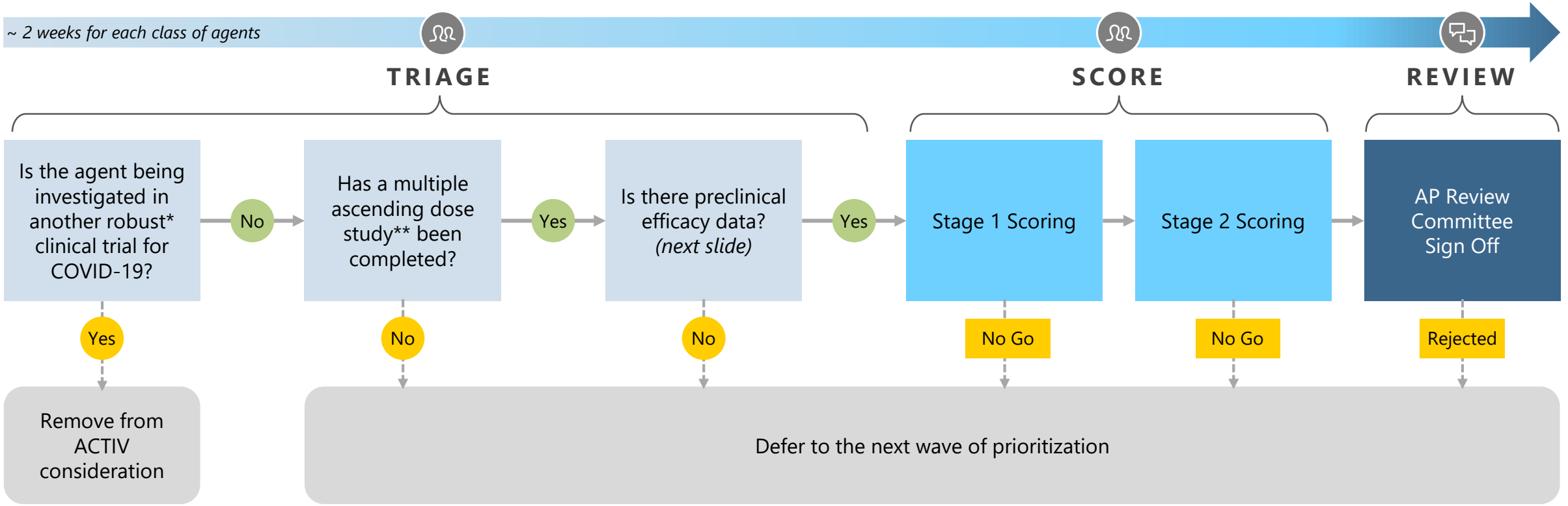
Prioritizing the most promising therapeutic agents for COVID-19

The Working identified agents that stop the virus or that treat its symptoms and placed them in appropriate master protocols for Phase II or III testing – so far ACTIV has reviewed more than 800 agents.



Agent Prioritization | *Triage and Scoring Process*

Candidate agents are triaged based on concurrent clinical trials, completion of a multiple ascending dose study, and availability of preclinical data before being scored based on predefined criteria.



NOTES

**Criteria for "robust trial" (to be defined by Prioritization Team)*
*** Sufficient safety data to support 14-day exposure*

Prioritization Objectives

Identify therapeutics agents that can be placed in a master protocol for a Phase II/III Progressive trial

GO

For agents that don't meet this criteria, classify

Compounds that need short term preclinical and clinical development support

- Potential to enter clinical trials later this year

Compounds that may require longer term preclinical and clinical development

DEFER

Compounds that should not be considered for future rounds of prioritization

NO GO

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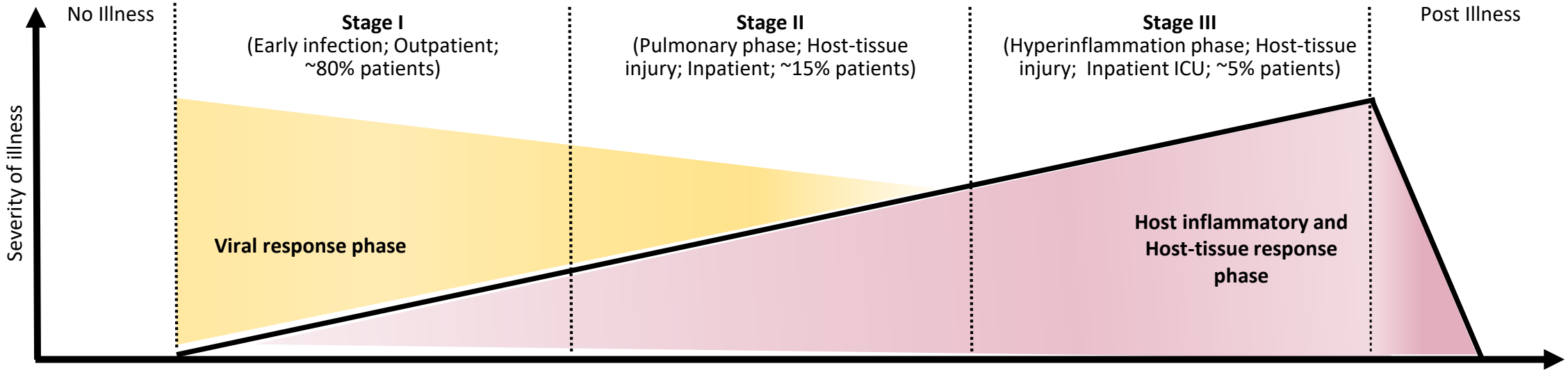
ACTIV Clinical Trials Targeting Different Stages of Disease Pathobiology



Clinical signs and symptoms	No Infection	Infected; Not Hospitalized (With or without limitations)	Hospitalized; (No active medical problems → On O_2)	Hospitalized; (High Flow O_2 → 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

ACTIV Therapeutics Master Protocol Descriptions

Master Protocol	Protocol Description
ACTIV-1	• Inpatient, RCT, Double-blind Phase III Master Protocol for Host-targeted Immune Modulators • NCATS TIN + DCRI + TRI + CRO Target Sample Size (Patients per Arm): 540
ACTIV-2	• Outpatient, RCT, Double-blind Phase II/III Master Protocol for Neutralizing Monoclonal Antibodies and Oral Antivirals • NIAID ACTG + CRO Target Sample Size (Patients per Arm): 110 [Phase II] & 600 [Phase III]
ACTIV-3	• Inpatient, RCT, Double-blind Phase III Master Protocol for Neutralizing Monoclonal Antibodies and Other Antivirals • NIAID INSIGHT + NHLBI PETAL + CTSN + VA + CRO Target Sample Size (Patients per Arm): 500
ACTIV-3B	• Inpatient, RCT, Double-blind Phase III Master Protocol for Host-targeted Immune Modulators for ARDS Patients • NIAID INSIGHT + NHLBI PETAL + CTSN + VA + CRO Target Sample Size (Patients per Arm): 620
ACTIV-4A	• Inpatient, Pragmatic, Randomized, Open Label Phase III Master Protocol for Host-tissue Directed Antithrombotics • NHLBI CONNECTS Network Target Sample Size (Patients per Arm): 1000
ACTIV-4B	• Outpatient, Randomized, Double-blind Phase III Master Protocol for Host-tissue Directed Antithrombotics • NHLBI CONNECTS Network Target Sample Size (Patients per Arm): 1750
ACTIV-4C	• Outpatient, Convalescent, RCT, Double-blind Phase III Master Protocol for Host-tissue Directed Antithrombotics • NHLBI CONNECTS Network Target Sample Size (Patients per Arm): 2660
ACTIV-4HT	• Inpatient, RCT,Phase II/III Master Protocol for Host-tissue Targeted Therapies • NHLBI CONNECTS Network Target Sample Size (Patients per Arm): 300+
ACTIV-5	• Inpatient, RCT, Double-blind Phase II Master Protocol, Screening Study to Identify Promising Immune Modulators • NIAID + CRO Target Sample Size (Patients per Arm): 200 (expansion to 500)
ACTIV-6	• Outpatient, RCT, Double-blind Phase III Master Protocol for Existing Prescription and Over-the-counter Medications • NCATS + DCRI + PCORnet + SignalPath + CRO Target Sample Size (Patients per Arm): 600 (expansion to 1200)

Key Design Decisions to Allow Master Protocols to Fulfill ACTIV Mission

Research Objectives	Screening trial (Phase 2) to identify promising agents versus confirmatory trial (Phase 3) to generate evidence that could support product approval
Evaluation Framework	Comparative analyses to evaluate each agent versus control, rather than analyses comparing agents to each other
Randomization	Two steps, with treatment assignment at the first step followed by active vs matching placebo assignment at the second
Shared Controls	Control participants pooled across agents and mode of administration, but caution advised in pooling across time
Power	Adequate power to detect moderately sized treatment effects with respect to primary endpoints
Early Stopping Rules *(For Futility)*	Moderately aggressive futility boundaries considered essential to make room for more promising agents
Design Adaptations	Blinded sample size review and adjustment considered optional for each protocol
Graduation Rules *(For Seamless 2/3 Designs)*	Bayesian analyses to refine these rules during the study based on accumulating information about the ability for early assessments to predict later clinical endpoints
Endpoint Alignment	Alignment of endpoints to existing trials was imperative in streamlining efforts and promoting comparative analyses across trials

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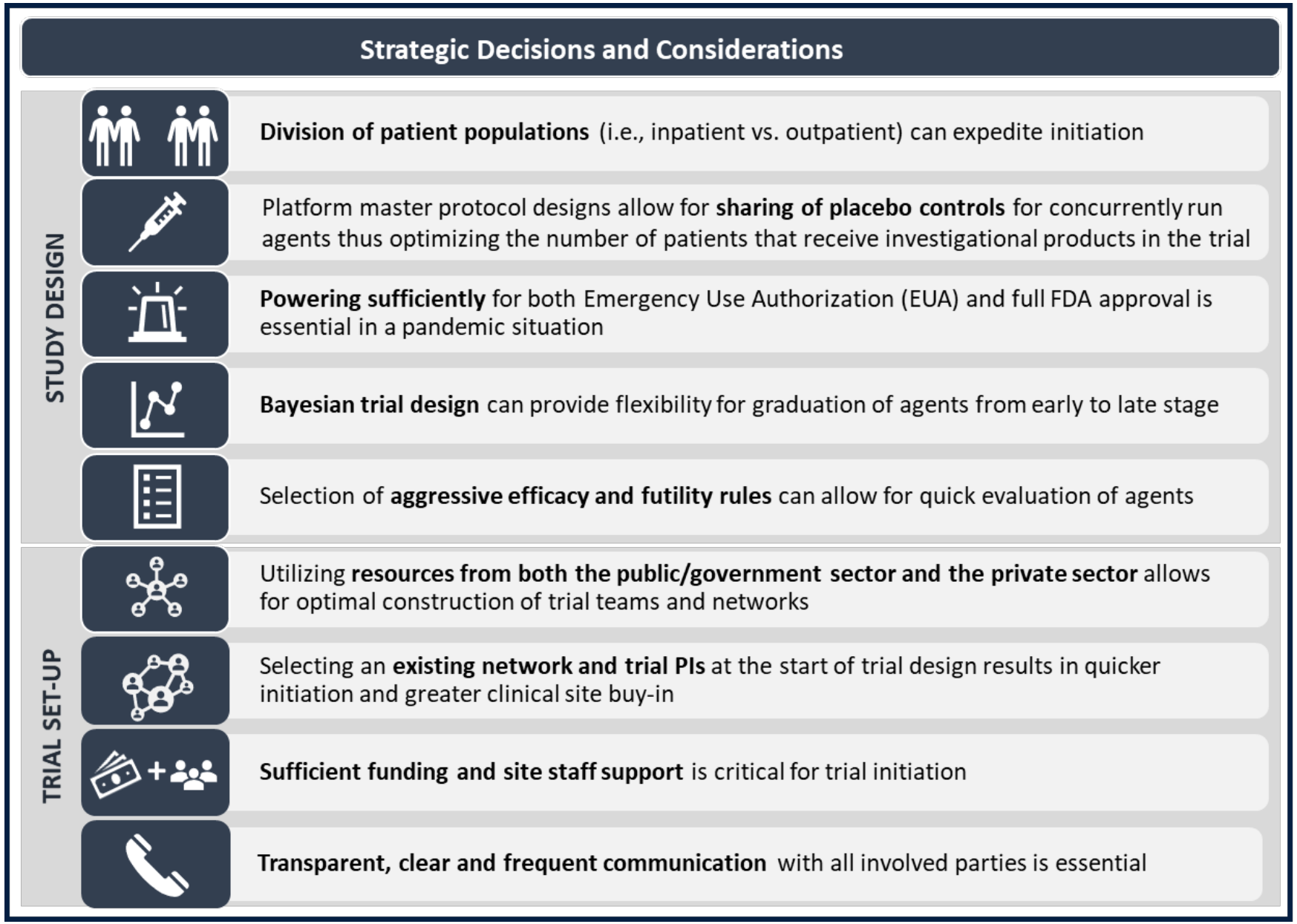
Significant Lessons Learned that Can Be Applied to Future Protocols



ACTIV Therapeutics-Clinical Working Group Published Manuscripts

The ACTIV Therapeutics-Clinical Manuscript Sub Teams have published two sister manuscripts documenting the strategy, process, and lessons learned for **agent prioritization** and **master protocol development**.

TITLE	**Accelerating COVID-19 Treatment Interventions and Vaccines (ACTIV) – Selecting Compounds for Clinical Evaluation in COVID-19 Clinical Trials**	**Accelerating COVID-19 Treatment Interventions and Vaccines (ACTIV) – Designing Master Protocols for Evaluation of Candidate COVID-19 Therapeutics**
OVERVIEW	Overall strategy, process, and evaluation criteria that allowed for a streamlined and standardized assessment of hundreds of therapeutic agents with potential application for COVID-19	Approach and process by which seven master protocols to test investigational agents against COVID-19 were designed, developed, and launched, as well as lessons learned on critical design decisions for future pandemic situations
AUTHORS	*Timothy G. Buchman, Ruxandra Draghia-Akli, Stacey J. Adam, Neil R. Aggarwal, Joshua Fessel, Elizabeth S. Higgs, Joseph Menetski, ACTIV Therapeutics Clinical Working Group, Sarah W. Read, and Eric A. Hughes*	*Lisa LaVange, Stacey J. Adam, Judith S. Currier, Elizabeth S. Higgs, Lora A. Reineck, ACTIV Therapeutics Clinical Working Group, Eric A. Hughes, and Sarah W. Read*
STATUS	**Published in *Critical Care Medicine (CCM)*** **Manuscript Link:** https://journals.lww.com/ccmjournal/Abstract/9000/Accelerating_Coronavirus_Disease_2019_Therapeutic.95104.aspx	**E-published in *Annals of Internal Medicine (AIM)*** **Manuscript Link:** Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): Designing Master Protocols for Evaluation of Candidate COVID-19 Therapeutics | Annals of Internal Medicine (acpjournals.org).

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ACTIV Therapeutics Clinical Trials Success Thus Far: At-A-Glance

ENROLLMENTS & ACTIVATION

20,000+ Patients enrolled into ACTIV trials

620+ Sites in partnership with **multiple networks** including ACTG, CONNECTS, DCRI, INSIGHT, PETAL, CTSN, PCORnet, CTSA, IDeA Sites, ACTT, and others

PUBLICATIONS

26 Scientific Publications on ACTIV Trials released in **13 Medical Journals**

These publications have been **cited 500+ times** (*Google Scholar*)

AGENT REVIEWS & SUCCESSES

800 Total agents reviewed by ACTIV Tx-Clinical and CONNECTS WGs Agent Review Panels

27 Agents fully enrolled and completed testing through the ACTIV Master Protocols

6 Agents proven efficacious against COVID-19 in analysis of data from ACTIV Trials. Other priority agents being tested.

- ACTIV-4 work on heparin and other anticoagulants **changed clinical practice**
- Brii Bio monoclonal antibody combination **submitted for EUA** based on data from ACTIV trials
- ACTIV-1 and ACTIV-3 have shown **Euvashield, Infliximab, and Abatacept decrease mortality in hospitalized patients**
- Of note:
  - 3 other monoclonal antibody products tested in ACTIV trials received EUAs based on separate, industry-supported trials
  - Industry trials of Merck & Pfizer antivirals were harmonized with ACTIV protocols

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Status Summary of Current ACTIV Agents

	Not Yet Reviewed for Efficacy / Futility	Ceased Enrollment (due to futility / low clinical value)	Continuing Enrollment (i.e., passed interim futility assessment)	Completed Enrollment
ACTIV-1		• **Cenicriviroc**		• **Infliximab** • **Abatacept**
ACTIV-2/2D	• Shionogi-217622	• **AZD7442 (IM)** • **AZD7442 (IV)*** • **Camostat Mesylate** • **BMS-986414/BMS-986413**		• **Brii-196/Brii-198*** • **LY-CoV-555** • SAB-185 *(awaiting TLR)* • SNG001 IFN-beta (Ph 2) *(awaiting TLR)*
ACTIV-3/3B		• **LY-CoV-555** • **Brii-196/Brii-198** • **VIR-7831** • **DARPin MP0420*** • **Pfizer PF-07304814** • **Aviptadil + Remdesivir** • Remdesivir *(ceased by trial leads)*		• **AZD7442 (IV)***
ACTIV-4A		• **Therapeutic Heparin and P2Y12 Inhibitors in Moderately-ill Pts** • Prophylactic Heparin and P2Y12 Inhibitors in Critically-ill Pts (*closed due to operational futility; awaiting TLR)*	• Crizanlizumab • SGLT2 inhibitors	• **Un-fractionated and Low Molecular Weight Heparin**
ACTIV-4B		• **Aspirin** • **Apixaban**		
ACTIV-4C		• Apixaban *(closed due to operational futility; awaiting TLR)*		
ACTIV-4HT		• **TRV027** • **TXA127**	• Fostamatinib	
ACTIV-5				• **Lenzilumab** • Risankizumab *(awaiting TLR)* • Danicopan *(awaiting TLR)*
ACTIV-6	• Ivermectin (600)			• **Ivermectin (400)** • **Fluticasone** • Fluvoxamine *(awaiting TLR)*

Denotes *enrollment ceased at company's request*
Denotes *agent lack of efficacy*
Denotes *proven agent efficacy based on target primary endpoint*

Denotes *missed primary endpoint, but showed significant effect on mortality*
**Denotes data from an ACTIV trial has or will contribute to an EUA filing*

ACTIV-1 Inpatient Trial

Company	Therapeutic	Class	Administration	New/Repurposed	Status/Estimated End Date	Results
AbbVie	Cenicriviroc	Immune Modulator	Oral	New	Ended/Failed interim analysis	DSMB reviewed the interim analysis of the safety and efficacy data on 9/3/2021; interim analysis indicated agent futility
BMS	Orencia® (abatacept)	Immune Modulator	Intravenous	Repurposed	Enrollment closed/Efficacy Shown	**Reduced mortality in patients,** except those on mechanical ventilation or ECMO at time of randomization
Janssen	Remicade® (Infliximab)	Immune Modulator	Intravenous	Repurposed	Enrollment closed/Efficacy Shown	**Reduced mortality in patients,** except those on mechanical ventilation or ECMO at time of randomization

Contributions

- Compared to placebo, participants on infliximab (Remicade) displayed a strong but not statistically significant improvement in the primary endpoint of time to recovery as measured by day of discharge from hospital. **Participants receiving infliximab showed a 40.5% lower adjusted odds of dying.** Relative improvement in mortality was similar in both moderately and severely ill participants. People in the infliximab group had 43.8% better odds of clinical improvement than those in the placebo group.
- Compared to placebo, participants receiving abatacept (Orencia) displayed a strong but not statistically significant improvement in the primary endpoint of time to recovery as measured by day of discharge from hospital. **Participants receiving abatacept showed a 37.4% lower adjusted odds of dying.** Relative improvement in mortality was similar in both moderately and severely ill participants. People in the abatacept group had 34.2% better odds of clinical improvement than those in the placebo group.

Lessons Learned

- Investigators who will implement the trial should always be at the table for trial design.
- **There may be merit to administration of additional targeted immune therapies in hospitalized patients in addition to SOC (aka Dex and Remdesivir).**
- The ACTIV-1 team is working with the STRIVE platform to determine what, if any, next steps in studying these agents would be helpful to the field.

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ACTIV-2 Outpatient Trial

Company	Therapeutic	Class	Administration	New/Repurposed	Status/Estimated End Date	Results
AstraZeneca	AZD7442	Monoclonal Antibody Cocktail	Intramuscular	New	Enrollment closed due to company decision	Enrollment closed due to company decision
AstraZeneca	AZD7442	Monoclonal Antibody Cocktail	Intravenous	New	Enrollment closed/Awaiting topline results	Enrollment closed/awaiting topline results
Brii Biosciences	Brii-196 & Brii-198	Monoclonal Antibody Cocktail	Intravenous	New	Ended/Efficacy shown/EUA filed/Approved in China	**Combination demonstrated 78% reduction in the combined endpoint of hospitalization and death compared with placebo; EUA submission to FDA is underway**
Bristol Myers Squibb	BMS-986414 & BMS-986413	Monoclonal Antibody Cocktail	Subcutaneous Injection	New	Ended/Graduation criteria unmet	Did not graduate to Phase III
Eli Lilly	LY-CoV-555	Monoclonal Antibody Single	Intravenous	New	Ended/Efficacy shown/EUA granted	FDA granted EUA on 11/9/2020
SAB Biotherapeutics	SAB-185	Polyclonal antibody	Intravenous	New	Passed interim analysis/Enrollment closed due to operational futility	DSMB concluded that event rates were so low following the emergence of Omicron, awaiting topline results
Sagent	Camostat Mesylate	Antiviral	Oral	Repurposed	Ended/Graduation criteria unmet	Did not graduate to Phase III

Contributions

- Lilly included data from the ACTIV-2 study in FDA submission package
- AZ included data from ACTIV-2 study in FDA submission package
- **Brii Bio is undergoing rolling submission of its combination therapy to FDA; the combination received approval in China, which marks the first locally-discovered and approved SARS-CoV-2 target-specific treatment in the country, through a randomized, double-blind, placebo-controlled trial**
- Correlative studies looking at viral load from nasal swabs and blood to determine merit for surrogate endpoints

Lessons Learned

- **Need to be exceptionally nimble with trial endpoints and design to keep pace with the stage of the pandemic**
- **Need for a diverse and extensive communications, outreach, and recruitment strategy for outpatient trials**
  - Engaged in various communications strategies utilizing different PR firms and USG resources
  - Used barbershop and faith-based organizational recruitment strategies – essential to work with those already in the community with built trust
  - Found value in general social media and online search strategies as opposed to health marketing initiatives

ACTIV-3/3B Inpatient Trials

Company	Therapeutic	Class	Administration	New/Repurposed	Status/Estimated End Date	Results
AstraZeneca	AZD7442	Monoclonal Antibody Cocktail	Intravenous	New	Enrollment closed/Efficacy shown	Did not meet primary endpoint of sustained recovery, **but did show benefit in mortality**
Brii Biosciences	Brii-196 & Brii-198	Monoclonal Antibody Cocktail	Intravenous	New	Ended/Graduation criteria unmet	Enrollment was halted due to interim futility; by day 90, the BRII-196 plus BRII-198 group had 88% sustained clinical recovery; LPI Mar 2021
Eli Lilly	LY-CoV-555	Monoclonal Antibody Single	Intravenous	New	Ended/Graduation criteria unmet	Unblinded Feb 2021; after five days, 50% of LY-CoV555 recipients showed favorable outcomes; results published Dec 2021 in NEJM
Gilead/NeuroRx	Zyesami™ (aviptadil acetate) & Veklury® (remdesivir)	Immune Modulator/Antiviral	Intravenous	Repurposed	Enrollment closed/Awaiting topline results	Awaiting study completion / TLR
GSK-Vir	VIR-7831	Monoclonal Antibody Single	Intravenous	New	Ended/Graduation criteria unmet	Enrollment halted due to interim futility; by day 90, the VIR-7831 group had 88% sustained clinical recovery; Manuscript for BRII, GSK/Vir published in Lancet ID Dec 2021
Molecular Partners/Novartis	Ensovibep (MP0420)	DARPin	Intravenous	New	Ended/Graduation criteria unmet	MP did not meet predefined futility criteria; data unblinded Mar 11; manuscript in preparation
Pfizer	PF-07304814	Protease inhibitor	Intravenous	New	Ended due to company decision	FDA requested to halt enrollment for due to potential safety concern; TLR expected Jun 2022

Contributions

- **Baseline SARS-CoV-2 NC antigen from the periphery and SARS-CoV-2 seropositivity status is predictive of progression of disease**
- **95% of hospitalized patients have SARS-CoV-2 NC antigen**, an indication of **ongoing viral replication in their blood**
- "Evaluating Primary Endpoints for COVID-19 Therapeutic Trials to Assess Recovery" manuscript looking at meta-analysis antiviral in hospitalized patients submitted to the *American Journal of Respiratory and Critical Care Medicine*
- "Tixagevimab/cilgavimab for treatment of hospitalised COVID-19 patients: A randomized, double-blind, phase 3 trial" manuscript on AZD7442 published in *The Lancet Respiratory Medicine:* Link

Lessons Learned

- **Most monoclonal antibodies did not have beneficial effect in hospitalize patients, but serostatus of the patient mattered**
- **Evidence suggests that there could still be benefit to administration of a direct acting antiviral in hospitalized patients**
- A strong need to review an agent provider's manufacturing capabilities for consistency and scalability. Challenges were faced with smaller companies due to pandemic scarcity.

ACTIV-4A and 4B Trials

Company	Therapeutic	Class	Administration	New/Repurposed	Status/Estimated End Date	Results
Inpatient						
Other	Un-fractionated (UF) Heparin	Anticoagulant	Intravenous	Repurposed	Ended/Efficacy shown	Moderate arm enrollment closed June 2021
Other	Low Molecular Weight (LMW) Heparin	Anticoagulant	Injection	Repurposed	Ended/Efficacy shown	Moderate arm enrollment closed June 2021
Other	Therapeutic Heparin and P2Y12 Inhibitors	Anticoagulant	Intravenous and Oral	Repurposed	Ended/Failed interim analysis	Moderate arm enrollment closed June 2021 due to futility; results published
Other	Prophylactic Heparin and P2Y12 Inhibitors	Anticoagulant	Intravenous and Oral	Repurposed	Enrollment stopped	DSMB recommended to stop enrollment due to slow recruitment rate of participants with severe SARS-CoV-2 symptoms who meet study requirements
Novartis	Crizanlizumab	Monoclonal Antibody Single	Intravenous	Repurposed	Continuing enrollment/Q1 2023	Study ongoing – awaiting study completion / TLR
Various	SGLT2i	Sodium/glucose cotransporter-2 inhibitors	Oral	Repurposed	Continuing enrollment/Q1 2023	Study ongoing – awaiting study completion / TLR
Outpatient						
BMS/Pfizer	Eliquis ® (apixaban)	Anticoagulant	Oral	Repurposed	Enrollment closed due to operational futility	Enrollment closed June 2021 dure to futility
BMS/Pfizer	Aspirin	Antiplatelet	Oral	Repurposed	Enrollment closed due to operational futility	Enrollment closed June 2021 dure to futility

Contributions

- Manuscripts reporting on moderate and critically-ill patients treated with heparin published at NEJM: Link & Link
- Manuscript reporting on Moderate arm P2Y12 published at JAMA: Link

Lessons Learned

- **Treating with antithrombotics is valuable is some populations, but potentially harmful in others.**
- Testing of existing widely available medications is important to influence treatment guidelines, even if no regulatory filing will be made.
- **Collaborating with other platform trials is a viable mechanism to enhance sample size.** ACTIV-4A which was a pragmatic study was able to combine data for analysis with REMAP-CAP and ATTACC.
- **Working with third party recruitment sites and home health agencies to conduct remote follow up visits can present challenges in a pandemic, not only on bandwidth, but in state licensure regulations.**
- Sometimes less is more and patients should be treated with as minimal a regime as possible.

ACTIV-4C and 4HT Trials

Company	Therapeutic	Class	Administration	New/Repurposed	Status/Estimated End Date	Results
Convalescent						
BMS/Pfizer	Eliquis ® (apixaban)	Anticoagulant	Oral	Repurposed	Enrollment stopped	DSMB recommended to stop enrollment due to slow enrollment challenges and low primary outcome rates across the study
Outpatient						
Constant Therapeutics	TXA127	Mas Receptor Agonist	IV	New	Ended/Failed interim analysis	DSMB recommended to stop drug; crossed the prespecified stopping boundary for inferiority
Trevena	TRV027	AT1R Beta-arrestin Agonist	IV	New	Ended/Failed interim analysis	DSMB recommended to stop drug; crossed the prespecified stopping boundary for inferiority
Rigel	Fostamatinib	Syk Inhibitor	Oral	Repurposed	Continuing enrollment/Q3/4 2022	Study ongoing – awaiting study completion / TLR

Contributions

- **ACTIV-4HT is experimenting with novel methods to perform automated data extraction from EHRs for clinical trial report forms.**

Lessons Learned

- Changing dynamic within the pandemic can change the operational feasibility of trials.

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ACTIV-5 Inpatient Trial

Company	Therapeutic	Class	Administration	New/Repurposed	Status/Estimated End Date	Results
AbbVie/Boehringer Ingelheim	Skyrisi™ (risankizumab)	Immune Modulator	Intravenous	Repurposed	Enrollment closed/Awaiting topline results	TLR shared with Internal Team for Discussion July 5, 2022
Humanigen	Lenzilumab	Immune Modulator	Intravenous	New	Enrollment closed/Primary endpoint not met	**Press release of TLR on July 12, 2022, primary endpoint not met**
Alexion	Danicopan	Factor D Inhibitor	Oral	New	Enrollment closed/Awaiting topline results	TLR expected July 2022

Lessons Learned

- **A need exists for a trial design that allows agents recruit quick and close if they don't show a sizeable effect**; screening Phase 2
- Need for methodical and consistent data capture are essential to spare extra data cleaning and preparation after trial conclusion

ACTIV-6 Outpatient Trial

Company	Therapeutic	Class	Administration	New/Repurposed	Status/Estimated End Date	Results
Apotex	Fluvoxamine	Immune Modulator/Antiviral	Oral	Repurposed	Enrollment Completed/Q2 2022	Awaiting TLR
GlaxoSmithKline	Fluticasone	Immune Modulator	Oral	Repurposed	Enrollment closed/No efficacy shown	No evidence of improvement in time to recovery compared with placebo
Ingenus	Ivermectin 400mcg	Immune Modulator/Antiviral	Oral	Repurposed	Enrollment closed/No efficacy shown	No evidence of improvement in time to recovery compared with placebo
Ingenus	Ivermectin 600mcg	Immune Modulator/Antiviral	Oral	Repurposed	Continuing enrollment/Q1 2023	Study ongoing – awaiting study completion / TLR

Contributions

- Application for EUA for Fluticasone will note ACTIV-6 data in the resubmission package if submitted
- Preprints on both **Ivermectin 400 and Fluticasone** showing **no significant effect in non-hospitalized patients with COVID-19**.
- **Development of a novel composition symptomatic/hospitalization/emergency care/death outcome**
- Trial design for conducting and outpatient trial in the presence of changing standard of care in allcomers population
- **Novel methods and best practices for conducting a fully remote trial in an emergency (repurposed agents)**
- Valuable information on standard risk patient populations in the changing pandemic

Lessons Learned

- **Patient choices when testing agents with some existing data that emerge as the trial enrolls are not always what you'd expect.**
- **Maintaining patient choice for treatments is essential**
- Ways to **strategically navigate** testing an agent that has significant **political association**, including **being thoughtful about study press releases and general communication updates**.

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Future of ACTIV Trials

INPATIENT SUBGROUP	OUTPATIENT SUBGROUP	RECOVER SUBGROUP
Monitored by a healthcare team in a hospital throughout treatment and recovery	*Not requiring hospitalization throughout treatment and recovery*	*Working in partnership with RECOVER- devoted to preventing, mitigating, and treating "long COVID"*

Proposals by the **Inpatient, Outpatient, and RECOVER Subgroups** aim to identify key thoughts for **potential strategy and/or new agent trials,** currently **available resources** that may be repurposed for such trials, and **gaps in resources** needed to conduct such trials.

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Future of ACTIV Trials | *Inpatient Subgroup* | *STRIVE Platform*

The new inpatient platform **STRIVE (Strategies and Treatments for Respiratory & Viral Emergencies)** will serve as a master protocol platform to study interventions against respiratory infections.

- *Protocol will utilize the network of inpatient trial sites from ACTIV-1, ACTIV-3, and ACTIV-5*
- *Infections include SARS-CoV-2, influenza, and others, with therapeutic interventions being either novel or existing*

CURRENT PROGRESS

PROTOCOL DEVELOPMENT

- The STRIVE concept has been discussed with **leadership from ACTIV-3, ACTIV-1, and ACTIV-5 and with individual networks**
- One agent/trial, both related to SARS-COV-2, are **planned for entering the platform**

ORGANIZATIONAL STRUCTURE

- **Two Committees Overseeing STRIVE**: **1)** Leadership Committee; **2)** Scientific Steering Committee
- **Seven Working Groups**
- **Eight ICCs** Coordinating 200+ Sites

NEXT STEPS

- Review suggestions based on **FDA Safe to Proceed on July 7, 2022**
- Expect **FPI in August 2022**
- Continue to meet twice weekly to **resolve infrastructure, funding, and other logistical and strategic issues**

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Future of ACTIV Trials | *Outpatient Subgroup*

KEY CONSIDERATIONS FOR FUTURE OUTPATIENT PROPOSAL	
Periods of trial accrual with varying case rates and speed, making prediction of completion challenging	EUAs for Outpatient treatment (Paxlovid, Molnupiravir, etc.)
Loss of effect of certain monoclonal antibody therapies	Combination Therapies (potential to partner with Pfizer or Merck to do a combination study with Paxlovid or Molnupiravir)
Continued changing COVID-19 variant landscape	Continuous Trial Platform Design
Change in severity of the disease pathobiology, making traditional hard endpoints exceedingly difficult	Making platform generalizable to other diseases/sustainabillity

OUTPATIENT SUBGROUP NEXT STEPS

1. Continue assessing the **impact of potential changes in standard of care, emerging variants, and potential emerging resistance**

2. **Conducted a public forum discussion with FDA on paths forward for outpatient trial design**

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NIH RECOVER Initiative

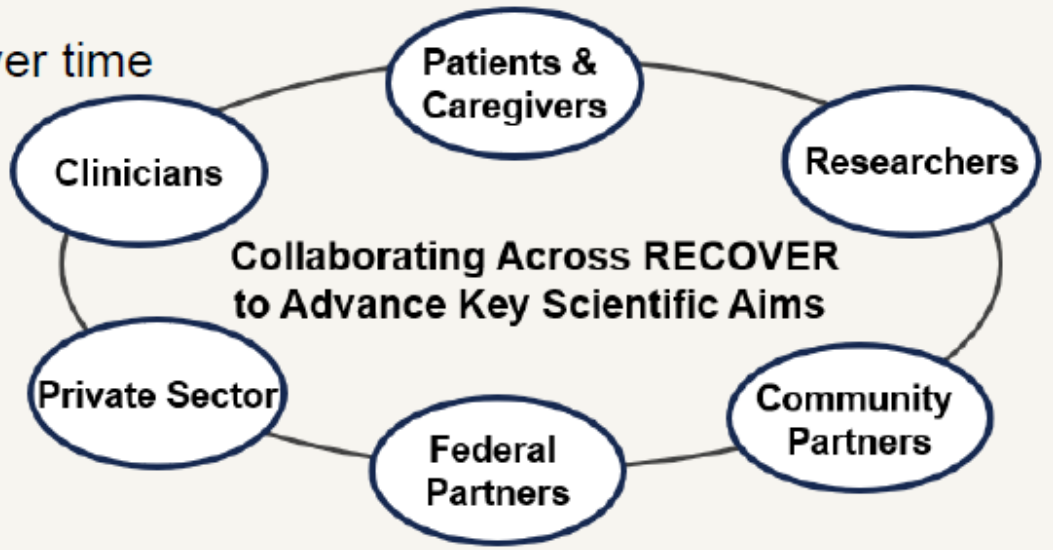
$1.15B investment

Goal

Rapidly improve our **understanding** of and ability to **predict, treat, and prevent** PASC

Key Scientific Aims

1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct PASC sub-phenotypes
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC



Guiding Principles

Patient-centered, participants as partners

recoverCOVID.org

National Scale with inclusive, diverse participation & community engagement

Platform protocols, standardized methodologies, and common data elements

Adaptive approaches based on emerging science

Acknowledgements

ACTIV-2

ACTIV-5: BIG EFFECTS TRIAL (BET)

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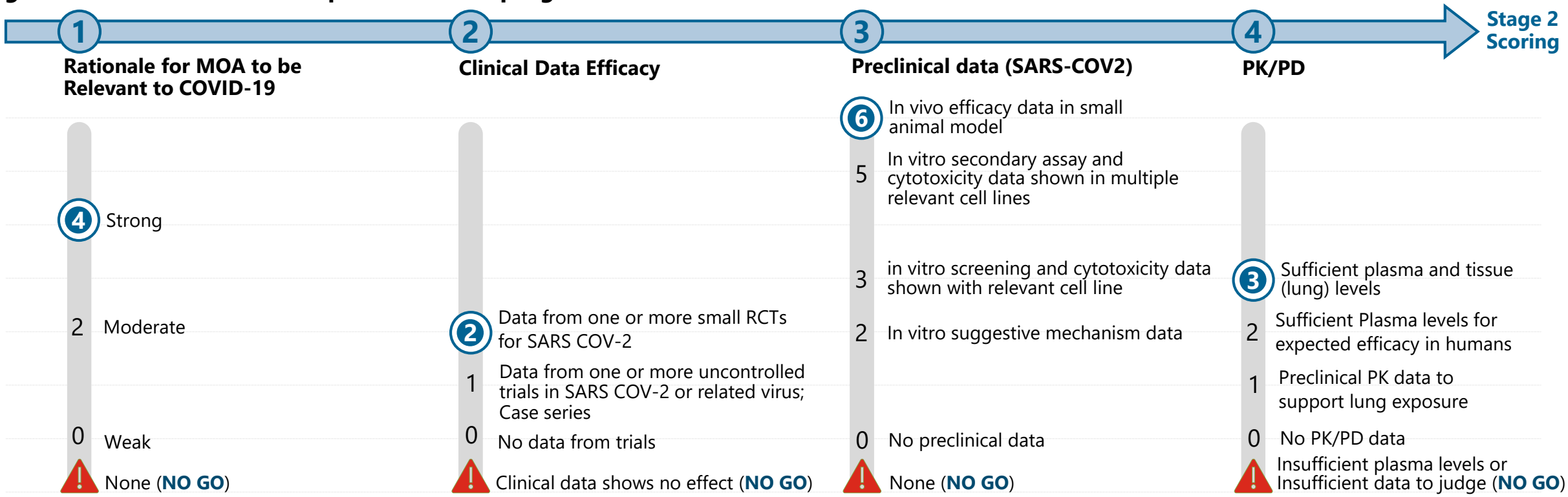
APPENDIX
Agent Prioritization Criteria

Original April 2022

Stage 1 Scoring Criteria | *Antivirals*

Antiviral Prioritization Team members will conduct a first stage of scoring with a greater emphasis on rationale for MOA, SARS-CoV-2 trials, and preclinical data (including PK)

Criteria in Stage 1 will be reviewed in order. If the reviewer determines an agent is a NO GO for a given criteria, then other criteria will go unreviewed, and the compound will not progress further.



NOTES

Criteria 1: Rational needs to include proof of target engagement. Strong rationale alone, without additional supporting preclinical/clinical data, is not sufficient to prioritize an antiviral candidate.

Criteria 2: SARS-CoV-2 Trials refer to the quality of clinical data from smaller completed / ongoing trials (Phase 1 or 2), NOT the existence of ongoing Phase 3 trials for an agent or another in the same class. The existence of Phase 3 trials with an agent should be considered during triage. Appropriate reference population (e.g. critical care patients) needs to be defined when evaluating clinical data.

Criteria 3: For antiviral agents, need to identify (1) molecular target; (2) EC50 (protein-adjusted, if available); (3) pK; (4) toxicity / maximum tolerated dose; (5) peak-to-trough plasma ratios; (6) half-life; and (7) clinical stage.

Highest score possible for category

Stage 1 Scoring Criteria | *Immunomodulators & Symptomatic / Supportive Tx*

Immunomodulators and Symptomatic / Supportive Therapies Prioritization Team members will conduct a first stage of scoring with a greater emphasis on rationale for MOA, SARS-CoV-2 trials, and preclinical data (including PK)

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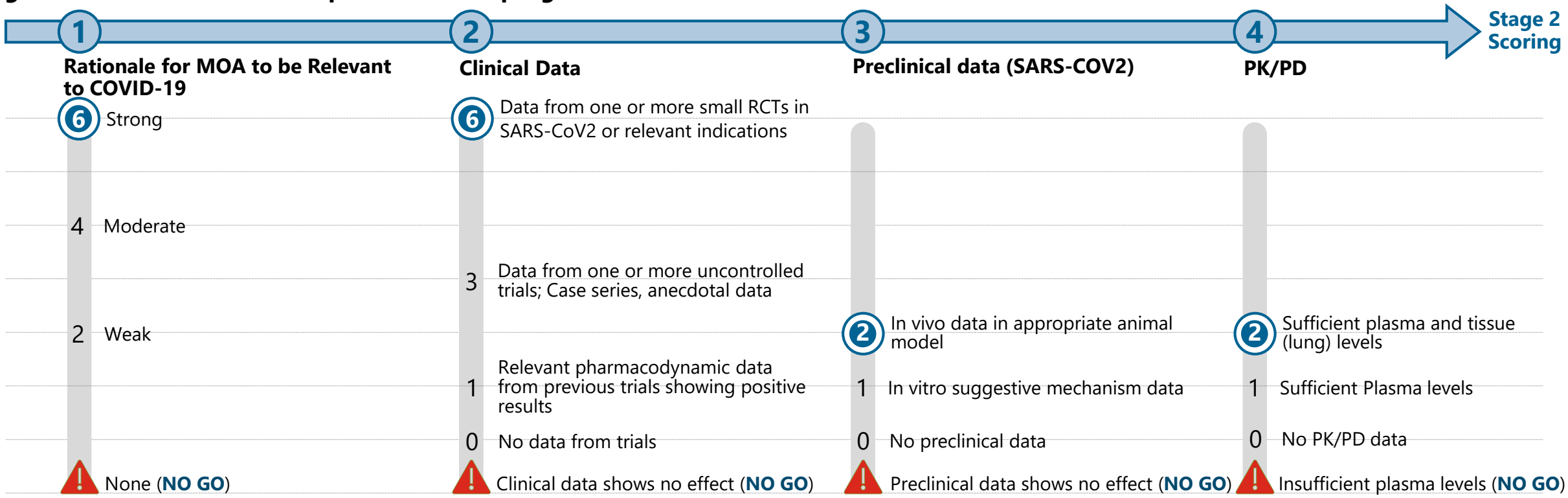

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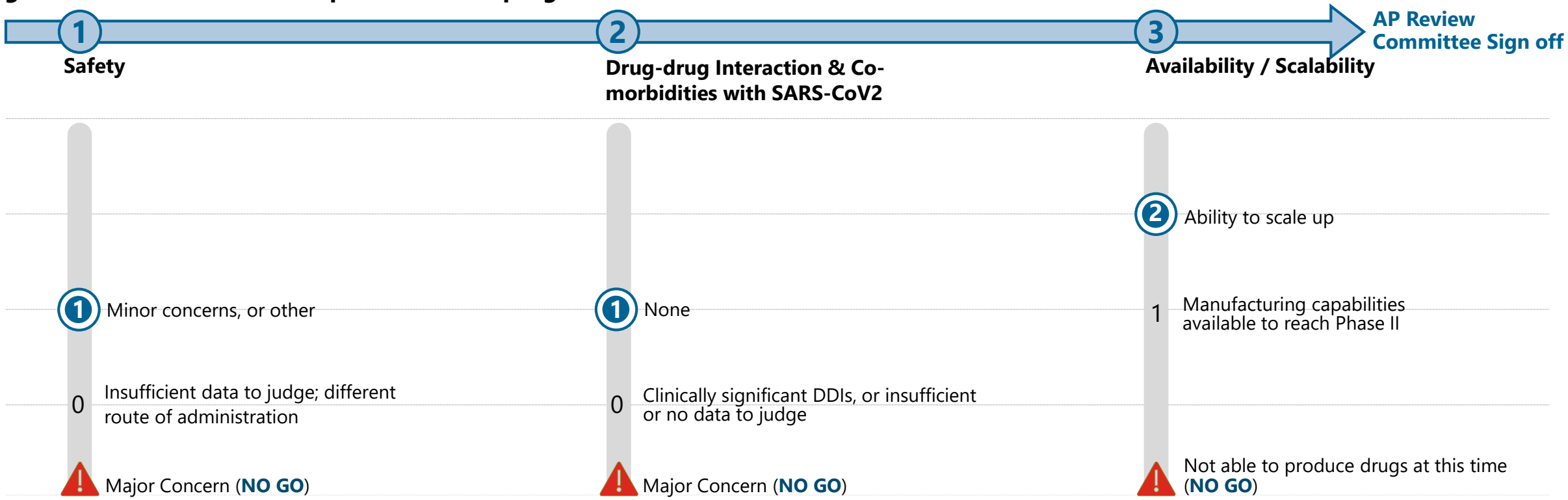
Highest score possible for category

Stage 2 Scoring Criteria | *All Classes of Agents*

The second stage of scoring based on safety, drug-drug interactions, and availability / scalability) will only be conducted for those agents that passed Stage 1 scoring

Criteria in Stage 2 will be reviewed in order. If the reviewer determines an agent is a NO GO for a given criteria, then other criteria will go unreviewed, and the compound will not progress further.



NOTES

Criteria 1: When considering the safety of compounds, clinical context is important. Safety of a compound may vary in prophylaxis/outpatient populations compared to critical patients. For the critical patient population, it may be difficult to separate safety from rationale.

Highest score possible for category

ACTIV-6 Repurposed Agents | *Scoring Criteria*

Scoring Criteria		No Go	0	1	2	3	4
Triage & Must-Have	**Safety**	Not approved for any other disease indication in proposed formulation	Previously approved for other disease indication, but lacks safety data in proposed dose			Adequate safety profile with suitable benefit/risk profile (with safety warning that needs to be adjudicated)	Strong safety profile [previously approved for other indication in broad patient populations (i.e., elderly, and/or patients with co-morbidities) and adequate amount of historical safety data]
	Route of Admin-istration	Difficult to administer (e.g., IV) or store (e.g., requiring specialized equipment)				Moderately difficult to administer (e.g., inhaled, intranasal, SubQ) and store (e.g., refrigerated / 4ºC)	Easy to administer (e.g., oral, metered-dose inhaler) and store (e.g., room temp)
Must-Have	**Rationale for MOA to be relevant to COVID-19**		Unknown	Weak	Moderate	Strong (reasonable rationale for use with COVID-19 and appropriate for outpatient setting)	
	Relevant Clinical Trial Data for Early COVID-19	Majority of clinical data shows no effect in outpatient setting	No data from outpatient trials	Data from one or more outpatient trials in **mechanistically relevant disease** with promising initial results	Mixed / inconclusive results from **outpatient uncontrolled trials and/or RCTs** in SARS CoV-2 or related virus	Overall promising initial results from **uncontrolled outpatient trials** for SARS CoV-2 or related virus	Overall highly promising initial results including data from **one or more outpatient RCTs** for SARS CoV-2 or related virus
	Real World Evidence		No evidence of efficacy from use in the clinical setting / no data to judge	Valid data from **one** RWE case study suggesting clinical efficacy	Valid data from **multiple** RWE case series suggesting clinical efficacy		
	Drug-drug Interaction	Major concern (clinically significant DDIs)	Insufficient / no data to judge	Minor concern / manageable drug interactions	None		
Nice-to-Have	**Preclinical Data**		No preclinical data / shows no effect	In vivo data in appropriate animal model			
	PK / PD		No PK/PD data / insufficient plasma levels	Sufficient plasma and / or tissue levels			
	Need for Scientific Clarity (i.e., strong public interest)		No expressed interest from the public / scientific community		Significant interest from the public / scientific community, with no current plans to study the agent in an adequately powered trial		

***Note: Availability / scalability will be assessed after prioritization of any agent before official entry into the trial**

Modified 03/11/2022

Stage 1 Scoring Criteria | *Antivirals*

Antiviral Prioritization Team members will conduct a first stage of scoring with a greater emphasis on rationale for MOA, SARS-CoV-2 trials, and preclinical data (including PK)

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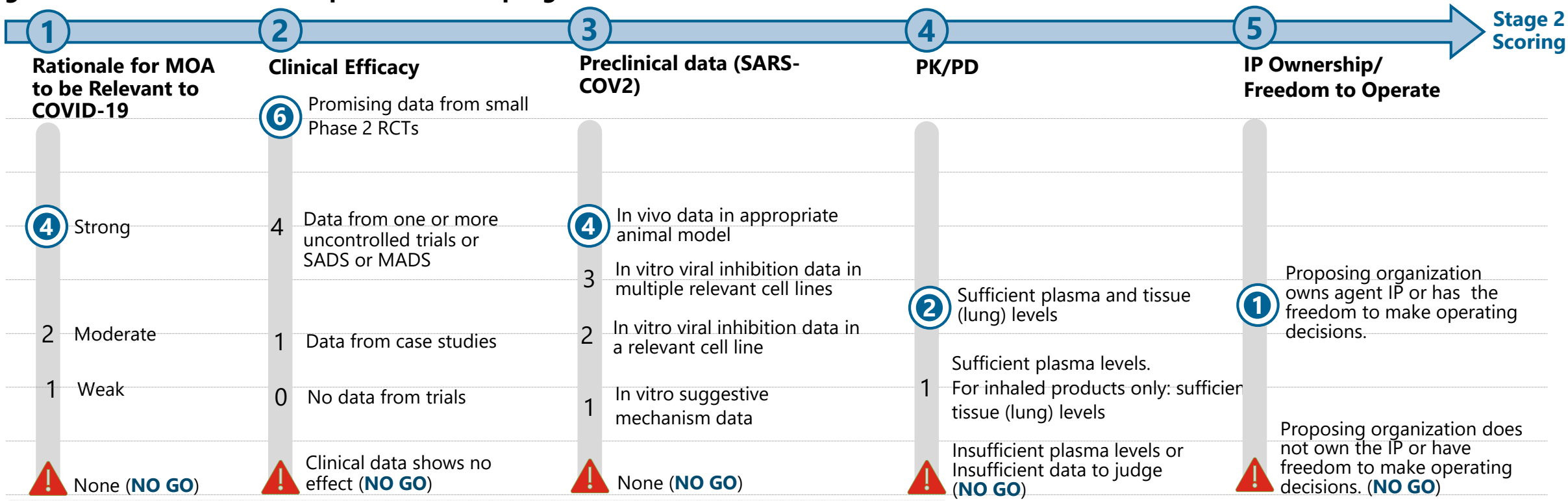

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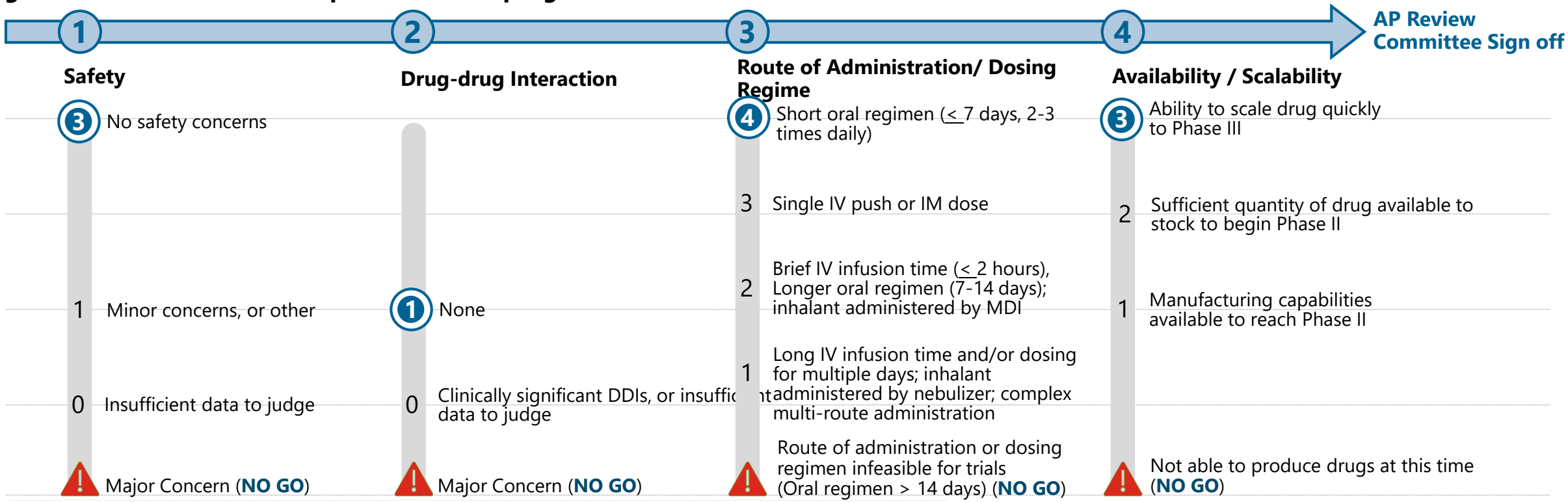
Criteria 3: For antiviral agents, need to identify (1) molecular target; (2) EC50 (protein-adjusted, if available); (3) pK; (4) toxicity / maximum tolerated dose; (5) peak-to-trough plasma ratios; (6) half-life; and (7) clinical stage.

Highest score possible for category

Stage 2 Scoring Criteria | *Antivirals*

The second stage of scoring based on safety, drug-drug interactions, and availability / scalability) will only be conducted for those agents that passed Stage 1 scoring

Criteria in Stage 2 will be reviewed in order. If the reviewer determines an agent is a NO GO for a given criteria, then other criteria will go unreviewed, and the compound will not progress further.



NOTES

Criteria 1: When considering the safety of compounds, clinical context is important. Safety of a compound may vary in prophylaxis/outpatient populations compared to critical patients. For the critical patient population, it may be difficult to separate safety from rationale.

Highest score possible for category

Stage 1 Scoring Criteria | *Immunomodulators & Symptomatic / Supportive Tx*

Immunomodulators and Symptomatic / Supportive Therapies Prioritization Team members will conduct a first stage of scoring with a greater emphasis on rationale for MOA, SARS-CoV-2 trials, and preclinical data (including PK)

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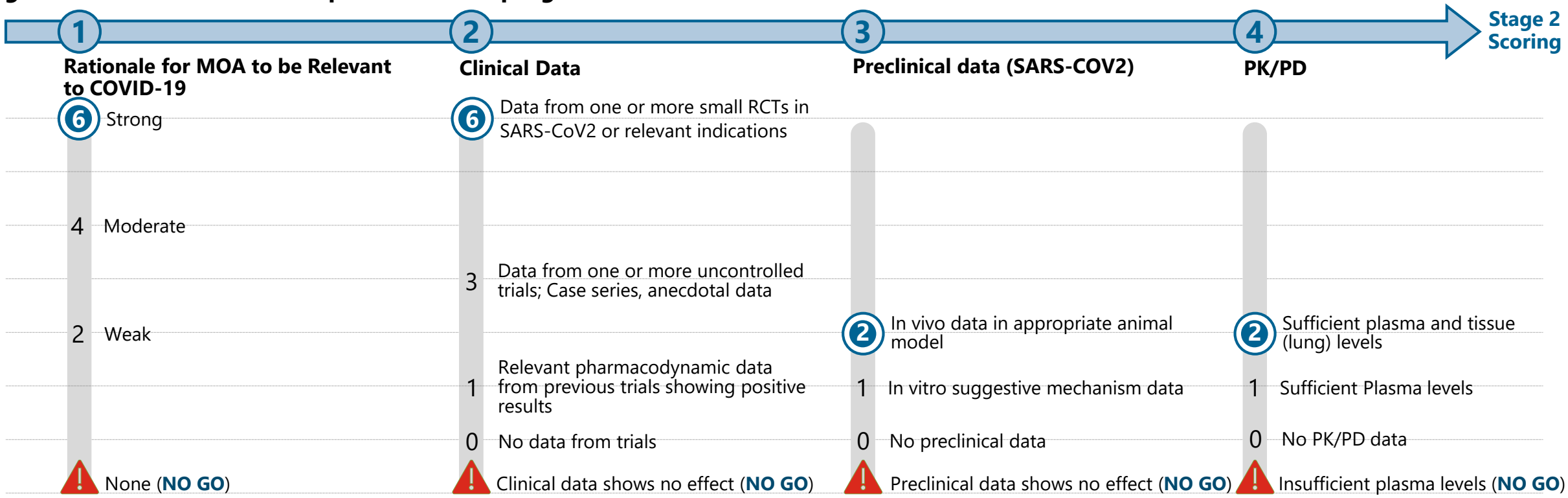

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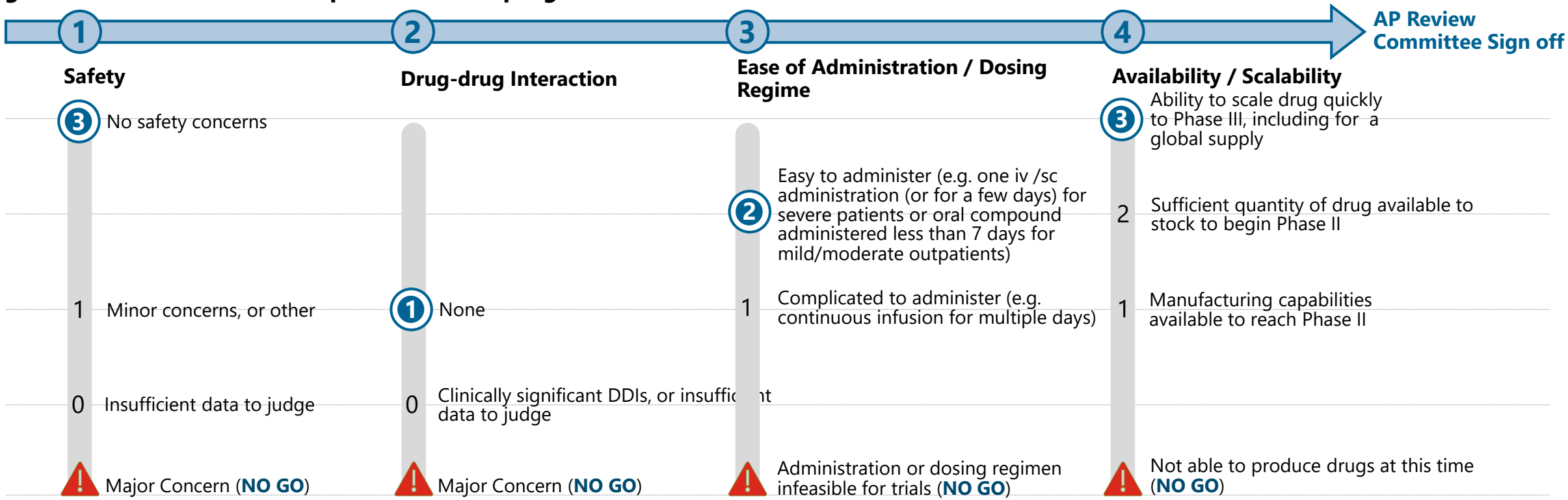
Highest score possible for category

Stage 2 Scoring Criteria | *Immunomodulators & Symptomatic / Supportive Tx*

The second stage of scoring based on safety, drug-drug interactions, and availability / scalability) will only be conducted for those agents that passed Stage 1 scoring

Criteria in Stage 2 will be reviewed in order. If the reviewer determines an agent is a NO GO for a given criteria, then other criteria will go unreviewed, and the compound will not progress further.



NOTES

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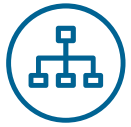
Highest score possible for category

APPENDIX
SNAPSHOT PROTOCOL SUMMARIES

ACTIV-1 | *Protocol Overview*

Study Design



The ACTIV-1 master protocol is a **Phase III** trial designed to evaluate multiple therapeutic agents for the treatment of **moderately or severely ill** patients infected with SARS-Cov-2.

The research objectives are to evaluate each agent with respect to **speed of recovery**, **mortality**, **illness severity**, and **hospital resource utilization**.

Each agent will be evaluated as **add-on therapy to the local standard of care** including remdesivir (provided) as well as convalescent plasma and dexamethasone per guidelines.

A sample size of **2,160 patients overall (3 agents)** provides for an 85% chance to detect a recovery rate ratio (RRR) = 1.25.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	To evaluate the clinical efficacy of treatment in adults hospitalized with COVID-19 with respect to **time to recovery**.	• Time to recovery by Day 29
Key Secondary	To evaluate the clinical efficacy (**clinical status and mortality**) assessed on Day 15 and Day 29 for the previous day.	• Clinical status on Day 14 and Day 28 (as defined by the 8-point ordinal scale) • 14-day and 28-day mortality
Exploratory	To evaluate the effect of treatment on **National Early Warning Score (NEWS)**.	• NEWS assessed daily while hospitalized and on Days 15 and 29, if feasible

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ACTIV-2 | *Protocol Overview*

Study Design

The ACTIV-2 master protocol is a randomized, blinded, controlled platform **Phase II trial that can expand seamlessly to Phase III** that allows agents to be added and dropped during the study.

The trial enrolls adults with COVID-19 who are not hospitalized and aims to evaluate **safety**, and efficacy of the investigational treatment on **reducing duration of symptoms** and **increasing the proportion of participants with undetectable virus**.

~110 participants per investigational agent in the **Phase II** evaluation. For **infused agents**, **~421 participants** per investigational agent in the **Phase III** evaluation (incl. those in Phase II). For non-infused agents, the number of participants in Phase III depends on the patient populations selected and the desired endpoint.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	Determine **safety and efficacy** of an agent **to reduce the duration of COVID-19** symptoms and nasopharyngeal SARS-CoV-2 RNA detection through 28 days after study entry.	• Proportion of negative NP Swabs • Relative reduction of symptoms • Proportion of oxygen saturation
Key Secondary	Determine if an agent will **prevent either hospitalization or death** through 28 days after study entry.	• Reduction of COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28
Exploratory	To explore the impact of the investigational agent on participant-reported **rates of SARS-CoV-2 positivity** of household contacts.	• Symptom diary for Severity Score

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ACTIV-3 | *Protocol Overview*

Study Design

The ACTIV-3 master protocol is an **inpatient, Phase III** trial to evaluate **safety** and to understand the investigational treatment's effect on **time to recovery** and on **extrapulmonary complications and respiratory dysfunction**.

Randomization will be stratified by study site pharmacy and disease severity (2 strata). **At study onset, only participants in disease severity stratum 1 will be enrolled**. For agents passing the futility assessment, enrollment of participants will be **expanded into both strata**.

This phase III trial is planned to provide **90% power to detect a 25% increase** in the rate of sustained recovery. Randomization of up to **1,000 participants** is estimated to result in the required number of primary events.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	Determine whether investigational agents are **safe and superior** to control (e.g., placebo) when given with Standard of Care.	• Time to sustained recovery evaluated up to 90 days after randomization
Key Secondary	Compare each investigational agent with control for **all cause mortality.**	• All-cause mortality • Composite outcome which considers both time to sustained recovery and mortality

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ACTIV-3b | *Protocol Overview*

Study Design

ACTIV-3b is a **Phase III randomized, blinded, controlled platform trial** that evaluates the safety and efficacy of investigational agents.

A sister protocol to the ACTIV-3 master protocol, ACTIV-3b is aimed at **patients with critical respiratory failure** (i.e., those receiving high-flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation).

The planned **sample size is 620 participants (310 per group)** for each investigational agent / placebo and can be re-estimated by investigators who are blinded to interim results.

The trial is planned to **provide 80% power to detect an odds ratio of 1.5** for improvement in clinical status at Day 90 for an investigational agent versus placebo with use of the ordinal outcome.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	Determine whether investigational agents are **safe and superior** to control (initially and primarily placebo) when given with Standard of Care.	• Recovery evaluated at 90 days after randomization
Secondary	Compare each investigational agent with control for **primary ordinal endpoints of recovery**.	• Time to mortality up to 90 days • Composite endpoint that considers the umber of days at home off new supplemental oxygen and the time to death • Time to recovery
Exploratory	Compare the primary endpoint of **time to sustained recovery** between subgroups.	• Time to sustained recovery • Mortality

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ACTIV-4a | ***Protocol Overview***

Study Design

ACTIV-4a is a **randomized, open label, adaptive platform** trial to compare the effectiveness of antithrombotic strategies for prevention of adverse outcomes in COVID-19 positive inpatients.

The trial will evaluate the safety and effectiveness of **varying doses of heparin, with or without P2Y12 inhibitor**, to prevent or reduce the formation of blood clots in hospitalized COVID-19 patients.

Co-enrollment in other trials is permitted as long as the other trial does not test agents with antithrombotic properties and there is no other scientific contraindication.

There are currently four arms of the trial: two arms for the **critically-ill cohort** and two arms for the **moderately-ill cohort**.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	Determine the most effective antithrombotic strategy for **increasing the number of days free of organ support** and reducing death.	• 21 Day Organ Support Free Days (OSFD)
Key Secondary	Determine the most effective antithrombotic strategy on the **composite endpoint** of death, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, or other systemic arterial thrombosis (AT).	• A composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke during hospitalization or at 28 days after enrollment (whichever is earlier)
Safety & Exploratory	Compare the effects of treatment on **bleeding**.	• Major bleeding as defined by ISTH • Individual endpoints of the thrombotic endpoint • Length of Hospital stay

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ACTIV-4b | ***Protocol Overview***

Study Design

ACTIV-4b is one of three **Phase III multi-center, adaptive, randomized controlled platform trials** of the safety and efficacy of Antithrombotic strategies.

The trial investigates whether **anticoagulants or antithrombotic therapy can reduce life-threatening cardiovascular or pulmonary complications** in newly diagnosed COVID-19 patients who do not require hospital admission.

The **drug is shipped** to the randomized patient, the patient then calls to confirm received and start date, and then there is a **weekly follow up.**

The estimated sample size is **~7000 participants**. Incorporating an adaptive design strategy will alter the final number of enrolled subjects.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	Determine the **rate of the composite endpoint**.	• Composite primary endpoints of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke for up to 45 days after initiation of assigned treatment
Secondary	Compare the effects of treatment on **individual outcomes** of the composite endpoint.	• Individual outcomes of the composite primary endpoint
Safety & Exploratory	Compare the effects of treatment on **bleeding**.	• Major bleeding (as defined by the ISTH) at the end of randomized therapy (45 days) and after an additional 30 days of safety follow up (day 75).

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“Low Touch” to “No Touch” Trial Design

ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

ENROLLMENT

FOLLOW-UP

Age 40-80
PCR or Ag Positive COVID-19
Within last 14 days
Platelets > 100,000
eGFR > 30 ml/min
Pregnancy Testing WOCBP
Outpatient Destination

R

“Morning Bottle”		“Evening Bottle”
Placebo	+	Placebo
Aspirin 81 mg	+	Placebo
Apixaban 2.5 mg	+	Apixaban 2.5 mg
Apixaban 5.0 mg	+	Apixaban 5.0 mg

Local Site Phase

- Inclusion, exclusion, bloodwork
  - Pregnancy Test as needed
  - D-dimer and CRP can be pending at randomization
- Central Simple Internet EDC

Centralized Telemedicine Phase

- Pt receives Study Drug overnight by FedEx
- Pt followed every 7 days electronic “chatbot” or call to address adherence, compliance, and flag potential endpoints
- 24/7 Pt Call Center for safety, endpoint reporting

First Video + Consent

Second Video
Telephone Introduction to Trial

ACTIV-4c | *Protocol Overview*

Study Design

ACTIV-4c is one of three **Phase III multi-center, adaptive, randomized controlled platform trials** of the safety and efficacy of Antithrombotic strategies.

This study will compare the effectiveness and safety of **antithrombotic therapy with no antithrombotic therapy after hospitalization** for 48 hours or longer for COVID-19.

Participants will be randomized to **either prophylactic anticoagulation or no anticoagulant therapy for** 30 days, and then followed for an additional 60 days after the completion of treatment.

The estimated sample size (for Stage 1) is **2,660 participants per study arm** based on an estimated baseline rate of the primary endpoint of ~4%.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	Determine the **optimal antithrombotic strategy** to minimize the composite endpoint of venous and arterial thromboembolic outcomes, and all-cause mortality.	• Composite endpoint of venous and arterial thrombotic complications and all-cause mortality at Day 30
Key Secondary	Compare the effects of treatment on the **incidence of composite outcomes, new, symptomatic VTE or ATE**.	• Composite endpoint of venous thromboembolic events at Day 30 • Composite endpoint of arterial thromboembolic events at Day 30 • Composite endpoint for the primary outcome at Day 45 and Day 90
Safety & Exploratory	Compare the effects of treatment on **bleeding**, **all-cause mortality**, and **all-cause re-hospitalization**.	• Major bleeding as defined by the ISTH • Clinically-relevant, non-major bleeding as defined by the ISTH • All-cause mortality at Day 30 • All-cause re-hospitalization at Day 90

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ACTIV-4HT | *Protocol Overview*

Study Design

ACTIV-4d is designed to **investigate promising agents targeting the host response to SARS-CoV-2 infection** for the treatment of COVID-19 patients hospitalized with hypoxemia. Multi-armed platform, blinded, placebo-controlled trial

This study will compare the effectiveness and safety of

- **Renin-angiotensin-aldosterone system**
- **Immuno-thrombotic pathways**
- **Investigational and re-purposed**

Participants will be randomized to **either a host targeted agent or placebo for duration of hospitalization**, and then followed for an additional 90 days post hospital discharge

The estimated sample size is **1,600 participants – 300 per study arm (4 arms) + 400 shared placebo.**

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	**Oxygen free days at day 28**	• Days alive and not on standard oxygen therapy, HFNC, NIV, IMV between randomization and 28 days later.
Key Secondary	• **Respiratory failure free** days at day 28 • **WHO 8-point ordinal scale** at 14 days, day 28 and day 60 • **90-day mortality**	
Laboratory Assessments	• Myocardial markers • RAAS-specific markers	• hsTroponin, NTproBNP • renin activity, AngII, Ang(1-7)
Safety & Exploratory	Hypotension Allergic reaction Incident renal replacement therapy.	

FNIH

ACTIV-5 | ***Protocol Overview***

Study Design

The ACTIV-5 master protocol is a **randomized, double-blind, placebo-controlled, inpatient, Phase II** trial to find those agents that may have large treatment effects but with insufficient data to move directly to large study.

ACTIV-5 is **not** designed as a definitive efficacy trial, for investigational agents with a high likelihood of success, or for testing agents with marginal improvements.

Compounds that do not demonstrate efficacy based in interim evaluations will be dropped, while **those that demonstrate efficacy will move forward to Phase III trials.**

Approximately 100 subjects will be assigned to each arm entering the platform and a given site will generally have no more than 3 interventions at once.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	Evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adults hospitalized with COVID-19 according to **clinical status (8- point ordinal scale) at Day 8**.	• COVID-19 Symptom Burden Scale
Key Secondary	Evaluate the clinical efficacy, as assessed by **time to recovery**.	• Day of recovery
Exploratory	Evaluate the **virologic and immunological efficacy**.	• Viral load and/or shedding • Cytokines, PBMC, proteomic, and transcriptomic analyses

FNIH

ACTIV-6 | ***Protocol Overview***

Study Design

ACTIV-6 is a **randomized**, **blinded**, **placebo-controlled Phase III platform trial** that allows study drug arms to be added or removed according to adaptive design and/or emerging evidence.

Eligible participants will be randomized to either the study drug arm or placebo arm. As additional study drug arms are added, the randomization may be altered to **leverage placebo data across arms**.

All study visits will be remote. Unplanned visits may occur in-person, as deemed appropriate by the site investigator. Participants will be asked to complete **questionnaires and report safety events via an online system** throughout the study.

An estimated sample size of over **~600 participants distributed among study drug arms** is needed to have 90% power to detect an odds ratio of 1.75 or greater assuming a traditional proportional odds model and a type I error of 0.05.

Objectives & Endpoints

	OBJECTIVE	*ENDPOINT*
Primary	To evaluate the **effectiveness** of repurposed oral medications [(study drug(s)] in **non-hospitalized participants with mild to moderate COVID-19**	• Symptom burden scale from baseline through Day 14 in which hospitalization will be the worst symptom state plus one and death will be the worst symptom state plus two
Key Secondary	To evaluate the **clinical outcomes** in participants in a study drug arm versus those in the placebo arm	• Modified COVID Ordinal Outcomes Scale through Day 28 • Hospitalization through Day 28 • Mortality through Day 28
	To describe the **quality of life (QOL)** in participants in a study drug arm versus those in the placebo arm	• Change in Patient-Reported Outcomes Measurement Information System (PROMIS) - 29 from baseline through Day 90 Follow-up
Exploratory	To describe **long-term COVID-19-related symptoms** in participants in a study drug arm versus those in the placebo arm	• Symptom burden scale at Day 90 Follow-up

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