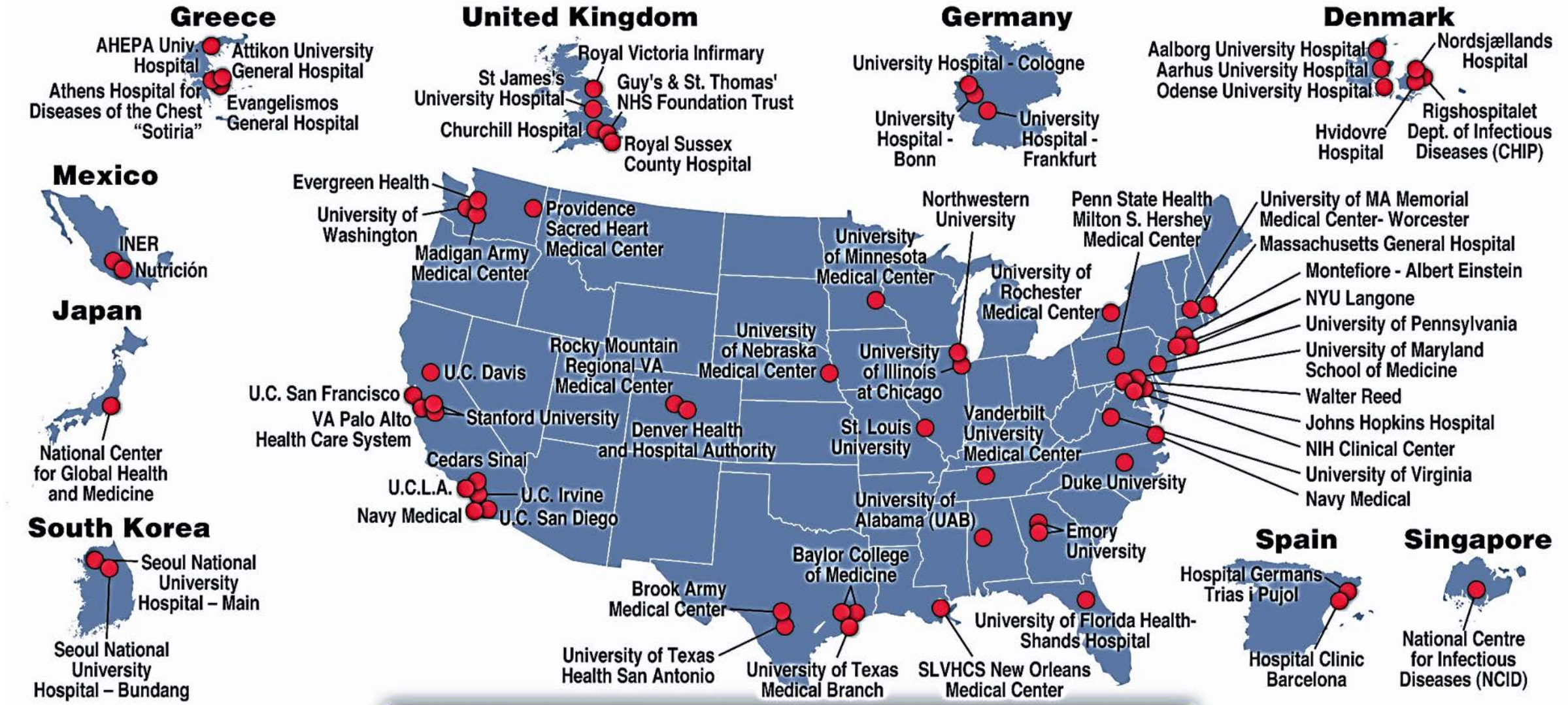
The Adaptive COVID-19 Treatment Trial (ACTT; DMID/NIAID; John Beigel, PI)

- A randomized, controlled trial with an adaptive platform
- Eligibility: Adult patients hospitalized with COVID-19 and evidence of pulmonary disease
- Primary Endpoint: Time to recovery (ordinal scale 1, 2 or 3)
- Timeline: Study opened Feb. 21, 2020
- Has completed first three versions; enrolling into the fourth
  - ACTT-1: Standard of care vs. remdesivir
  - ACTT-2: Remdesivir vs. remdesivir + baricitinib
  - ACTT-3: Remdesivir vs. remdesivir + interferon-β
  - ACTT-4: Dex + remdesivir vs. baricitinib + remdesivir

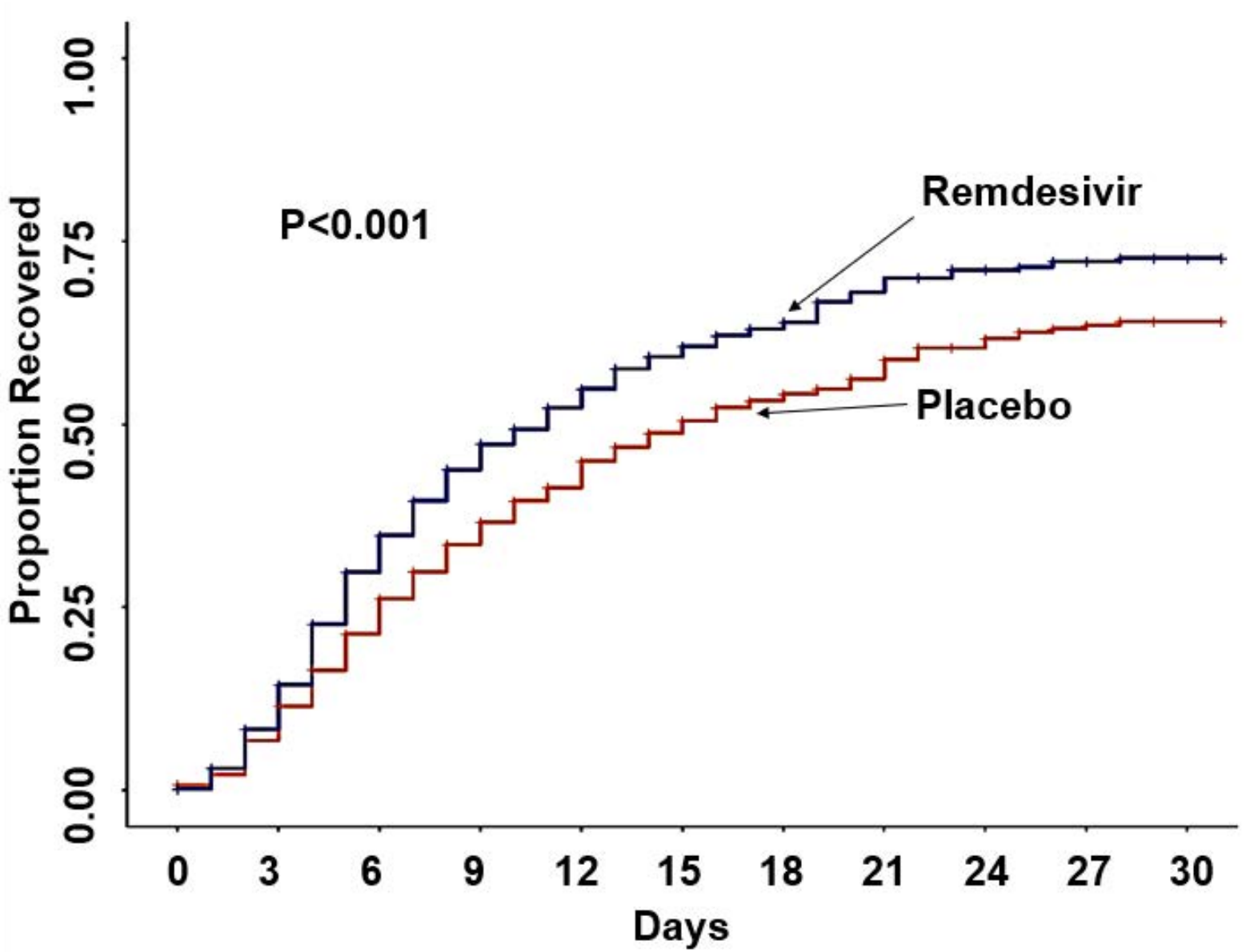
NIAID Adaptive Randomized, Controlled Treatment Trial for COVID-19



AS Fauci/NIAID

1,062 enrollees at trial close, 4/19/2020

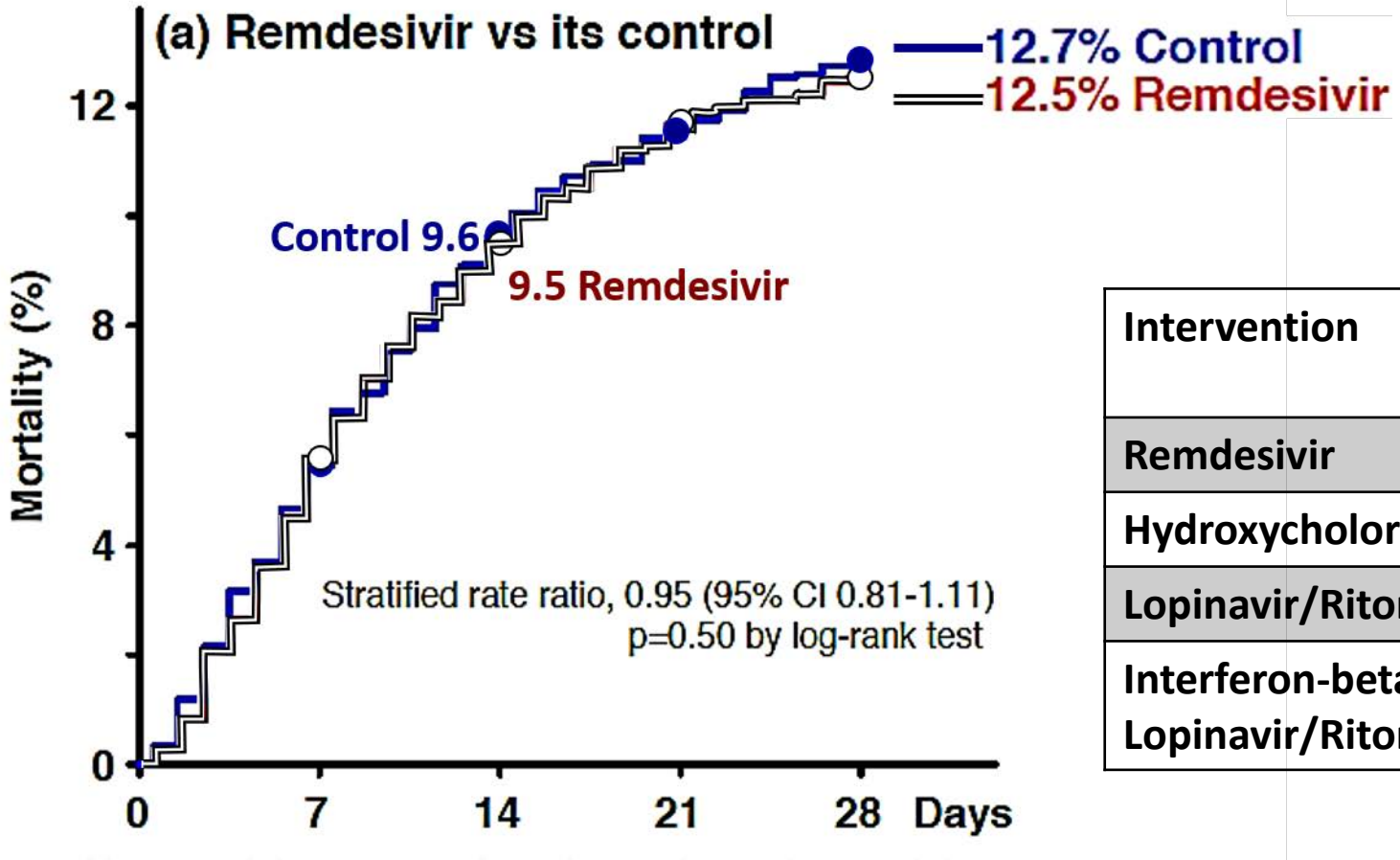
Time to Recovery* for Remdesivir and Placebo Arms



Ordinal Scale	Definition
1*	Not hospitalized, full activity
2*	Not hospitalized, limited activity
3*	Hospitalized, Non-medical
4	Hospitalized, not requiring O_2
5	Hospitalized, requiring O_2
6	High-flow O_2 or non-invasive vent.
7	Mechanical vent. or ECMO
8	Death

JH Beigel et al. N Engl J Med 2020
DOI: 10.1056/NEJMoa2007764

WHO Solidarity Trial



- 405 sites in 30 countries
- Death through 28 days
- Randomization to remdesivir ongoing

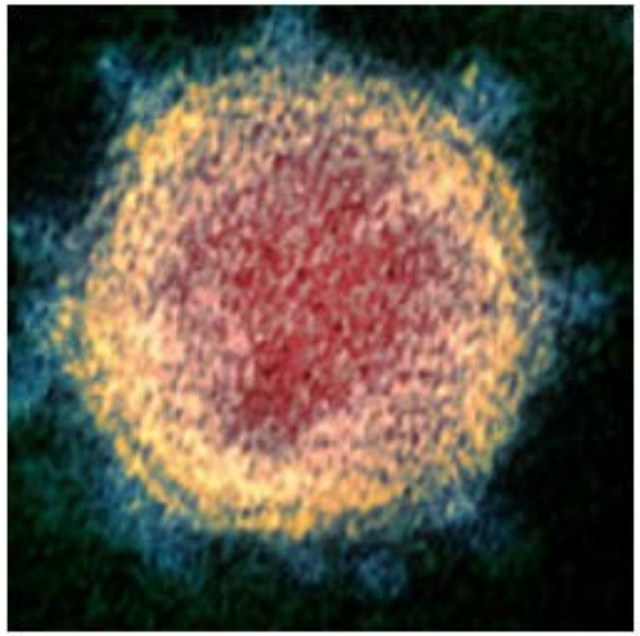
Intervention	N	Mortality (%Exp. / %Con)	Mortality Rate Ratio
Remdesivir	2750	12.5 / 12.7	0.95
Hydroxycholorquine	954	10.2 / 8.9	1.19
Lopinavir/Ritonavir	1411	9.7 / 10.3	1.00
Interferon-beta +/- Lopinavir/Ritonavir	2063	12.9 / 11.0	1.16

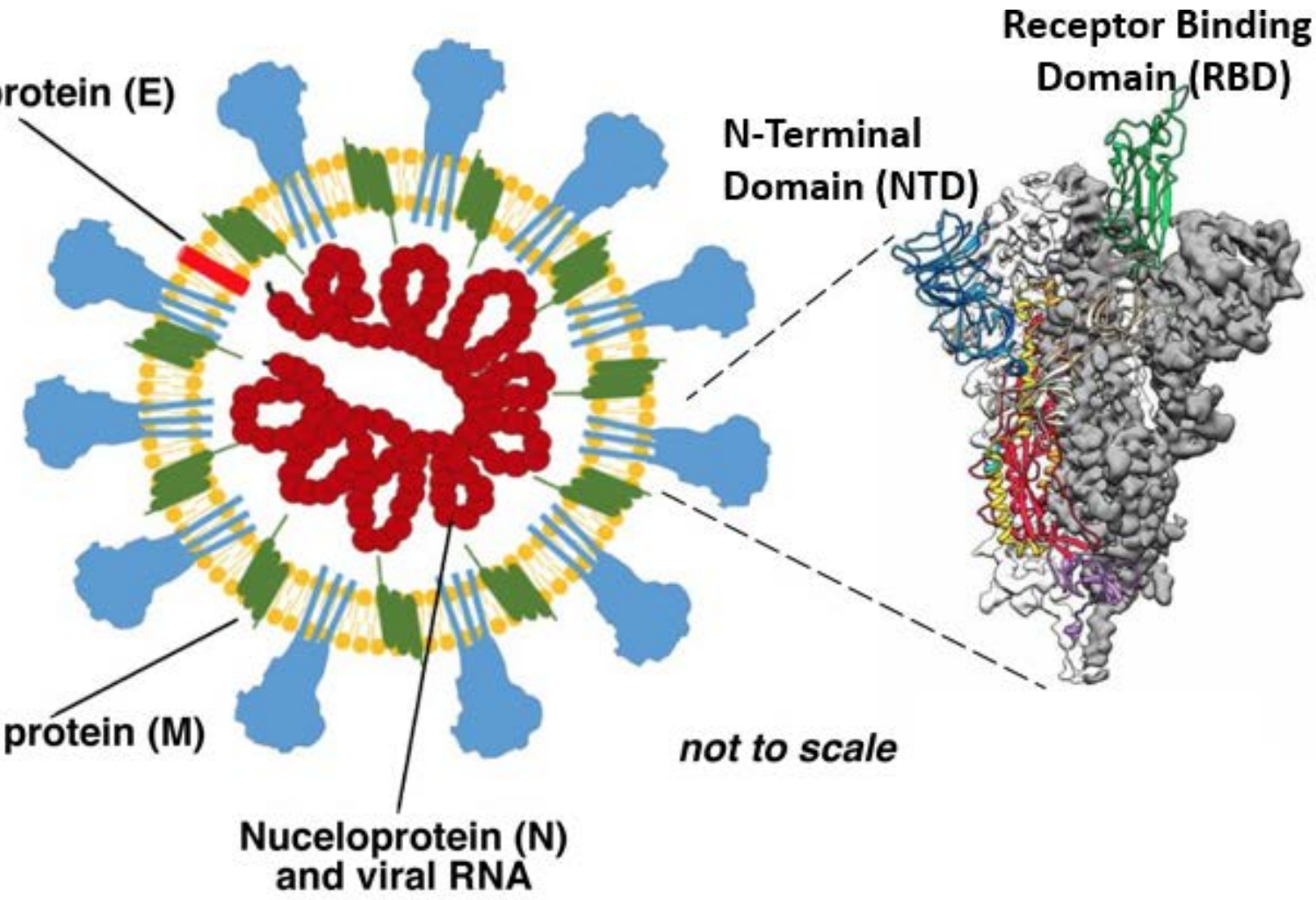
Nos. At risk at start of each week, and nos. dying

	Week 1		Week 2		Week 3		Week 5		Week 5	
	At Risk	Deaths	At Risk	Deaths	At Risk	Deaths	At Risk	Deaths	At Risk	Deaths
Remdesivir	2743	129	2159	90	2029	48	1918	18	1838	16
Control	2708	126	2138	93	2004	43	1908	27	1833	14

WHO Solidarity Trial Consortium. N Engl J Med. DOI: 10.1056/NEJMoa2023184.

SARS-CoV-2 and the Surface Spike Protein





Images: RML, Florian Krammer and NIAID VRC

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Trials (1)

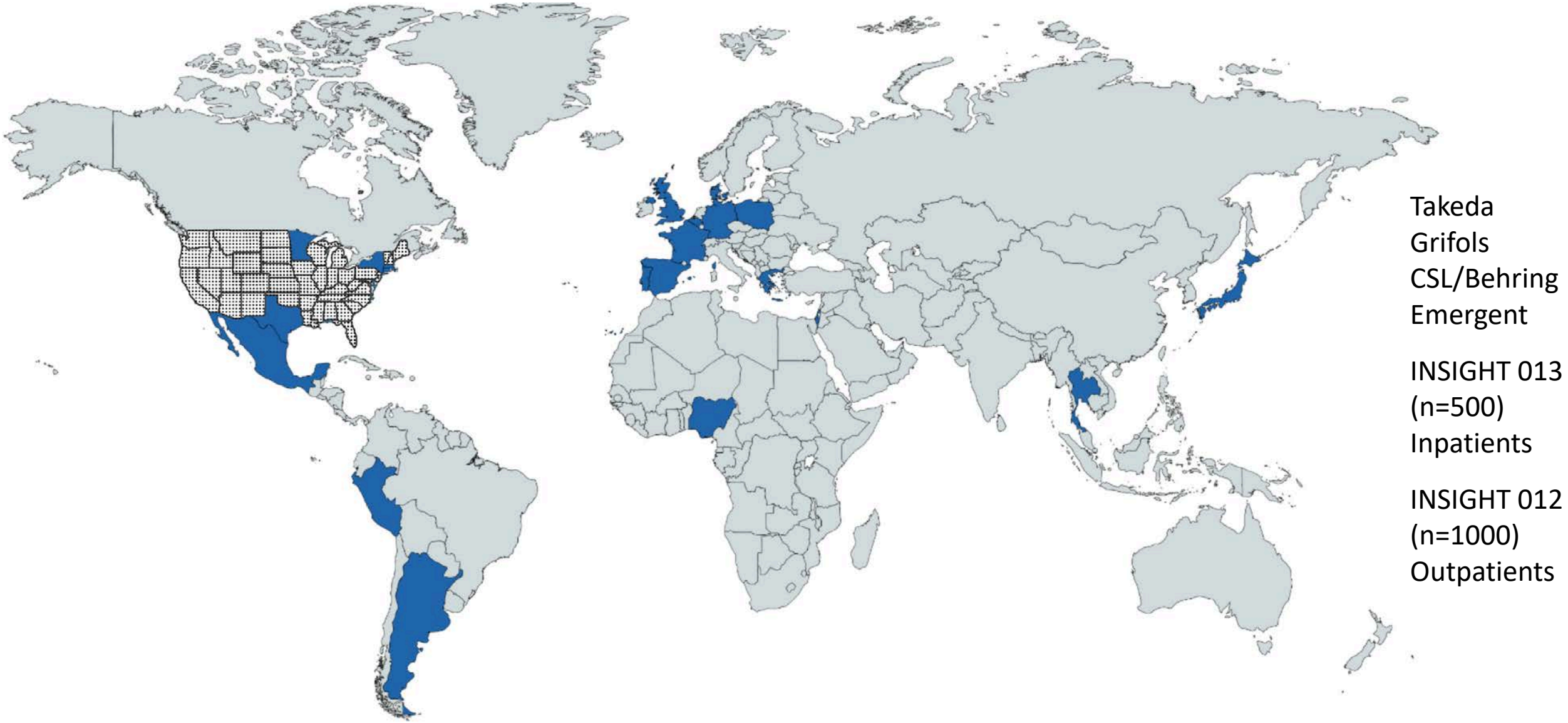
- ACTIV-2: 2-stage adaptive trial in outpatients
  - Initially studied placebo vs. MoAb bamlanivimab (ACE2)
  - Currently open-label bam; will soon study a second Ab
- ACTIV-3: 2-stage adaptive trial in hospitalized patients
  - Initially studied remdesivir + (placebo vs. bamlanivimab)
    - No evidence of efficacy at Stage 1 (in press, NEJM)
  - Version 2.0 will look at antibodies from two companies
    - 1 cross-reacts with SARS-CoV-1; a highly conserved site
    - The other is a combination of two antibodies

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

- ACTIV-5/Big Effect Trial (DMID/NIAID): Several different interventions looking for a big effect to then take into one of the other ACTT or ACTIV platforms
  - Currently looking at two agents + remdesivir:
    - Risankizumab (anti-IL23A, licensed for treating psoriasis)
    - Lenzilumab (anti-GM-CSF, under investigation for cytokine-release syndrome)

Immune IVIg Studies

Two Randomized, Controlled Trials of Immune IVIg

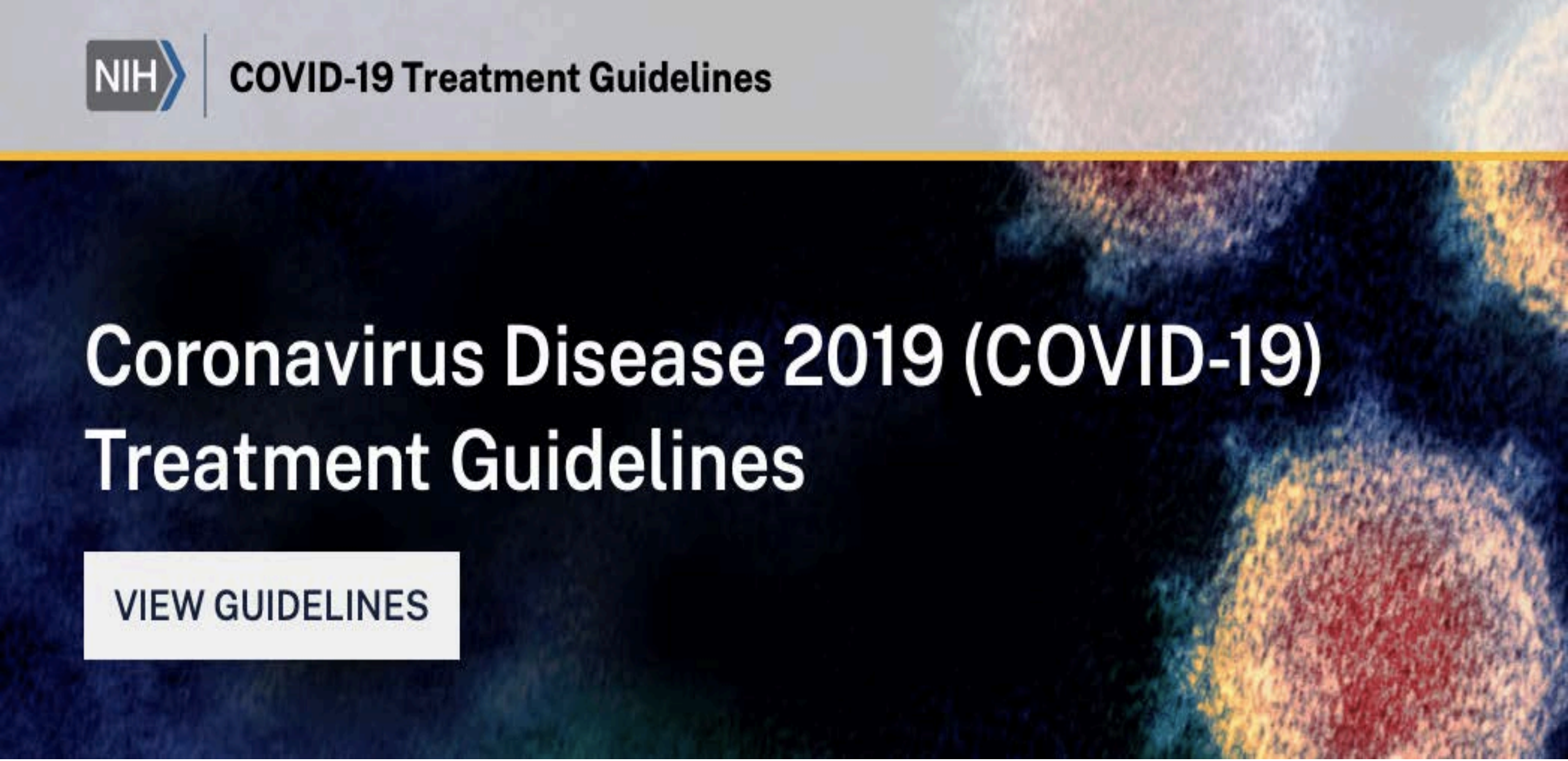


Takeda
Grifols
CSL/Behring
Emergent

INSIGHT 013
(n=500)
Inpatients

INSIGHT 012
(n=1000)
Outpatients

There are Currently 2543 Studies for the Treatment of COVID-19 Listed on ClinicalTrials.gov



http://covid19treatmentguidelines.nih.gov

NIH Treatment Guidelines Panel Recommendations for Treatment of COVID-19

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
No Hospitalized, Mild to Moderate COVID-19	There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab** or **casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk of disease progression.[a] These EUAs do not authorize use in hospital patients. **Dexamethasone** should not be used **(AIII).**
Hospitalized but Does Not Require Supplemental Oxygen	**Dexamethasone** should not be used **(AIIa).** There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increased amounts of supplemental oxygen) **(BIII)**[e,f] • **Dexamethasone**[d] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d,f] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)**[e,f]
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d] **(AI)**[g]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

- March 20 – request from HHS
- March 22 – initial 37 members identified; 6 USG agencies; 8 professional societies
- March 24 – first meeting
- April 7 – first release ready
- April 21 – final approval
- Since then:
  - 6 major revisions
  - 8 rapid communications
  - 7,213,718 page views