A Clinical Trial in Response to a Pandemic

September 9, 2020
Mat Makowski, PhD

ACTT Treatment Trial (Remdesivir):
A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults
DMID Protocol Number: 20-0006
ACTT-1: NCT04280705 ACTT-2: NCT04401579 ACTT-3: NCT04492475

Overview

- **About Emmes/CRID**
- **ACTT Treatment Trial**
  - Design
  - Endpoints
  - Challenges-Logistic
  - Challenges-Analyses
  - Preliminary Results
- **Questions**

CRID Project

- Statistical and Data Coordinating Center (SDCC) for the Division of Microbiology and Infectious Disease at the National Institute Allergy and Infectious Diseases (DMID/NIAID/NIH).
- First awarded to Emmes in 1996
- Approximately 100 people
- 154 active clinical trials/protocols

CRID Contract SDCC Role

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1. Data collection and management
2. Data quality assurance and control
3. Protocol and other study-related materials
4. Clinical study websites
5. Study communication, collaboration and reporting
6. Statistical design and analysis
7. Clinical site training, assessment & technical help
8. Electronic specimen tracking system
9. Data storage
10. Project Management

Emmes Responsibilities as SDCC

- **Data Collection**
  - Data entry system (Advantage eClinical®)
  - Data System Training and User's Guides
  - Data Collection Forms
  - Electronic Case Report Forms (eCRFs)
  - Query Generation and Resolution Tracking
- **Specimen tracking**
  - Electronic tracking system (GlobalTrace℠)
  - Specimen picklists (for testing)
- **Randomization**
- **Study Web Site**
  - Manual of Procedures and Other Study Materials
  - Operational Data Listings and Summaries

ACTT Treatment Trial

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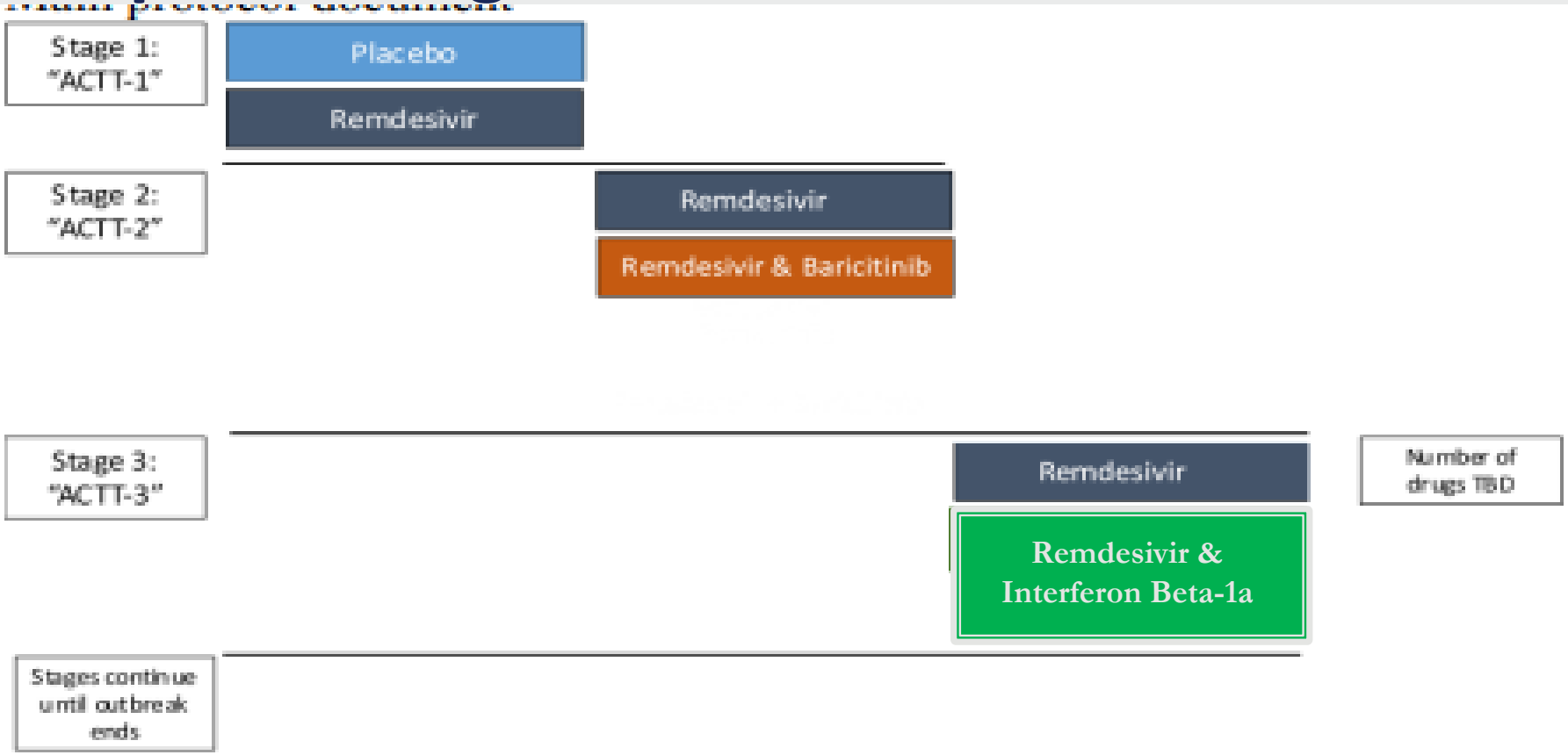
ACTT Treatment Trial

- **Adaptive design:**



ACTT Treatment Trial

- **Study conducted at 100+ sites in the US and internationally**
- **Stage 1 enrolled Feb 21 – April 19**
  - DSMB recommended early unblinding of Stage 1. This data supported FDA Emergency Use Authorization. First drug for treatment of COVID
- **Stage 2 enrolled May 8 – June 30**
- **Stage 3 started August 3**

https://www.niaid.nih.gov/news-events/nih-clinical-trial-testing-remdesivir-plus-interferon-beta-1a-covid-19-treatment-begins

ACTT Design

- **Each stage is ~1000 hospitalized subjects with SARS-CoV-2 infection with lung involvement, including a need for supplemental oxygen, abnormal chest X-rays, or illness requiring mechanical ventilation**
- **Subjects assessed on Ordinal Scale and NEWS each day while hospitalized and Day 15, 22 and Day 29. Collected adverse events to Day 29**

ACTT Study Drugs

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- **Remdesivir – investigational anti-viral drug with activity against MERS and SARS. Administered via IV daily for up to 10 days**
- **Baricitinib - anti-inflammatory drug approved for rheumatoid arthritis. Tablet for up to 14 days.**
- **Rebif - Subcutaneous interferon beta-1a, has antiviral and anti-inflammatory properties. Licensed for treatment of MS. Given every other day for up to 4 injections.**

https://www.niaid.nih.gov/news-events/nih-clinical-trial-testing-remdesivir-plus-interferon-beta-1a-covid-19-treatment-begins

ACTT Ordinal Scale

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Category 8: Death;

Category 7: Hospitalized, on invasive mechanical ventilation or ECMO;

Category 6: Hospitalized, on non-invasive ventilation or high flow oxygen devices;

Category 5: Hospitalized, requiring supplemental oxygen;

Category 4: Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise);

Category 3: Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; This would include those kept in hospital for quarantine/infection control, awaiting bed in rehabilitation facility or homecare, etc.

Category 2: Not hospitalized, limitation on activities and/or requiring home oxygen;

Category 1: Not hospitalized, no limitations on activities

https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

Choice of Endpoint

- Original endpoint was Day 15 ordinal Scale compared using proportional odds model.
- As more data became available, the team realized Day 15 may not capture the full disease progression
- Blinded team members ran simulations and then proposed time to recovery as an endpoint change to the DSMB.
- The DSMB agreed to the change and Day 15 ordinal scale was moved to a key Secondary Endpoint.

Primary Outcome

Primary endpoint: The log-rank test will be used to compare treatment arms with respect to time to recovery. For the log-rank test, the two key determinants of power are the total number of events (i.e., recoveries) E and the treatment-to-control ratio of the rate of recovery, R. The number of events required for power $1-\beta$ to detect a recovery rate ratio of θ using a two-tailed test at alpha=0.05 is approximately

$$E = \frac{4\left(1.96 + z_\beta\right)^2}{\{\ln(\theta)\}^2},$$

where z_β is the $100(1-\beta)$th percentile of the standard normal distribution.

Primary Outcome

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Recovery rate ratio (θ)	Number of recoveries needed for 85% power
1.20	1080
1.25	723
1.30	523
1.35	400
1.40	318

Primary Outcome

- **Deaths are censored at Day 29.**
- **This is similar to the Fine-Gray competing risks model.**

Key Secondary Outcome

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Key secondary: A sample size can be computed using an (assumed) ordinal scale distribution for the control arm and the odds ratio representing clinical improvement. The odds ratio represents the odds of improvement in the ordinal scale for combination treatment relative to the control arm [Whitehead, 1993]. The sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level α is given by

$$\frac{12\left(z_{\alpha/2}+z_{\beta}\right)^{2}}{\lambda^{2}\left(1-\sum_{i=1}^{K}p_{i}^{3}\right)},$$

where λ is the log odds ratio, p_i is the overall probability (combined over both arms) of being in the ith category of the K ordinal outcomes, and $z_{\alpha/2}$ and z_{β} are the $1-\alpha/2$ and $1-\beta$ quantiles of the standard normal distribution.

Choice of Endpoint

- Trials must be able to start rapidly in order to identify treatments in response to the outbreak.
- COVID-19 presentation is heterogeneous ranging from mild disease to weeks long that can end in death.
- Severity scores can be used but if wrong day is picked then clinical benefits may be missed.

Choice of Endpoint

- A mortality outcome would provide a definitive evidence of significance of treatment.
- Sample sizes may be impractical in the COVID-19 setting.
- Time to recovery outcomes may be used without having to choose an optimal day and with reasonable sample sizes.

Choice of Endpoint

Table 2. Possible endpoints for trials in COVID-19, corresponding target population, categorization of whether the endpoint is clinically meaningful, captures the diverse nature of disease, easy to measure, and reproducible.

Endpoint	Example	Population	Clinically meaningful	Multiple disease states	Time element	Easily measurable	Reproducibility	Additional comments
Binary outcomes								
Mortality	Death by 28	Moderate Severe Critical	+	o	o	+	+	+ Most relevant in severe/critical disease – May miss other meaningful improvements in patient status – Requires large sample size
Recovery(discharge, discharge-eligible)	Recovered by day 28	Moderate Severe	+	o	o	+	o	– May require long observation times in higher severity populations – Deaths require special consideration
Respiratory failure	ECMO or mechanical ventilation	Moderate Severe	+	o	o	+	o	– Depends on resources – Deaths require special consideration
Hospitalization	Admission within 28 days	Mild	+	–	o	+	o	– Depends on resources – Does not capture improvement – Deaths require special consideration
ICU admission	Admission within 28 days	Moderate	+	–	o	+	o	– Depends on resources – Does not capture improvement – Deaths require special consideration
Ordinal outcomes								
Ordinal disease severity scale	WHO scale at a fixed day	Moderate Severe	+	+	–	o	o	– Depends on resources – Defining clinical benefit less straightforward
Time-to-event outcomes								
Time to recovery	Time to discharge or eligible for discharge	Moderate Severe	+	o	+	+	o	– Depends on resources – Potential for "relapse" (sustained improvement removes this concern) – Deaths require special consideration
Time to 1- or 2-point improvement in ordinal scale[1]	Time to 2-point improvement in WHO ordinal scale	Moderate Severe Critical	+	o	+	o	+	– Changes in categories must be meaningful and should be considered equally important – Potential for "relapse" (sustained improvement removes this concern)
Time to intubation or death		Moderate Severe	+	-	+	+	o	
Continuous outcomes								
National Early Warning Score (NEWS score)		Moderate Severe	o	+	o	–	+	+ Familiar measure – Not disease-specific and hence not as sensitive to certain aspects of COVID – Deaths need special consideration

Choice of Endpoint

Table 2. Continued

Endpoint	Example	Population	Clinically meaningful	Multiple disease states	Time element	Easily measurable	Reproducibility	Additional comments
Viral load/viral clearance		Mild Moderate Severe Critical	–	o	o	–	–	– Difficult to reliably measure – Relation to clinical outcomes not well established – Deaths need special consideration
Oxygen, SpO_2/FiO_2 or paO_2/FiO_2	Daily SpO_2/FiO_2 until discharge, death or 28 days	Mild Moderate	o	o	o	–	+	– Relation to clinical outcomes not well established – Modified by oxygen supplementation – SpO_2/FiO_2 not well-validated – paO_2/FiO_2 only broadly available for ICU patients – Deaths need special consideration
Duration of a specific ordinal state	Hopitalization days; mechanical ventilation days	Severe Critical	o	–	o	+	o	+ Captures dimension meaningful to health system + Depends on the resources available + Deaths need special consideration
FLU-PRO	Change from baseline to day 14	Mild Moderate Critical	o	+	–	o	o	+ Captures aspects important to patients – Deaths need special consideration – Not validated for COVID-19
SOFA score	Change from baseline to day 14	Severe Critical	o	+	–	o	+	+ Captures disease severity and incorporates most relevant organ systems – Familiar for ICU setting – Not validated for COVID-19 and not disease-specific – Deaths need special consideration

COVID-19: coronavirus-induced disease; ECMO: extracorporeal membrane oxygenation; WHO: World Health Organization; ICU: intensive care unit; FLU-PRO: InFLUenza patient-reported outcome; SOFA score: sequential organ failure assessment score.
" + " indicates good performance; "–" indicates poor performance on this characteristic; neutral is denoted by "o."

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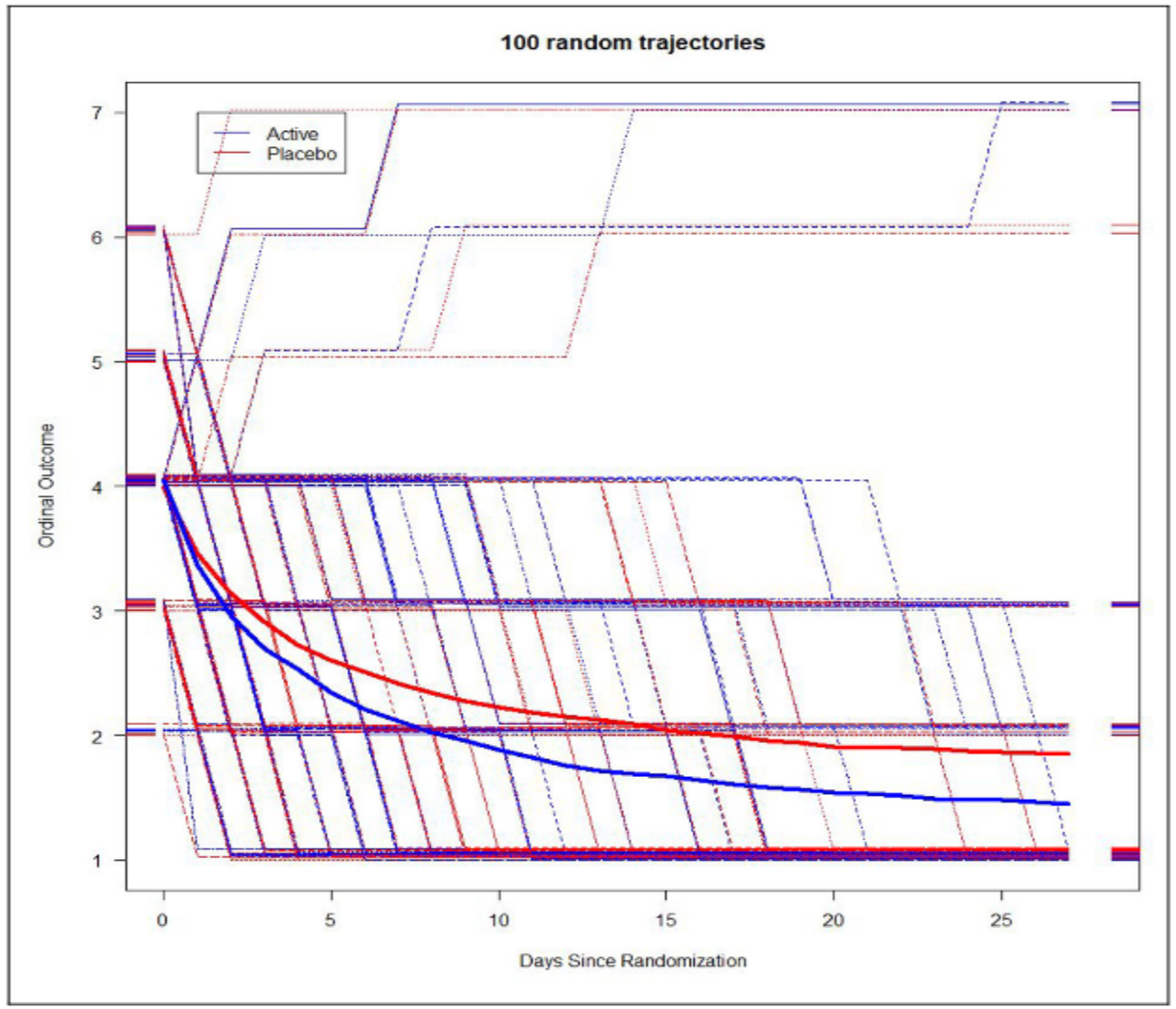
Choice of Endpoint

- By Dichotomizing an ordinal outcome we potentially lose power in exchange for flexibility of not having to choose an optimal timepoint.

Choice of Endpoint



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Choice of Endpoint

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Table 3. Simulated power for different analysis methods under various scenarios for simulations (type I error rate = 5%).

	Proportional odds					Time to event			Proportion
Scenario	Day 1	Day 7	Day 14	Day 28	Mean score	Time to 2-point improvement	Time to recovery	Time to death	28-day mortality
Reference	0.05	0.76	0.85	0.88	0.80	0.81	0.82	0.63	0.58
Lagged treatment effect	0.05	0.05	0.76	0.86	0.66	0.82	0.78	0.58	0.73
Faster recoveries	0.05	0.86	0.93	0.93	0.87	0.87	0.89	0.65	0.59
Higher mortality rate	0.05	0.76	0.85	0.88	0.80	0.81	0.82	0.75	0.71
Mortality differences only	0.05	0.23	0.26	0.32	0.24	0.31	0.28	0.51	0.46

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Challenges - Timelines

- **All Timelines are compressed- Feb 21 first enrollment to database lock on June 26 (approximately 4 months)**
- **With Multiple ACTTs, there may be concurrent deliverables (CSR ACTT1, DSMB ACTT2)**
- **FDA requests for preliminary data**

Challenges - Sites

- **International Trial – Some sites not used running clinical trials**
- **Pandemic – How do you monitor at sites if not allowed on site**
- **Paper forms can not leave patient rooms so paper forms are a problem**

Challenges - Analyses

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- **Time to event usually based on when x number of events occur**
- **Enrollment may be so fast that determining timing of interim analyses is difficult**
- **When to release data if unblinding occurs**
- **Trial is highly scrutinized so no matter what you choose someone will be unhappy**

Challenges - DSMB

- **Enrollment is so fast that normal meeting schedules do not work.**
- **DSMB receives weekly safety summaries and has access to website safety data that updates 4 times per day.**
- **Full meetings occur only for interim analyses.**
- **Shorter virtual meetings occur every 2 weeks or more if requested by the DSMB.**

Challenges - DSMB

- **ACTT1 interim analysis was actually done at over 100% information fraction (enrollment was increased to help with sub-group analyses).**
- **DSMB recommended unblinding prior to completion of follow-up.**
- **Next day a data freeze was completed and summary information was presented at the White House.**

Challenges – Data Reporting

- **After unblinding bias was introduced into those still in follow-up.**
- **An Early Analysis was done on data collected prior to unblinding.**
- **An analysis on all data was also completed.**

Challenges – Data Reporting

- **Should you report preliminary data in a pandemic?**
- **Data is not clean but result is pretty convincing.**
- **Not other treatments currently available.**
- **Face criticism no matter what choice you make.**
- **Everyone wants to see the data broken down in different ways and is not shy of saying so…**

Challenges – Alpha Spending

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- **What should be considered the final analysis?**
- **100% Information will be reached well before enrollment/follow-up are complete.**
- **Once 100% recoveries are reached, is that final analysis?**
- **Do you wait till Data lock and do a complete analysis?**

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ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., Kerry Dierberg, M.D., M.P.H., Victor Tapson, M.D., Lanny Hsieh, M.D., Thomas F. Patterson, M.D., Roger Paredes, M.D., Ph.D., Daniel A. Sweeney, M.D., William R. Short, M.D., M.P.H., Giota Touloumi, Ph.D., David Chien Lye, M.B., B.S., Norio Ohmagari, M.D., Ph.D., Myoung-don Oh, M.D., Guillermo M. Ruiz-Palacios, M.D., Thomas Benfield, M.D., Gerd Fätkenheuer, M.D., Mark G. Kortepeter, M.D., Robert L. Atmar, M.D., C. Buddy Creech, M.D., M.P.H., Jens Lundgren, M.D., Abdel G. Babiker, Ph.D., Sarah Pett, Ph.D., James D. Neaton, Ph.D., Timothy H. Burgess, M.D., M.P.H., Tyler Bonnett, M.S., Michelle Green, M.P.H., M.B.A., Mat Makowski, Ph.D., Anu Osinusi, M.D., M.P.H., Seema Nayak, M.D., and H. Clifford Lane, M.D. for the ACTT-1 Study Group Members*

https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

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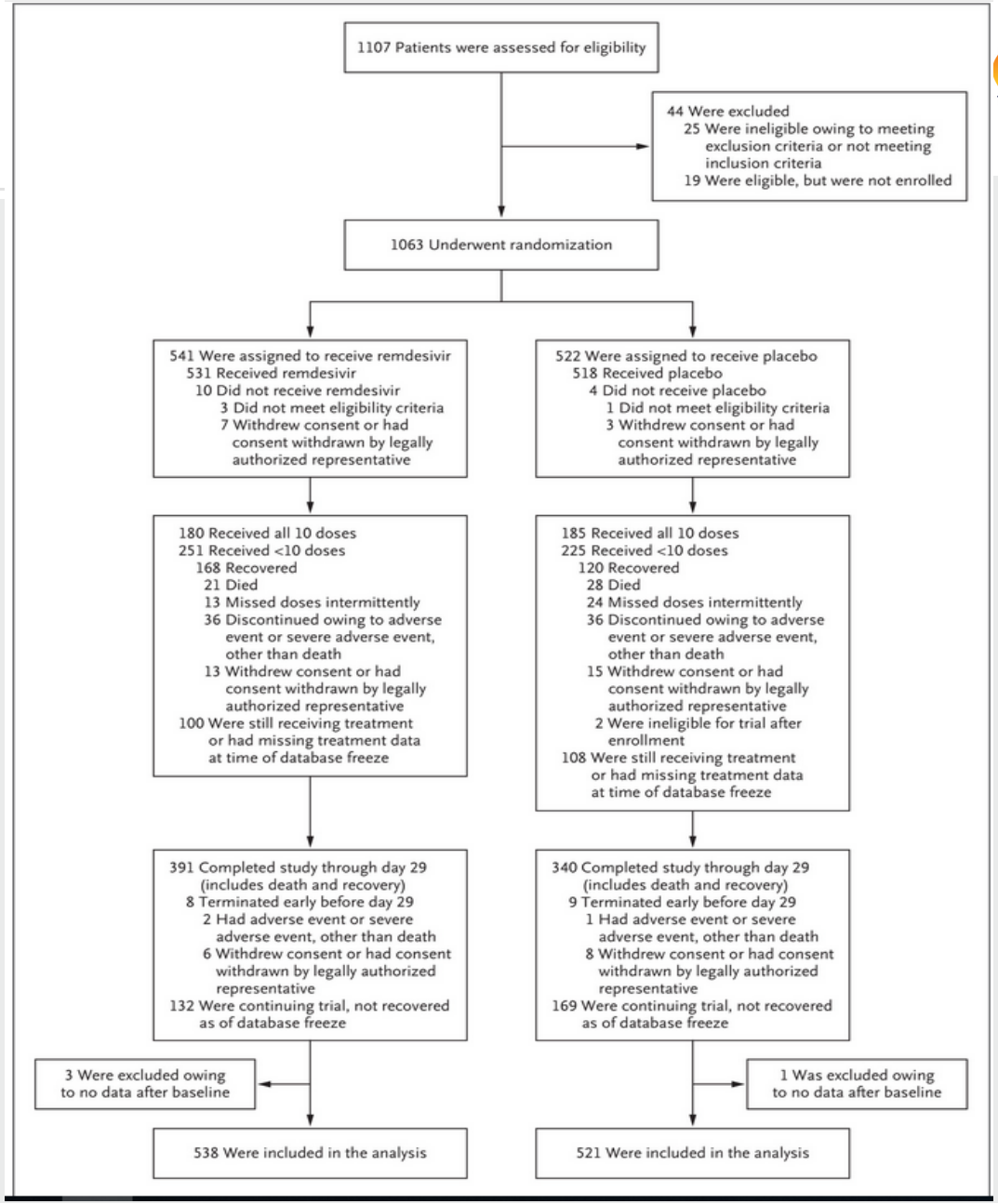

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Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	All (N=1063)	Remdesivir (N=541)	Placebo (N=522)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.3)	352 (65.1)	332 (63.6)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	134 (12.6)	77 (14.2)	57 (10.9)
Black or African American	219 (20.6)	108 (20.0)	111 (21.3)
White	565 (53.2)	279 (51.6)	286 (54.8)
Hispanic or Latino — no. (%)	249 (23.4)	132 (24.4)	117 (22.4)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	193/920 (21.0)	91/467 (19.5)	102/453 (22.5)
One	248/920 (27.0)	131/467 (28.1)	117/453 (25.8)
Two or more	479/920 (52.1)	245/467 (52.5)	234/453 (51.7)
Coexisting conditions — no./total no. (%)			
Hypertension	460/928 (49.6)	231/469 (49.3)	229/459 (49.9)
Obesity	342/925 (37.0)	177/469 (37.7)	165/456 (36.2)
Type 2 diabetes	275/927 (29.7)	144/470 (30.6)	131/457 (28.7)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)
Baseline score missing	46 (4.3)	29 (5.4)	17 (3.3)

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MedDRA System Organ Class	Preferred Term	Remdesivir (N = 541) No.(%)	Placebo (N = 522) No.(%)
Any System Organ Class	Any Preferred Term	114 (21.1)	141 (27.0)
Cardiac disorders	Cardiac arrest	6 (1.1)	5 (1.0)
	Atrial fibrillation	4 (0.7)	2 (0.4)
Infections and infestations	Septic shock	6 (1.1)	7 (1.3)
	Pneumonia viral	3 (0.6)	7 (1.3)
Investigations	Glomerular filtration rate decreased[a]	3 (0.6)	2 (0.4)
Renal and urinary disorders	Acute kidney injury[a]	4 (0.7)	7 (1.3)
Respiratory, thoracic and mediastinal disorders	Respiratory failure	28 (5.2)	42 (8.0)
	Acute respiratory failure	9 (1.7)	12 (2.3)
	Respiratory distress[b]	9 (1.7)	10 (1.9)
	Hypoxia[b]	4 (0.7)	5 (1.0)
	Pneumothorax	3 (0.6)	3 (0.6)
	Pulmonary embolism	3 (0.6)	3 (0.6)
Surgical and medical procedures	Mechanical ventilation	1 (0.2)	5 (1.0)
	Endotracheal intubation	2 (0.4)	3 (0.6)
Uncoded	Uncoded	19 (3.5)	22 (4.2)
Vascular disorders	Hypotension	2 (0.4)	12 (2.3)
	Shock	4 (0.7)	3 (0.6)

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Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

	Overall*		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=538)	Placebo (N=521)	Remdesivir (N=67)	Placebo (N=60)	Remdesivir (N=222)	Placebo (N=199)	Remdesivir (N=98)	Placebo (N=99)	Remdesivir (N=125)	Placebo (N=147)
Recovery										
No. of recoveries	334	273	61	47	177	128	47	43	45	51
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)	5 (4–6)	6 (4–8)	7 (6–8)	9 (7–11)	16 (NE– 10)	22 (NE– 12)	NE–NE	28 (NE– 22)
Rate ratio (95% CI)†	1.32 (1.12–1.55 [P<0.001])		1.38 (0.94–2.03)		1.47 (1.17–1.84)		1.20 (0.79–1.81)		0.95 (0.64–1.42)	
Mortality										
Hazard ratio (95% CI)	0.70 (0.47–1.04)		0.46 (0.04–5.08)		0.22 (0.08–0.58)		1.12 (0.53–2.38)		1.06 (0.59–1.92)	
No. of deaths by day 14	32	54	1	1	4	19	13	13	13	19
Kaplan–Meier estimate — % (95% CI)	7.1 (5.0–9.9)	11.9 (9.2–15.4)	1.5 (0.2–10.1)	2.5 (0.4–16.5)	2.4 (0.9–6.4)	10.9 (7.1–16.7)	15.2 (9.0–25.0)	14.7 (8.7–24.3)	11.3 (6.7–18.8)	14.1 (9.2–21.2)
Ordinal score at day 15 (±2 days) — no. (%)‡										
Patients with baseline and day 15 score data — no.	434	410	60	51	196	161	71	77	101	115
1	99 (22.8)	76 (18.5)	22 (36.7)	15 (29.4)	54 (27.6)	45 (28.0)	13 (18.3)	7 (9.1)	10 (9.9)	8 (7.0)
2	158 (36.4)	127 (31.0)	25 (41.7)	21 (41.2)	95 (48.5)	66 (41.0)	28 (39.4)	27 (35.1)	6 (5.9)	10 (8.7)
3	11 (2.5)	6 (1.5)	7 (11.7)	4 (7.8)	4 (2.0)	2 (1.2)	0	0	0	0
4	23 (5.3)	20 (4.9)	1 (1.7)	3 (5.9)	12 (6.1)	7 (4.3)	4 (5.6)	4 (5.2)	6 (5.9)	6 (5.2)
5	34 (7.8)	40 (9.8)	3 (5.0)	5 (9.8)	14 (7.1)	6 (3.7)	2 (2.8)	7 (9.1)	15 (14.9)	22 (19.1)
6	16 (3.7)	14 (3.4)	1 (1.7)	0 (0)	1 (0.5)	3 (1.9)	6 (8.5)	6 (7.8)	7 (6.9)	5 (4.3)
7	60 (13.8)	72 (17.6)	0 (0)	2 (3.9)	12 (6.1)	12 (7.5)	5 (7.0)	13 (16.9)	43 (42.6)	45 (39.1)
8	33 (7.6)	55 (13.4)	1 (1.7)	1 (2.0)	4 (2.0)	20 (12.4)	13 (18.3)	13 (16.9)	14 (13.9)	19 (16.5)
Odds ratio (95% CI)	1.50 (1.18–1.91 [P=0.001])		1.51 (0.76–3.00)		1.31 (0.89–1.92)		1.60 (0.89–2.86)		1.04 (0.64–1.68)	

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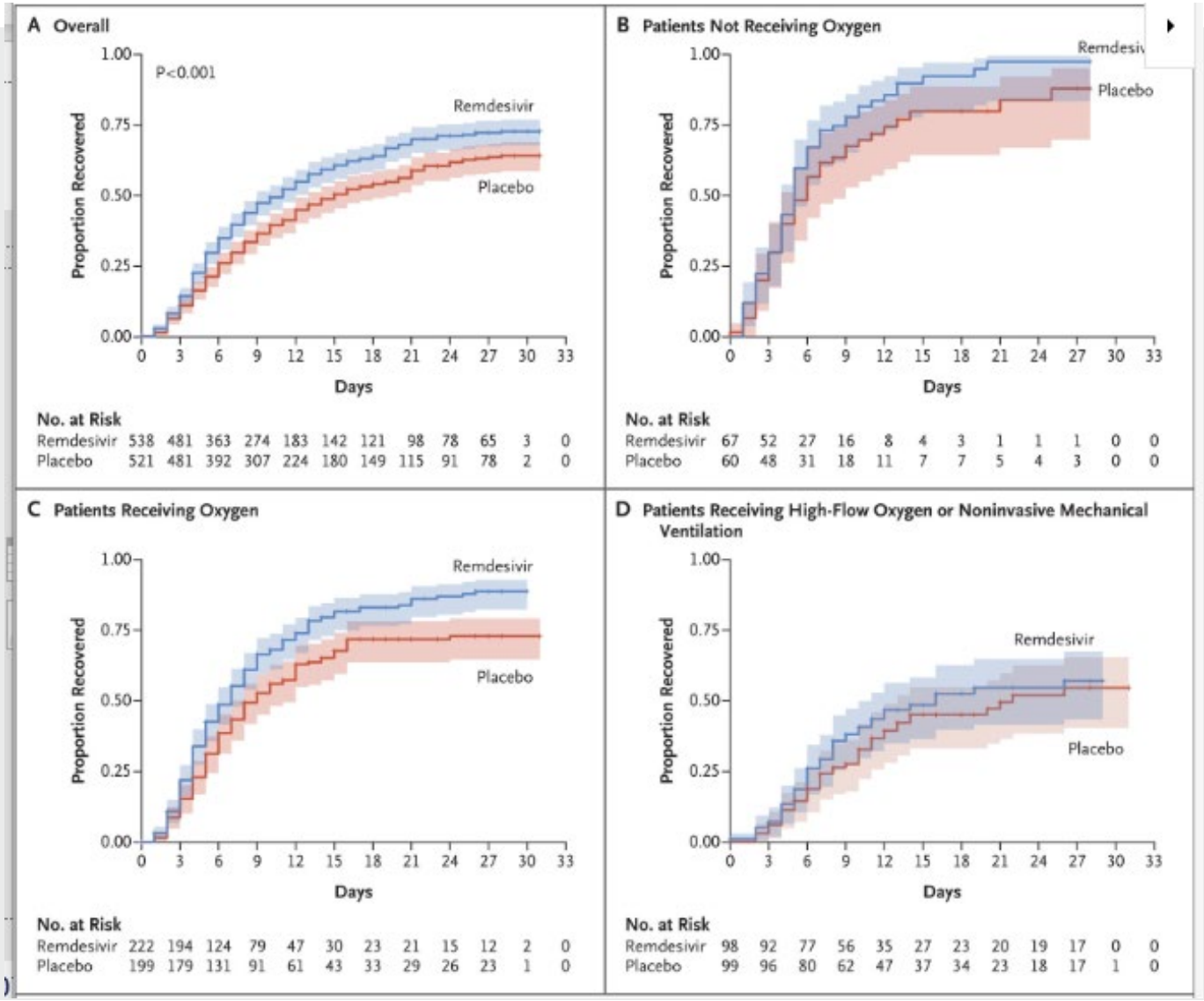

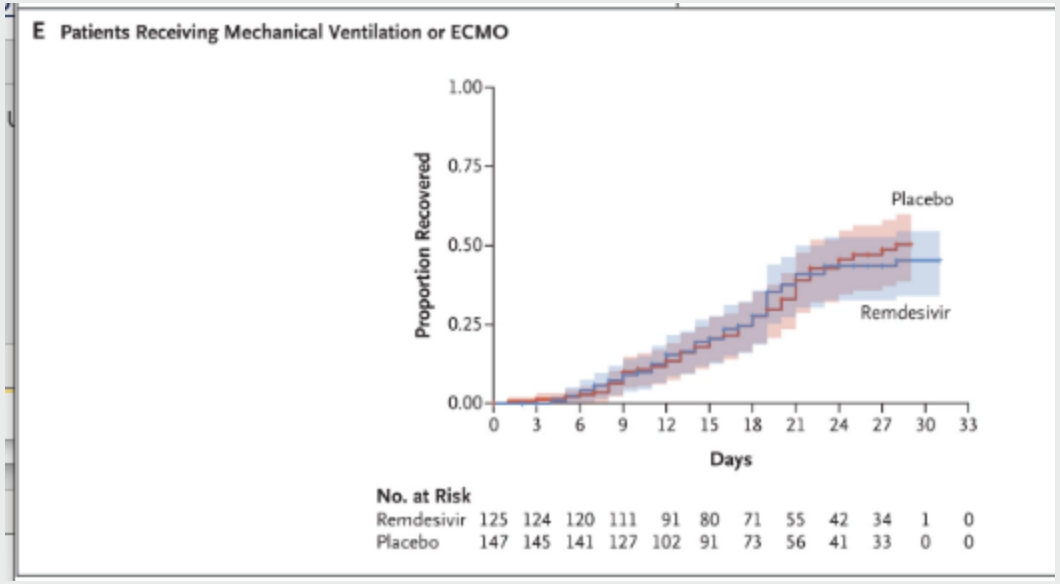

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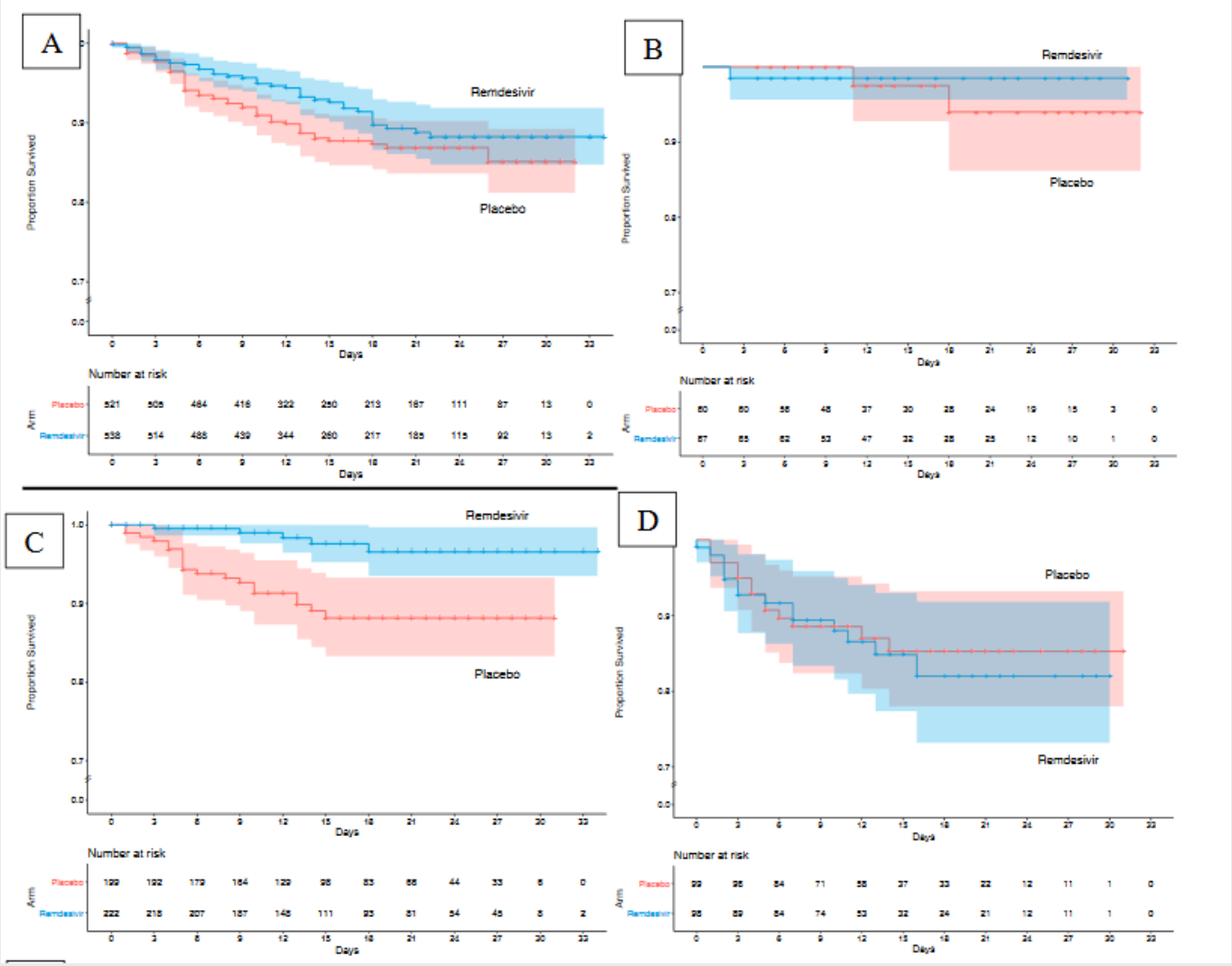

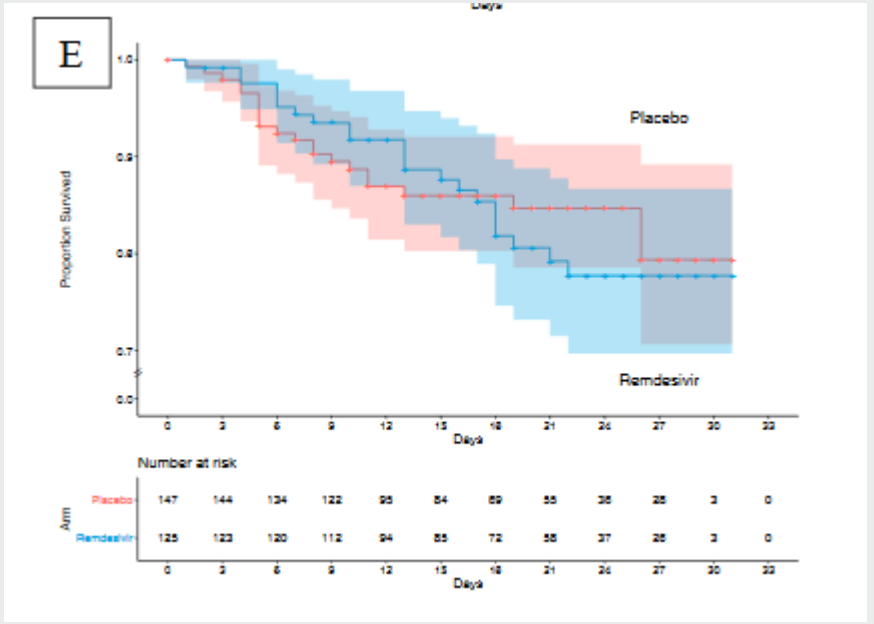

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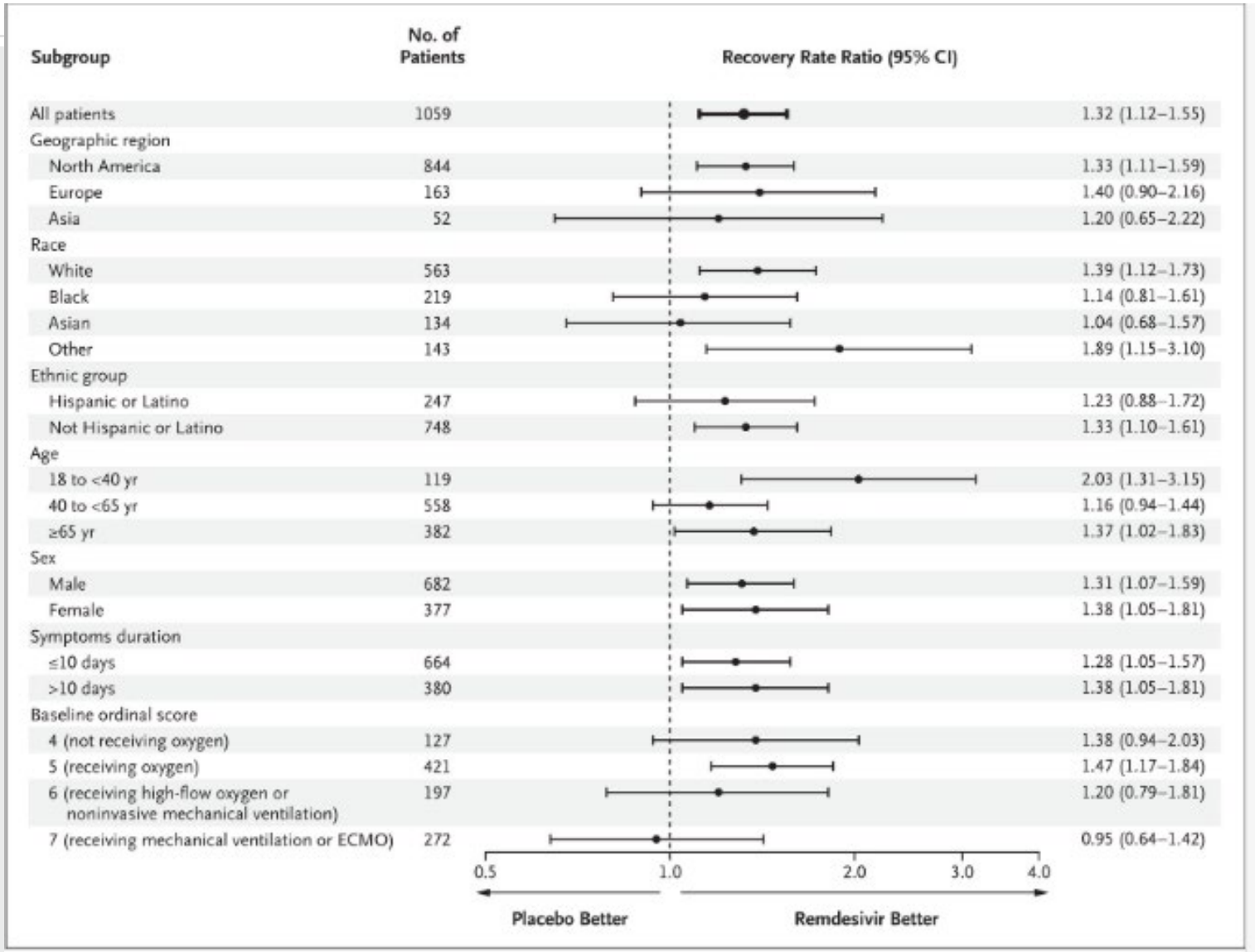
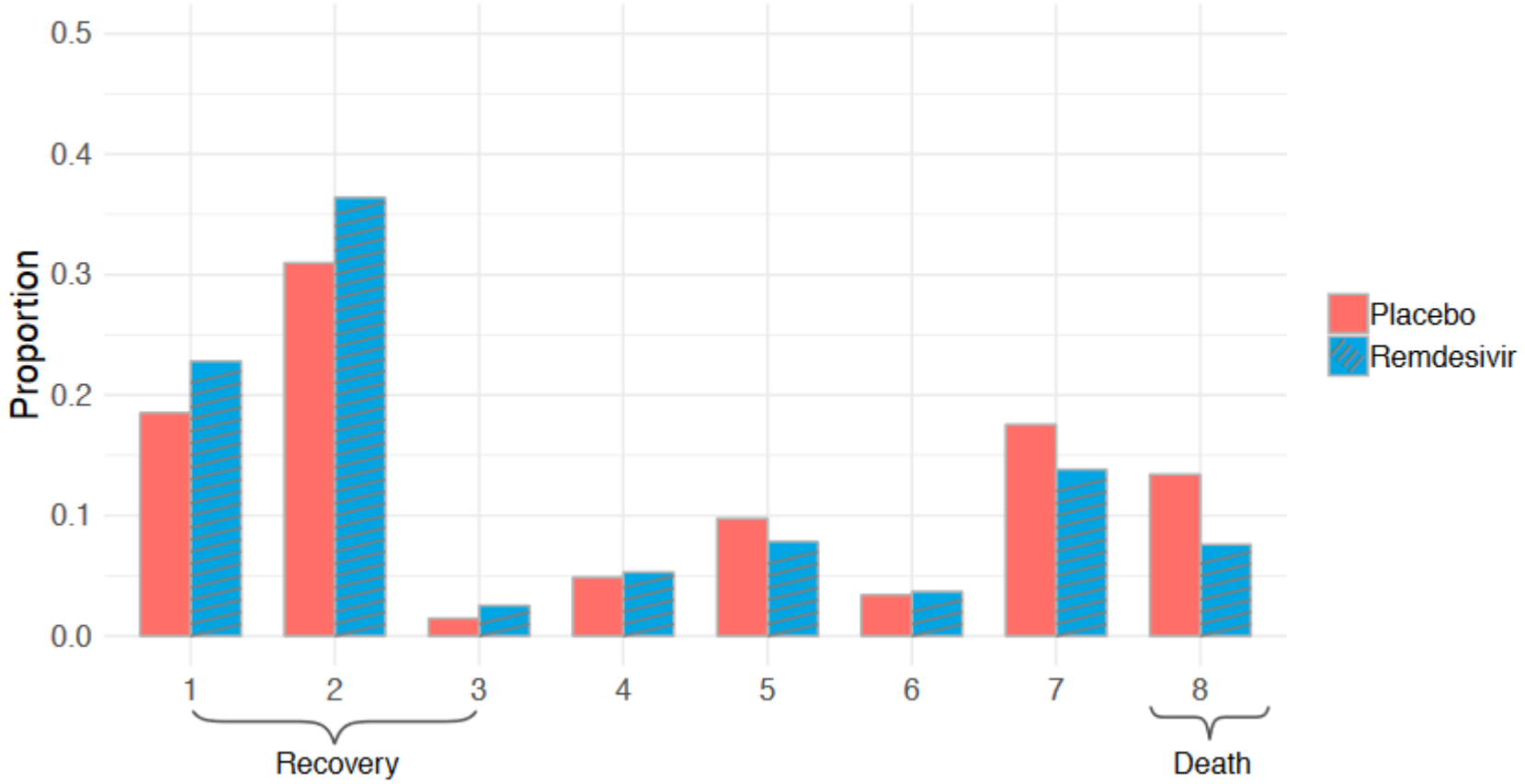


Subgroup	No. of Patients	Recovery Rate Ratio (95% CI)
All patients	1059	1.32 (1.12–1.55)
Geographic region		
North America	844	1.33 (1.11–1.59)
Europe	163	1.40 (0.90–2.16)
Asia	52	1.20 (0.65–2.22)
Race		
White	563	1.39 (1.12–1.73)
Black	219	1.14 (0.81–1.61)
Asian	134	1.04 (0.68–1.57)
Other	143	1.89 (1.15–3.10)
Ethnic group		
Hispanic or Latino	247	1.23 (0.88–1.72)
Not Hispanic or Latino	748	1.33 (1.10–1.61)
Age		
18 to <40 yr	119	2.03 (1.31–3.15)
40 to <65 yr	558	1.16 (0.94–1.44)
≥65 yr	382	1.37 (1.02–1.83)
Sex		
Male	682	1.31 (1.07–1.59)
Female	377	1.38 (1.05–1.81)
Symptoms duration		
≤10 days	664	1.28 (1.05–1.57)
>10 days	380	1.38 (1.05–1.81)
Baseline ordinal score		
4 (not receiving oxygen)	127	1.38 (0.94–2.03)
5 (receiving oxygen)	421	1.47 (1.17–1.84)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation)	197	1.20 (0.79–1.81)
7 (receiving mechanical ventilation or ECMO)	272	0.95 (0.64–1.42)

https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

Figure S5. Histogram of ordinal scores at Day 15 by treatment arm



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Next Steps for the ACTT Trial

- ACTT-1 Final results will inform FDA decision for approval of Remdesivir
- ACTT-2 – Data Lock Just occurred
- ACTT-3 – Currently Enrolling
- ACTT4 – Currently being planned

- Questions?
- The protocol is available on the NEJM site
- If interested in updates on study results, follow Emmes and NIAID on social media