

## **Accepted Commentary – In Press**

**Title:** Endpoints used in phase III randomized controlled trials of treatment options for COVID-19

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Studies to identify potential drugs effective in treating the coronavirus disease 2019 (COVID-19) are currently ongoing at a rapid pace, although no drug has yet shown improved mortality outcomes in a randomized clinical trial (RCT). Whether the ongoing RCTs are using endpoints that matter remains unknown. Here we provide a summary of the endpoints used in the actively recruiting phase III RCTs for the treatment of COVID-19.

We extracted clinical trial information, including the primary endpoint, on treatment trials for SARS-CoV-2 from [www.clinicaltrials.gov](http://www.clinicaltrials.gov) using the search keyword “COVID-19” or “SARS-CoV-2”. We excluded clinical trials which were not listed as Phase III/Clinical, not randomized and not actively recruiting as of April 23<sup>rd</sup>, 2020. We focused primarily on the use of endpoints only for the phase 3 RCTs. Phase I and II trials and their endpoints inform phase III trial design, while phase III trials change practice. Hence it is important to assess the nature of endpoints being used in these trials. Furthermore, mortality outcomes are best assessed in phase III RCTs. We also excluded trials studying prophylaxis or treatment in the outpatient setting.

Forty-nine phase III RCTs met our inclusion criteria. The commonest endpoint used was ordinal scales in 42.9% (21/49) which could be a 6-point, 7-point or 8-point scale. For example, a commonly used 7-point ordinal scale was: 1. Death 2. Hospitalized, on invasive mechanical ventilation or Extracorporeal Membrane Oxygenation 3. Hospitalized, on non-invasive ventilation or high flow oxygen 4. Hospitalized, requiring low flow supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) 6. Hospitalized, not requiring supplemental oxygen - no longer required ongoing medical care 7. Not hospitalized.

Other endpoints include viral clearance (6.1% , 3/49) and clinical remission or stability (4.0% , 2/49). Only 2.0% (3/49) of trials had overall or all-cause mortality as primary endpoint (Figure). Only 57.1 % (28/49) of trials were placebo controlled.

The most commonly assessed drugs in the intervention arms were Hydroxychloroquine (38.7%, 19/49), Azithromycin (14.3%, 7/49), Remdesivir (10.2%, 5/49), steroids (8.2%, 4/49), Sarilumab and Lopinavir-Ritonavir (6.1%, 3/49 each), and Tocilizumab (4.0%, 2/49).

Overall mortality is the most direct measure of clinical benefit in a lethal pandemic. Overall mortality also takes fatal adverse events into account and thus is a composite measure of net benefit. It is also resistant to subjective bias which is particularly important for trials where the investigators are not blinded. Also from policy standpoint, reducing mortality from COVID-19 remains the biggest priority. Apart from mortality, endpoints such as ICU admissions, intubation or even a composite endpoint of death, ICU and mechanical ventilation represent clinically relevant benefit. These represent only a couple of points in the 7 or 8 point scales.

Given the high lethality of COVID-19, mortality endpoints should be achieved relatively quickly. The recent clinical trial data on remdesivir from China suggests that we may lose the window of opportunity to enroll enough patients in RCTs to evaluate mortality endpoint which would preclude evidence-based treatment for future patients.<sup>1</sup> This trial ultimately enrolled 237 patients and did not find a difference in time to clinical improvement defined as a two-point improvement in a 6 point ordinal scale (HR: 1.23 [95% CI 0.87–1.75]) with remdesivir versus

placebo.<sup>2</sup> However, on the same day, a press release issued by National Institute of Allergy and Infectious Disease discussed the preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT) which demonstrated a 4 day improvement in median time to recovery (11 days versus 15 days,  $p < 0.001$ ) versus placebo without a significant difference in mortality rates (8% vs. 11.6%,  $p = 0.059$ ).<sup>3</sup> Notably, the primary endpoint of this trial was changed after the trial started from an 8 point ordinal scale as previously described to a surrogate of median time to recovery where recovery is defined broadly as hospitalized but not requiring oxygen, not hospitalized but requiring oxygen or not hospitalized and not requiring oxygen. This doesn't include death or mechanical ventilation as in the original 8 point scale. However, US FDA has granted the emergency use authorization for remdesivir based on these data<sup>4</sup>. Researchers continue to disagree about the need for mortality reduction as an endpoint for trials at the time of a pandemic.<sup>5</sup>

Recently, concerns have been raised about relaxing approval standards at the time of pandemic.<sup>6</sup> Our analysis shows that most trials testing new treatment options for SARS-CoV-2 include a surrogate measure which may or may not predict clinical benefit. The recent debate with remdesivir suggests the need for confidence in the efficacy of drug in saving lives at the time of a pandemic. Our findings suggest that, for most drugs, even after the trial is complete there would continue to be uncertainty in the beneficial effects of the drug due to the use of an endpoint that does not reflect clinical benefit. Indeed, being misled by a therapeutic that actually does not improve clinical outcomes can cost significant lives and money during a pandemic. When lives are at stake, the trials should literally measure if lives can be saved; any other endpoint would be like a straw in the river- a society drowning in a pandemic may clutch at it with optimism, but would nevertheless not be rescued.

Table 1: Endpoints used in treatment of COVID19 with actively enrolling clinical trials

<b>Study Endpoints</b>	<b>No. of studies (%)</b>
Ordinal Scale endpoints	21 (43%)
Survival without needs of ventilator utilization	4 (8%)
Overall/All-Cause Mortality	3 (6%)
Viral Clearance	3 (6%)
Clinical stability/remission endpoints	2 (4%)
Lung injury score	2 (4%)
No. of deaths/need for intubation	2 (4%)
Clear Chest CT/Negative PCR	2 (4%)
Change in PaO <sub>2</sub> /FiO <sub>2</sub>	1 (2%)
Rate of comprehensive adverse outcome	1 (2%)
% ICU transfers	1 (2%)
% Return to Room Air	1 (2%)
Hours to recovery	1 (2%)
Number of deceased participants or with persistent organ dysfunction	1 (2%)
Most severe outcome	1 (2%)
Time to normalize oxygen req	1 (2%)
Improvement in ARDS scale severity grade	1 (2%)
Time to first occurrence of either death from any cause or new/worsened organ dysfunction	1 (2%)

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