

## **Subgroup Mortality Results for Remdesivir in COVID-19: Real or the Play of Chance?**

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(based on joint work with Gail Potter, 2022)

The Adaptive COVID-19 Treatment Trial (ACTT-1) was the first randomized controlled trial showing a beneficial effect of a treatment for COVID-19. Hospitalized patients with COVID-19 randomized to remdesivir plus standard care had a shorter time to recovery and an improved WHO ordinal score at 28 days compared to patients randomized to placebo plus standard care. The secondary endpoint of 28-day mortality showed a non-significant trend for benefit. Subgroup analysis by baseline WHO ordinal score showed no hint of mortality benefit for patients in OS-4 (no oxygen), OS-6 (high-flow oxygen), or OS-7 (invasive mechanical ventilation/ECMO), but an apparently striking effect in OS-5 (supplemental oxygen). We attempt to answer two questions concerning the observed effect in OS-5: (1) Is it real? (2) If it is real, does it reflect an overall effect on mortality or is it a subgroup-specific effect? We illustrate the potential to be misled by multiple comparisons by analogy with a famous controversy outside the field of biostatistics concerning the “Bible code”. Believers, including the great Sir Isaac Newton, posit that a secret code exists in the first five books of the Old Testament that can be revealed only by skipping letters. For example, one might try reading every 50<sup>th</sup> letter, every 75<sup>th</sup> letter, and so on until important words and names appear. This Bible code seems to portend historical events such as the rise of Adolph Hitler and the terrorist attack on 9/11/2001, but skeptics argue that seemingly prescient messages are completely consistent with chance.