Business

Government researchers changed metric to measure coronavirus drug remdesivir during clinical trial

Death rate was eliminated as a primary outcome measure, replaced with the time it took patients to recover.

Lab technicians load vials of the drug remdesivir at a Gilead Sciences facility in La Verne, Calif., in March. (Gilead Sciences/Reuters)

By **Christopher Rowland**

May 1, 2020 at 8:29 p.m. UTC

Government clinical trial investigators changed the primary metric for measuring the success of Gilead's experimental drug remdesivir as a coronavirus treatment two weeks before Anthony S. Fauci's announcement that the drug would be the new "standard of care."

Instead of counting how many people taking the drug were kept alive on ventilators or died, among other measures, the National Institute of Allergy and Infectious Diseases said it would judge the drug primarily on a different outcome: how long it took surviving patients to recover.

Death and other negative outcomes were moved to secondary measure status: They would still be tracked, but they would no longer be the key

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measure of remdesivir's performance. The switch — which specialists said is unusual in major clinical trials but not unheard of — was publicly disclosed on the government's clinicaltrials.gov website on April 16 but did not receive much attention at the time.

The change reflects evolving scientific understanding of the fast-moving nature of the virus and uncertainties around how the lethal effects reveal themselves in patients, said NIAID, Gilead, and outside specialists. But the change also adds weight to the assessment of government and medical researchers that remdesivir is not a knockout drug that will change the trajectory of the coronavirus pandemic.

On Friday, as expected, the Food and Drug Administration approved an emergency use authorization for the drug that

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will allow it to be prescribed for hospitalized patients infected with the coronavirus.

The newly adopted criteria were a central feature of this week's declaration by Fauci, NIAID's director, that remdesivir reduced the time to recovery for surviving patients from 15 days to 11 days, a 31 percent improvement.

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"The data shows that remdesivir has a clear-cut, significant, positive effect in diminishing the time to recovery," Fauci said as he sat in an Oval Office meeting with President Trump and other members of the president's coronavirus task force. "It's highly significant."

The difference in death rate, one of the original primary measures,

was not statistically significant, Fauci said, showing only a marginal reduction from 11 percent in patients given a placebo to 8 percent in patients given remdesivir. Full release of the trial results would be made soon, Fauci said.

Some medical research specialists questioned the change in the primary outcome measure of the trial, which had 1,063 patients.

“I think that they thought they weren’t going to win, and they wanted to change it to something they could win on," said Steven Nissen, a Cleveland Clinic cardiologist and expert clinical investigator who has led numerous drug trials. “I prefer the original outcome. It’s harder. It’s a more meaningful endpoint.

“Getting out of the hospital early is useful," he said, “but it’s not a game-changer."

Nissen expressed dismay that the placebo phase of the trial was declared over so quickly, when a few more weeks might have provided a pool of patients large enough to show a statistically beneficial difference in death.

But Fauci said Wednesday that ethical considerations drove the announcement: As soon as a clear evidence of shorter hospitalizations was available, trial investigators owed it to patients on placebo to stop that phase of the trial so they could access the drug.

When the trial began on Feb. 21, it was designed to focus on collecting eight patient outcomes, to be measured on the 15th day after treatment. The list of outcomes was similar to guidance the World Health Organization issued in February for coronavirus clinical trials.

The original NIAID trial list started with death, followed by five categories of hospitalized patients: on ventilator or ECMO machine (which oxygenates blood outside the body); on high-flow oxygen therapy; on basic supplemental oxygen; not requiring oxygen but requiring ongoing care; not requiring care. The final two categories covered patients released from the hospital.

NIAID said in response to questions Thursday that it made the switch eight weeks later to the more limited measure of “time to recovery" based on modeling that took into account new information about the course of the disease. The initial measurement period of two weeks, it said, was deemed to be too short as scientists learned more about the lengthy time patients could be seriously ill with covid-19, NIAID said.

“Little was known regarding the natural course of covid-19 when the trial was initially designed, and the initial endpoint chosen specified a single timepoint for evaluation, namely day 14,” the institute said. “However, with the growing knowledge during the epidemic, we learned that covid-19 had a more protracted course

than previously known.

“NIAID statisticians performed modeling of what happens if the right day is not picked for assessment, which revealed that meaningful treatment effects could be missed with that primary endpoint," NIAID said. “Time to recovery avoids this issue, and the change in primary endpoint seemed appropriate given the evolving clinical data."

Government researchers who decided to make the switch in outcome measure did not have access to clinical data, NIAID added.

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Gilead did not respond to a question about whether it had input on the decision to change the endpoint.

“NIAID changed the primary endpoint while the study was blinded," Gilead spokesman Ryan McKeel said in an email, a decision he said was “based on continuing discussions and evolving understanding of the disease." He added that it is important to note that death, ventilation and other measures are included in the list of the trial’s secondary outcome measures “and will be reported when the data are published."

An exact timetable for publication of the results has not been disclosed. In the absence of any other treatment for coronavirus, Fauci declared that remdesivir would become the standard of care for certain hospitalized patients. Clinicians are eagerly awaiting more data from the trial so they will know which patients stand to benefit the most.

Fauci’s announcement coincided

with more negative results for remdesivir published in the medical journal The Lancet; that trial, a Chinese study that was stopped early because it did not recruit enough patients, showed no benefit of remdesivir over placebo, and also no benefit in survival.

Some experts in clinical trials raised questions about the change in outcome measures.

“It raises a lot of flags, and it requires a lot of answers,” Walid F. Gellad, a professor of health policy and management at the University of Pittsburgh’s Department of Medicine, said in an interview, “especially when people start saying it’s become the standard of care, and all we saw was a news release in a trial with an outcome that was changed two weeks ago. It really is striking."

An expert in transparency in

clinical trials at the University of Oxford, Henry Drysdale, said the Oval Office setting of Fauci's announcement, combined with the limited data disclosed, raised important questions about the outcomes change that will need to be answered when the full results are published in a peer-reviewed journal. Drysdale is part of a team of researchers who, in a landmark study published last year, found discrepancies in trial designs and reported outcomes in major academic journals.

"It's extremely worrying that those very important outcomes were dropped from the primary outcome," Drysdale said in an interview. Asked to assess NIAID's statement issued to reporters on Thursday, Drysdale said, "Whenever I see an explanation like this, when an outcome-switching has happened, that's fine, but you were not open about this when you reported your quote-unquote exciting results."

But a strong degree of transparency about the change, combined with NIAID's assurances that trial leaders did not know trial results when they switched the outcome, should settle any lingering questions, experts agreed.

Milton Packer, a cardiologist and clinical trial investigator at Baylor University Medical Center, said that, based on Fauci's disclosures, roughly 95 people died in both arms of the trial. That combined number may have led investigators to believe they would not have a large enough sample of deaths to be statistically significant, he said.

"If you knew that the number of observations was inadequate to answer the question, and you did not know the breakdown, then shifting the endpoint is not a problem," Packer said.

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Christopher Rowland

Chris Rowland joined The Washington Post business team in 2018 after serving as the Washington bureau chief for the Boston Globe, leading coverage of two presidential elections and overseeing political enterprise reporting. He previously covered health care for the Globe in Boston.

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BobNH 6 hours ago

There is a large and potentially important part of the map that hasn't been explored.

If remdesivir can accelerate the recovery of patients sick enough to require hospitalization, it is worth exploring the effect of administering it as soon as the patient is diagnosed. That would probably take a larger sample to prove the effectiveness but it might save more people.

If you started with 10,000 people who were diagnosed and underwent the current "standard" treatment that didn't include hospitalization, and another 10,000 who were administered remdesivir plus the current "standard" treatment, then the number of each group who required hospitalization and the number of each group who died might provide a statistically significant outcome.

The problem with that approach is that use of remdesivir is authorized only for hospitalized patients. It would also require a lot more remdesivir.

It would be interesting to know of Boris Johnson got remdesivir. He made a pretty quick recovery from ICU to release from hospital and return to work.

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freestate410 6 hours ago

I don't get all these scientists (some relatively young) comparing this drug to AZT in the mid 1980's. It was in pill form and did not require IV administration in a hospital. While it kept some people alive a little longer, many people could not handle the side effects. I would be more excited If they compared this drug to Crixivan (Indinovir) in 1996 which dramatically decreased HIV viral load in infected patients.

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nuanced 6 hours ago

This is going to be another stock pump and dump scam from the Trump crime family. There is a cover-up of results showing more deaths in the higher dose group.

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SineDie 7 hours ago

This drug is a not a game changer or a "knockout punch." I'm baffled by Fauci hyping a drug that has so little purpose and function. Gilead's drug will not help you avoid getting infected or getting very sick. It does not relieve specific symptoms. As I understand it, it is administered if a patient is on a ventilator and survives. If so, even if the drug does what Fauci says it does, four days less in the hospital is not high on the immediate needs in fighting C19.

Moving the goal posts is a red flag requiring a lot of backing and filling by the sources and reporters alike. Reinforces the impression that nothing coming from the federal level is consequential and not just PR.

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Genghis Trump 7 hours ago

+1 for maximal use of sports metaphors.

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Steve Haigh 6 hours ago

sure, i doubt there is a specific medical definition of "game changer", but statements like that given the limited application of this stuff make you question Fauci a bit

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BDQ71 7 hours ago

> *Instead of counting how many people taking the drug were kept alive on ventilators or died, among other measures, the National Institute of Allergy and Infectious Diseases said it would judge the drug primarily on a different outcome: how long it took surviving patients to recover.*

How much political pressure was placed on Dr. Fauci and National Institute of Allergy and Infectious Diseases to change the rules? and to give the carnival barker something about which he could brag, boast, and bluster?

Whoever thought that the "First, do no harm" doctors would be so frightened and cowed by the impeached president?

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Genghis Trump 7 hours ago

"How much political pressure was placed on Dr. Fauci"

About four lbs per square inch. Next question.

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BlackHawk7 7 hours ago *(Edited)*

If you know the scientific method applied to clinical trials, this is a violation of the study. The critical variable(s) must be established prior to data analysis. If they changed their outcome variables then the study is invalid. Those 'p's' mean little.

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Genghis Trump 7 hours ago

Relax. They didn't actually "change" them, they are just emphasizing the secondary metric, and the first has, unfortunately, not produced the results hoped for.

Saying that the "study is invalid" because of this proves beyond any doubt that you haven't the slightest clue about "science".

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nuanced 6 hours ago

So it doesn't matter if more people die on the drug because that metric was eliminated? You call that science? Get a clue.

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EVE2 7 hours ago *(Edited)*

Who changed the outcome measures midway? Was it statisticians and investigators with Gilead, who stands to make a lot of money off this? What is Fauci's financial relationship with Gilead?

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BlackHawk7 7 hours ago

You are absolutely correct.

Wonder if the study was double blinded?

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EVE2 7 hours ago

Yep. Somethin' stinks.

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Genghis Trump 7 hours ago *(Edited)*

It's not midway, fool; the data gathering part of this study is over, at least this phase of it.

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Jovalle 7 hours ago

Details matter.

It would be unfortunate if Fauci was getting ahead of the details- even if he was just being “hopeful.”

From this article, it sounds like we’re a ways from knowing if Remdesivir has any effect other than possibly getting patients out of hospitals a few days early. That’s helpful, for sure, but it not the cure we need.

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EVE2 7 hours ago *(Edited)*

Dude! Changing outcome measures in the middle of a trial is like moving the goalposts. Or like recovering a fumble and intentionally running the wrong way but calling it a touchdown nevertheless 'cause well, "that was actually my endzone!" that's sandlot ball. In research, stuff like this is usually done to stop a trial halfway when the statisticians recognize that the experimental treatment is much worse (killing people) than what you've been doing. Not to change its goals.

So yeah, I'm not impressed. In this case, the Chinese who stopped their trial may be more trustworthy. Let's just say it, "Fauci, you're messing up on this one." Still, given our limited options, I do think it's appropriate to try it in high risk patients. But calling it "the standard of care" - nope not buying it. Sounds like Trump. Looking in the wrong place guys.

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