ICAN
Informed Consent Action Network

May 6, 2020

Dr. Anthony S. Fauci, M.D.
Director, National Institute of Allergy and Infectious Disease
5601 Fishers Lane
Rockville, MD 20852

Dear Dr. Fauci,

The Informed Consent Action Network (ICAN) is dedicated to ensuring its members and the public are informed about consumer safety issues.

On April 29, 2020, you stated that "The data shows that remdesivir has a clear-cut, significant, positive effect in diminishing the time to recovery" for COVID-19 patients and that remdesivir "will be the standard of care" for this infection.[1] You made these definite assertions based on a single study conducted by your agency, the National Institute of Allergy and Infectious Disease (NIAID).

This study appears to have many serious irregularities as detailed below. Prior to sending these concerns to the appropriate federal ethics and oversight committees, we wanted to provide you an opportunity to respond.

The study at issue, a multi-center randomized clinical trial, commenced on February 21, 2020.[2] Like all such studies, before it commenced a detailed study protocol was established. It is critical that the protocol be set in stone before a study begins. This assures the validity of the study. As explained by the World Health Organization, "once a protocol for the study has been developed and approved, and the study has started and progressed, it should be adhered to strictly and should not be changed. This is particularly important in multi-centre studies. Violations of the protocol can discredit the whole study."[3]

1 https://www.livescience.com/remdesivir-will-be-new-standard-of-care.html
2 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=2&C=Side-by-Side#StudyPageTop
3 https://icahn.mssm.edu/files/ISMMS/Assets/Research/IHCDS/Guidelines%20for%20Writing%20the%20research%20_protocol%20by%20WHO.pdf

Despite the importance of adhering the study protocol, there were numerous substantive deviations in the NIAID's study of remdesivir.

i. Study Protocol

The first major change to the study protocol was modifying the "primary outcome" after the study was well underway. As you know, the primary outcome is the defined objective the study is seeking to evaluate. Like the remainder of the study protocol, it is well established that the "primary outcome needs to be defined at the time the study is designed."[4] Nonetheless, the primary outcome of the remdesivir study changed long after the study commenced and patient outcomes observed.

Indeed, when the study commenced on February 21, 2020, the primary outcome was defined as rating each subject on a 7 factor scale, including death and intubation, within 15 day days of treatment, and comparing the outcomes between the remdesivir group and placebo group.[5] But on April 16, 2020, 59 days into the study, the primary outcome was entirely changed, including removing death and intubation as criteria -- the study now only reviewed three criteria within 29 days of treatment.[6]

The serious concern with changing a study's primary outcome is explained by Dr. Ben Goldacre, senior clinical research fellow at the Centre for Evidence-Based Medicine, University of Oxford in an article entitled *Clinical trials and playing by the rules*:

> Let's imagine we're playing snakes and ladders. I roll the die three times in a row then pick the best score as my actual roll, as if the other two were just practice. I invite you, winningly, to ignore those other rolls. You would rightly kick the board

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[4] https://www.ncbi.nlm.nih.gov/pubmed/26528658

[5] The initial study protocol provided: "Percentage of subjects reporting each severity rating on the 7-point ordinal scale. The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities. [Time Frame: Day 15]." https:// clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=15&C=Side-by-Side#StudyPageTop

[6] The study protocol was modified on April 16, 2020 to provide: "Time to recovery. Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities. [Time Frame: Day 1 through Day 29]." https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=15&C=Side-by-Side#StudyPageTop

> over, declaring I was a cheat. I waited until after I knew the results and then I chose the score that suited me best.
>
> Similarly, in a trial, you might measure many things but you have to say which is the "primary outcome" before you start: you can't change your mind about what you're counting as your main outcome after you've finished and the results are in. It's not just dodgy, it also messes with the statistics.
>
> You cannot find your starting hypothesis in your final results, unless you are a time lord.[7]

The highly specific changes to the primary outcome, including the outcome criteria and timeframe for determining same, in the NIAID's remdesivir study appears designed to "fit the data" that was gathered during the first 59 days of the study.

That this is likely what occurred, is supported by another material change to the study protocol -- the number of subjects in the study.

ii. Study Size

On February 21, 2020, the study protocol provided for a total of 397 subjects, with 197 receiving remdesivir and 197 receiving placebo.[8] A few days later, on February 25, 2020, the NIAID issued a press release regarding this study explaining that "An independent data and safety monitoring board (DSMB) will monitor ongoing results to ensure patient well-being and safety as well as study integrity. The DSMB will recommend the study be halted if there is clear and substantial evidence of a treatment difference between drug and placebo."[9]

This means that if the 197 subjects receiving remdesivir were showing a better outcome than the 197 receiving placebo the study would be halted so that those receiving a placebo could also receive remdesivir. But that is not what happened.

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7 https://www.theguardian.com/commentisfree/2008/jan/05/1

8 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=2&C=Side-by-Side#StudyPageTop

9 https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

Instead, on March 20, 2020, 28 days into the study, NIAID changed the study protocol to have 440 subjects -- 220 receiving remdesivir and 220 receiving placebo.[10] Even with the enlarged sample size the study continued since there still was no clear evidence of a difference between receiving remdesivir and placebo.

On April 16, 2020, 55 days into the study, NIAID again increased the number of subjects to 572 individuals -- 286 receiving remdesivir and 286 receiving placebo.[11] That NIAID only decided on this increase well into the study is evident from the fact that the NIAID did not prepare enough placebos for 286 individuals.

The "placebo" according to the initial protocol contained all of the inactive ingredients in remdesivir.[12] But since apparently nobody anticipated 286 subjects to be in the placebo group, NIAID did not have enough of these placebos. Hence, simultaneous with increasing the placebo group to 286 subjects, the study protocol was also updated to provide that "a matching placebo of normal saline of equal volume may be given if there are limitations on placebo supplies."[13]

But it appears that even with 572 individuals, and even with the change in study protocol, the NIAID still was not able to identify a statistically significant difference in outcome between remdesivir and placebo.[14] If there was such a difference, as the NIAID said at the start of the study, the use of a placebo group would have been halted. But that is not what occurred.

Instead, on April 23, 2020, 62 days into the study, the total number of subjects was again increased to 800 individuals.[15] And apparently even more material changes to the study design were needed to obtain a statistically significant result.

iii. Inclusion & Exclusion Criteria

The study protocol included specific criteria which determine whether someone is included or excluded from the study. The NIAID however changed the eligibility and exclusion criteria for the study twice -- once on March 20, 2020 and again on April 16,

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10 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=10&C=Side-by-Side#StudyPageTop
11 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=15&C=Side-by-Side#StudyPageTop
12 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=15&C=Side-by-Side#StudyPageTop
13 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=15&C=Side-by-Side#StudyPageTop
14 https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19
15 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=16&C=Side-by-Side#StudyPageTop

2020.[16] This means that long after clinical outcomes would have been observed, the NIAID changed the inclusion and exclusion criteria which resulted in some of the patients they observed being, after-the-fact, included or excluded from the study.

After more than doubling the total subject population size, completely modifying the primary outcome, and changing the eligibility and exclusion criteria, you were finally able to announce on national television that remdesivir appeared to shorten "time to recovery" in COVID-19 patients.[17] However, as you noted, "the results were modest."[18] You promoted this drug to the American people on dozens of networks on April 29, 2020, explaining that with this modest finding you now had "an ethical obligation to immediately let the placebo group know so they can have access."[19]

As seen above, that purported ethical obligation did not arise under the initial study protocol. It only occurred after substantial changes to the primary outcome, multiple changes to the study size, and twice revising the eligibility and exclusion criteria. Respectfully, your ethical obligation is to explain to the American people why your agency made numerous substantial changes to the protocol for the only study you relied upon to support your multi-network media tour on April 29 promoting remdesivir.

Nonetheless, the next day, April 30, 2020, you were again on national television stating that remdesivir will be licensed "really quickly."[20] You told the television audience that you were "speaking to the commissioner of the FDA"[21] and the very next day, the FDA announced its approval for remdesivir for emergency use.[22] With that emergency use, sales of remdesivir are projected to be in the billions of dollars.

The fact that the FDA quickly licensed remdesivir based on a single study is especially troubling in light of the information recently mistakenly leaked by the World

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16 https://clinicaltrials.gov/ct2/history/NCT04280705?A=2&B=10&C=Side-by-Side#StudyPageTop; https://clinicaltrials. gov/ct2/history/NCT04280705?A=2&B=15&C=Side-by-Side#StudyPageTop

17 https://www.nbcnews.com/health/health-news/coronavirus-drug-remdesivir-shows-promise-large-trial-n1195171

18 https://www.today.com/video/dr-anthony-fauci-remdesivir-is-a-very-important-first-step-in-fighting-coronavirus-82800197863

19 https://www.nbcnews.com/health/health-news/coronavirus-drug-remdesivir-shows-promise-large-trial-n1195171

20 https://www.today.com/video/dr-anthony-fauci-remdesivir-is-a-very-important-first-step-in-fighting-coronavirus-82800197863

21 Ibid.

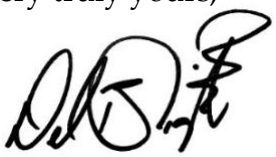
22 https://www.fda.gov/media/137564/download

Health Organization regarding another remdesivir study involving COVID-19 patients.[23] That study found that remdesivir was "not associated with a difference in time to clinical improvement" compared to a standard of care control, and that after one month, it appeared 13.9% of the remdesivir patients had died compared to 12.8% of patients in the control arm.[24]

I will not speculate as to your motives in seeking to have remdesivir licensed and pushed out to the public so quickly. What I will say is that you and NIAID can do better. The American people deserve better. They deserve science that is on solid footing. Not a sales pitch based on a single study in which every material element of its protocol was changed after patient outcomes were observed.

Please provide a response on or before May 20, 2020 to the serious irregularities regarding the NIAID remdesivir study detailed above. If we do not receive a response by then, we intend pursue ethics and related claim with the appropriate federal agencies.

Very truly yours,



Del Bigtree
President

[23] https://www.statnews.com/2020/04/23/data-on-gileads-remdesivir-released-by-accident-show-no-benefit-for-coronavirus-patients/

[24] https://www.statnews.com/2020/04/23/data-on-gileads-remdesivir-released-by-accident-show-no-benefit-for-coronavirus-patients/