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A protocol of trial of ivermectin in COVID-19 treatment critically changed after its completion

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To the editor,

We read the article by Abd-Elsalam et al.[1] in *Journal of Medical Virology* with great interest. The authors conducted a randomized controlled trial to evaluate the efficacy of ivermectin for COVID-19 infected patients. They demonstrated shorter length of hospital stay in ivermectin group than that in group without ivermectin, but the difference was not statistically significant. We have several concerns on this study regarding with study protocol and statistical analyses.

The authors stated that the trial started from March 2020 and ended in October 2020. Study protocol of this trial is first registered on ClinicalTrials.gov (NCT04403555) on May 27, 2020. According to the Ottawa statement[2], protocol registration should be done before first recruitment starts. We further examined the history of changes for this protocol[3], and found various items including arms and interventions have changed after completion of the recruitment (December 1, 2020). The changes are summarized in Table 1. The original study title was "The Efficacy of *Ivermectin and Doxycycline* in COVID-19 Treatment", and the authors planned to investigate a combination therapy of ivermectin and doxycycline compared with *chloroquine*. The intervention once changed to "Ivermectin plus standard of care treatment Dose 2 tablets 12mg per day for *4 days*" on Jan 9, 2021 and thereafter to "Ivermectin plus standard of care treatment Dose 2 tablets 12mg per day for *3 days*" on Jan 9, 2021. Finally, the protocol version 6 on Mar 3, 2021 had same items to those in published article.[1] We wonder when the authors conducted the trial and how they could change the intervention after its completion.

Another issue is addressed to statistical testing in this study. The authors examined differences in length of hospital stays between ivermectin group and control group by Mann–Whitney test. Mann–Whitney test is a nonparametric test for continuous values. In the section of statistical analysis, the authors stated "The normality of the variables was tested by the

Shapiro–Wilks test", but the results were not provided. Even though the test rejected the null hypothesis, small deviation from the normality does not affect the robustness of *t*-test.[4] If the normality was severely violated, why did the authors present mean and standard deviation (SD)? The means and SDs were 8.82 day (SD, 4.94) in ivermectin group and 10.97 day (5.28) control group, which are still reasonable for *t*-test. We conducted *t*-test for these values under equal variance assumption and found a p values of 0.00784. Hence, the actual data plots should be provided to show the distributions.

We hope that the authors would provide possible explanations on these issues.

AUTHOR CONTRIBUTIONS

KHH and AP drafted the manuscript. All the authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article.

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Table 1. Selected History of Changes for Study: NCT04403555

Version	1	2	3	4	5	6	7
Posted date	23-May-20	1-Aug-20	16-Dec-20	9-Jan-21	15-Jan-21	3-Mar-21	29-Jul-21
Title	The Efficacy of Ivermectin and Doxycycline in COVID-19 Treatment	(same)	(same)	The Efficacy of Ivermectin in COVID-19 Treatment	(same)	(same)	(same)
Overall Status	Not yet recruiting	Recruiting	(same)	(same)	(same)	(same)	Completed
Study Start	1-Jun-20	(same)	(same)	(same)	(same)	(same)	(same)
Study Completion	December 3, 2030 [Anticipated]	(same)	(same)	(same)	(same)	(same)	October 31, 2020 [Actual]
Inclusion criteria	COVID 19 positive patients	(same)	(same)	(same)	(same)	All Adult Patients aging from 20 to 65 years-old with COVID-19	(same)

						confirmed by pharyngeal swab PCR	
Number of enrollment	40 [Anticipated]	200 [Anticipated]	200 [Anticipated]	160 [Anticipated]	160 [Anticipated]	160 [Anticipated]	164 [Actual]
Intervention	Ivermectin and doxcycline	(same)	Ivermectin and doxycycline plus standard of care treatment	Ivermectin plus standard of care treatment Dose 2 tablets 12mg per day for 4 days	Ivermectin plus standard of care treatment Dose 2 tablets 12mg per day for 3 days	(same)	(same)
Comparator	Chloroquine	(same)	No Intervention: Standard of care	(same)	(same)	(same)	(same)
Primary outcome	The number of patients with resolved viral infection [Time Frame: 6 months]	The number of patients with improvement or mortality [Time Frame: 1 month]	(same)	(same)	(same)	The number of patients with mortality [Time Frame: 1 month]	(same)

Secondary outcomes	none	(same)	(same)	(same)	(same)	Length of hospital stay [Time Frame: 1 month] The need for mechanical ventilation [Time Frame: 1 month]	(same)

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