COVID-19 RETRACTIONS RAISE CONCERNS ABOUT DATA OVERSIGHT

Studies relied on health-record analyses from firm that declined to share its raw data for an audit.

By Heidi Ledford and Richard Van Noorden

Two weeks after a high-profile paper in *The Lancet*[1] reported that the antimalarial drug hydroxychloroquine might be dangerous to people with COVID-19, three of its four authors retracted the work because they were unable to independently verify their data set, a large proprietary collection of electronic health records analysed by the US company Surgisphere.

On the same day, 4 June, the researchers and other co-authors retracted a paper[2] in *The New England Journal of Medicine*, for the same reason. That study, published a month ago, had looked at the impact of certain heart medications on people with COVID-19, and found no safety concerns.

Scientists say the affair raises serious questions about how researchers and journals evaluate the data underlying papers that they publish, and might complicate the effort to trial drugs during the coronavirus pandemic. "This whole event is catastrophic — it is problematic for the journals involved, it is problematic for the integrity of science, it is problematic for medicine and it is problematic for the notion of clinical trials and evidence generation," says Ian Kerridge, a bioethicist at the University of Sydney, Australia.

Both papers relied on analysis of proprietary data from electronic health records on tens of thousands of people that were apparently gathered from hundreds of hospitals around the world by Surgisphere, which is based in Chicago, Illinois. But even after critics raised questions about the studies, the firm did not make its raw data available to third-party auditors for validation. According to the *Lancet* retraction notice, Surgisphere was concerned that transferring the data would violate "client agreements and confidentiality requirements".

"Since we do not have the ability to verify the primary data or primary data source, I no longer have confidence in the origination and veracity of the data, nor the findings they have led to," said Mandeep Mehra, a cardiologist at Brigham and Women's Hospital in Boston, Massachusetts, who was the lead author of both studies.

Hydroxychloroquine, an antimalarial drug.

NARINDER NANU/AFP/GETTY

Sapan Desai, the founder of Surgisphere and a co-author of the studies, declined to comment to *Nature* on the retractions and on concerns about the quality of the data behind the studies.

After the *Lancet* study appeared, some regulators paused enrolment in clinical trials of hydroxychloroquine as a treatment for COVID-19. The drug, which is cheap and easy to administer, has been widely endorsed during the pandemic, despite scant evidence of its effectiveness. Some of the halted trials, including one led by the World Health Organization, are starting up again.

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A third study authored by Desai, Mehra and others, which used Surgisphere data and reported finding a large reduction in COVID-19 mortality when patients were given the anti-parasitic drug ivermectin, has disappeared from the social-sciences preprint server SSRN, where it was posted in April. Mehra told *Nature* that he removed it because he "did not feel it was ready for peer review". It was not published in a peer-reviewed journal, but has nonetheless contributed to a surge in the popularity of ivermectin in South America, says Carlos Chaccour of the Barcelona Institute for Global Health in Spain, who is running a clinical trial of ivermectin and had raised questions about the preprint's data.

Researchers testing hydroxychloroquine in clinical trials are worried that the *Lancet* findings might make it harder for them to complete their research, despite the fact that the paper has been retracted. "We're hearing that people just aren't interested in hydroxychloroquine," says David Smith, an infectious-disease specialist at the University of California, San Diego, who is helping to run a trial of the drug in people with COVID-19 who have not been hospitalized.

Most data on hydroxychloroquine in COVID-19 have come from *in vitro* studies or small clinical trials. On 5 June, however, researchers working on a large randomized UK trial called RECOVERY announced that their data on more than 4,600 hospitalized people indicated that hydroxychloroquine didn't reduce the risk of death, and that they were stopping that arm of the trial.

It is not uncommon for studies that use large data sets to be published without external scrutiny of the raw data, says Smith. But an exception is when the paper is expected to have particularly high impact. In the *Lancet* study, he says, it seems that extra-careful review was skipped. "We are desperate for knowledge, and maybe we're skipping over some of our tried-and-true checks," he says.

Ivermectin effect

Surgisphere's ivermectin preprint might have a longer life. The Peruvian government included the drug in its national treatment guidelines a few days after a white paper cited the SSRN preprint, Chaccour says. A week after that, Bolivia added ivermectin to its treatment guidelines, citing the situation in Peru.

Since Chaccour gave a talk about ivermectin to the Peruvian Academy of Sciences, he says, people regularly text him to say that they have an infected family member and can get formulations of ivermectin intended for use in animals, not people. "They send me a photo of a veterinary formulation and ask me, 'Would you mind telling me what dose we should use?'" he says. "It is broadly available and people are broadly desperate and this could lead to misuse."

Because the preprint was not published in a journal, there is no retraction mechanism to limit its long reach, Chaccour worries. "Who retracts this ivermectin ghost in Latin America?" he says. "There's no high-profile journal saying this was wrong."

Additional reporting by Smriti Mallapaty and David Cyranoski

1. Mehra, M. R., Desai, S. S., Ruschitzka, F. & Patel, A. N. *Lancet* https://doi.org/10.1016/S0140-6736(20)31180-6 (2020).
2. Mehra, M. R., Desai, S. S., Kuy S., Henry, T. D. & Patel, A. N. *N. Engl. J. Med.* https://10.1056/NEJMoa2007621 (2020).