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Covid-19: Trial of experimental “covid cure” is among worst medical ethics violations in Brazil’s history, says regulator

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Violations of medical ethics and human rights committed in a trial of an experimental drug touted by President Jair Bolsonaro as a cure for covid-19 were the worst in Brazil’s history, the country’s research regulator has said.¹

The clinical trial of proxalutamide “disrespected almost the entire protocol” and may have contributed to the deaths of as many as 200 people, said the National Health Council (CNS), which oversees clinical research in Brazil.² Some of those people were not adequately informed of the risks they were undertaking in the trial, and some did not know that they were taking part in one, it said.

Brazil’s attorney general is investigating the possible violations of medical ethics and human rights on the recommendation of the National Research Ethics Commission (CONEP), which forms part of the CNS.² The trial’s principal investigator, Flavio Cadegiani, was identified in October along with 68 others by a parliamentary inquiry into Brazil’s management of the pandemic as having committed “crimes against humanity.”³

Proxalutamide is an anti-androgen that blocks the function of some male hormones. It is being tested by China’s Kintor Pharmaceuticals for prostate cancer, breast cancer, and other uses. It has not been approved for use in any country but was talked up by Bolsonaro as a treatment for covid-19. Shortly after recovering from covid-19 he asked why it had not been approved for use and promised to make it available to all of Brazil.^{4 5}

To test proxalutamide’s possible use against covid-19, Cadegiani—an endocrinologist and clinical director for Applied Biology—oversaw its prescription to a man exhibiting severe covid-19 symptoms. The report, which stated that after 24 hours the patient showed “marked improvement of symptoms and markers of disease severity,” was published in *BMJ Case Reports* on 26 February 2021.⁶

In February 2021 Cadegiani oversaw the drug’s administration to 645 patients with covid-19 at nine hospitals in Brazil’s Amazonas region as it was hit with a severe wave of infections. All patients were admitted to hospital, but none required mechanical ventilation at the start of the study. Usual care included medicines such as enoxaparin, colchicine, methylprednisolone, dexamethasone, or antibiotic therapy as necessary,⁷ and some were given unproven treatments such as ivermectin.⁸ Altogether, 317 patients received proxalutamide and 328 a placebo.

The treatment was prescribed by doctors as if it were an established medical treatment, said the CNS, although it was approved only for clinical studies. The number of people given the drug was also larger

than the number approved for the trial, and they were administered through a private hospital network in the Amazon when the trial was approved in the capital, Brasilia.²

Reported results

The trial, which was reported on the preprint server medRxiv⁷ and not peer reviewed, found that the 14 day recovery rate was 81.4% with proxalutamide and 35.7% with placebo (recovery ratio 2.28 (95% confidence interval 1.95 to 2.66); $P < 0.001$). At 28 days the all cause mortality rate was reported to be 11.0% with proxalutamide and 49.4% with placebo (hazard ratio 0.16 (0.11 to 0.24)).

Around 200 people died in the trial, mostly in the control group, although the CNS said that it had received different figures in different reports.

“The reported results would be a miracle—if they were true,” said Jesem Orellana, an epidemiologist who has closely followed the effects of the gamma variant of covid-19 on the Amazon region at Brazil’s leading public health institute, Fiocruz. “Everything about this trial is suspicious and anything but clinical and randomised.”

The mortality rate of 49.4% would not be high for the control group, as hospitals were collapsing under the pressure of the nascent gamma variant, Orellana added.

If the published results were true the trial should have been stopped and unblinded to ensure better treatment of the control group, said CONEP’s coordinator, Jorge Venâncio, in a statement. If they were not, “they subjected 200 people to die in research that has no scientific value at all.”² High rates of kidney and liver failure were observed in critically ill patients in intensive care, suggesting that they had severe conditions, although the trial was approved for mild and moderate illness.

Consent

The Spanish newspaper *El País* reported that patients had trusted doctors to provide the best available lifesaving treatment and were not told that they were being given an experimental drug as part of a clinical trial.⁸ Some said that they were not followed up by the medical team.

The consent form given to patients omitted key sections that guarantee the rights of research participants and explain the trial, said the CNS. “In the entire history of the National Health Council, there has never been such disrespect for ethical standards and research participants in the country,” it said in a statement.

Arthur Caplan, head of New York University's Division of Medical Ethics, told *The BMJ* that if the alleged practices were true the trial would be "an ethical cesspool of violations, from consent and design to over-optimistic reporting of results and hiding deaths." Falsified results have been dangerous during the covid-19 pandemic, Caplan said, as they have encouraged the popular use of unproven and sometimes dangerous drugs based on false claims.

Cadegiani denies having committed any violations of medical ethics or human rights. He told *The BMJ* that the trial was approved for a minimum of 294 patients rather than a maximum, that his team was well trained to inform patients of risks, and that the mortality rate was in keeping with that in the region at the time. He has taken legal action against the head of CONEP, Venâncio, for disclosing private information in his statement on the trial, which Venâncio denies. Political polarisation in Brazil is driving an "international movement" in opposition to proxalutamide and explains why his paper was rejected from other major science journals, he said.

The case report was made unavailable in November. An expression of concern said, "Following queries subsequently raised to BMJ, we are looking into the use of the drug prescribed in this case report (proxalutamide) and the circumstances surrounding its availability and license for use, and an expression of concern has been published online."

The preprint of the trial hosted by medRxiv remains available.⁷ BMJ, one of the founders of medRxiv, said, "Preprints on medRxiv are usually only withdrawn by authors, rather than the server, which steps in if it is notified of the results of an institutional investigation, or retraction of the peer reviewed article from a journal, or a legitimate legal or privacy concern."

Brazil's drug regulator, Anvisa, has suspended the import and use of proxalutamide for scientific research on humans, but this does not apply to ongoing clinical studies approved by Anvisa. Proxalutamide appears to be under investigation as a possible treatment for covid-19 in a number of countries, including Brazil and the US.

Correction: We amended this story on 18 November 2021 to state that Flavio Cadegiani is clinical director for Applied Biology, not Kintor Pharmaceuticals.

Correction: We further amended this story on 29 November 2021 to clarify that patients who were included in the study did not require mechanical ventilation at the start of the study. We also clarified that Brazil's drug regulator has not suspended the import of proxalutamide for trials that are already under way and that proxalutamide is being studied in a number of countries for treatment in covid-19 patients, not just in Argentina as previously stated.

Correction: We also amended this story on 10 December 2021 to replace the sentence "The report, which stated that the patient was relieved of all symptoms in three days, was published in BMJ Case Reports on 26 February 2021" to say, "The report, which stated that after 24 hours the patient showed 'marked improvement of symptoms and markers of disease severity,' was published in BMJ Case Reports on 26 February 2021." We also amended the link in reference 7.

Correction: On 6 January 2022 we removed a reference to a statement from Unesco's Network of Bioethics after The BMJ's editors decided that it was not appropriate to quote from a statement that has been retracted.

- 3 Magri D. Acusado de crime contra a humanidade na CPI recebeu dose inédita de proxalutamida a paciente com covid-19 [Accused of a crime against humanity in the CPI, he prescribed an unprecedented dose of proxalutamide to a patient with covid-19]. *El Pais* 2021 Oct 20. <https://brasil.elepa.com/brasil/2021-10-20/acusado-de-crime-contra-a-humanidade-na-cpi-receitou-dose-inedita-de-proxalutamida-a-paciente-com-covid-19.html> (in Portuguese)
- 4 Idoeta PA. Proxalutamide: os questionamentos e as suspeitas sobre a nova droga defendida por Bolsonaro contra a covid-19 [Proxalutamide: questions and suspicions about the new drug defended by Bolsonaro against covid-19]. *BBC News* 2021 Jul 20. <https://www.bbc.com/portuguese/brasil-57897387> (in Portuguese)
- 5 Stargardter G. The man behind Brazil's search for miracle COVID-19 cures. *Reuters* 14 May 2021. <https://www.reuters.com/business/healthcare-pharmaceuticals/man-behind-brazils-search-miracle-covid-19-cures-2021-05-14/>
- 6 Cadegiani F, Lin EM, Goren A, et al. Potential risk for developing severe COVID-19 disease among anabolic steroid users. *BMJ Case Reports* CP2021;14:e241572. <https://casereports.bmj.com/content/14/2/e241572>
- 7 Cadegiani AF, Fonseca D, McCoy J, et al. Efficacy of proxalutamide in hospitalized covid-19 patients: a randomized, double-blind, placebo-controlled, parallel-design clinical trial. *medRxiv* 2021 Jun 22 [preprint]. <https://www.medrxiv.org/content/10.1101/2021.06.22.21259318v1>
- 8 Magri D. "Cobaías" da proxalutamida: como o Brasil entrou no que pode ser uma das infrações éticas mais graves da história [Proxalutamide "Guinea Pigs": how Brazil got itself into what could be one of the most serious ethical infractions in history]. *El Pais* 2021 Oct 14. <https://brasil.elepa.com/brasil/2021-10-14/a-promessa-de-cura-para-a-covid-19-que-pode-se-tornar-uma-das-infracoes-eticas-mais-graves-da-historia.html> (in Portuguese)

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1 SUS Conecta. Nota pública: CNS elucida à sociedade brasileira fatos sobre estudo irregular com proxalutamide [Public statement: CNS clarifies the facts about irregular study with proxalutamide to Brazilian Society]. 15 Oct 2021. <http://www.susconecta.org.br/nota-publica-cns-elucida-a-sociedade-brasileira-fatos-sobre-estudo-irregular-com-proxalutamida/> (in Portuguese)

2 National Health Council (Brazil). Conep/CNS pede que Procuradoria Geral investigue 200 mortes em estudo irregular com proxalutamida para tratar Covid-19 [Conep/CNS asks the Attorney General to investigate 200 deaths in irregular study with proxalutamide to treat Covid-19]. 20 Sep 2021. <http://conselho.saude.gov.br/ultimas-noticias-cns/2033-conep-cns-pede-que-procuradoria-geral-investigue-200-mortes-em-estudo-irregular-com-proxalutamida-para-tratar-covid-19> (in Portuguese)