

An unethical trial and the politicization of the COVID-19 pandemic in Brazil: The case of Prevent Senior

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Funding information

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Grant/Award Number: Finance Code 001

Abstract

The Brazilian Federal Senate created a Parliamentary Inquiry Commission (CPI) to investigate the Bolsonaro government's irregularities in the management of the COVID-19 pandemic. One of the cases that drew attention was the research conducted by Prevent Senior, a private health insurance company, on the early treatment of COVID-19. The article analyzes the scientific validity of the research and the ethical problems related to its implementation. It is based on analysis of Prevent Senior's report of the clinical study, the Brazilian and USA clinical trial registries, the Senate's CPI report, and on the information reported by the media. This case of scientific fraud and political-ideological bias exemplifies how Prevent Senior, using a questionable protocol to enhance its reputation and gain government support, was instrumental in building the "early treatment" narrative for COVID-19, and shows how it served as a basis for a government public policy that promoted the use of ineffective drugs.

KEYWORDS

COVID-19, pandemic, public policies, research ethics, scientific integrity

1 | INTRODUCTION

There is no doubt that most countries and international agencies will have to think long and hard about how they responded to COVID-19 in order to avoid making the same mistakes again when the next pandemic comes along. In addition to the unjust distribution of vaccines and treatments, politics interfered with science in several countries and the design and implementation of clinical trials was modified as a result.

The World Health Organization (WHO) issued guidelines to direct resources to well-designed, large studies, such as the Solidarity trial,¹ but the eagerness of countries, researchers and companies to come up with the first treatment or preventive measure for COVID-19 led to an overabundance of small research projects of

limited clinical or scientific relevance, that consumed significant resources and might have put research participants at risk. Competition trumped collaboration and the few large multinational studies such as Solidarity failed to enroll the intended number of participants.² A high percentage of COVID-19 protocols have been deemed useless.³ Research protocols of little or no scientific value have a negative risk-benefit balance and are unethical; in addition to being wasteful, participants are exposed to unnecessary risks. Most Research Ethics Committees (RECs) have not distinguished clinical trials with robust designs from those without the potential to contribute to science, including those created "ad hoc" to exclusively evaluate COVID-19. When this responsibility was assigned to a national committee, as in the case of Brazil where all COVID-19

¹World Health Organization. (2022). WHO COVID-19 Solidarity Therapeutics Trial. Retrieved March 16, 2022, from <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>

²Ireland, N. (2021). Accelerating vaccine trials. *Bulletin of the World Health Organization*, 99(7), 482–483. <https://doi.org/10.2471/BLT.21.020721>

³Bramstedt, K. A. (2020). The carnage of substandard research during the COVID-19 pandemic: A call for quality. *Journal of Medical Ethics*, 46(12), 803–807. <https://doi.org/10.1136/medethics-2020-106494>

protocols were evaluated by the National Research Ethics Commission (CONEP), monitoring their implementation was delegated to the institutional RECs.⁴

Compared to 2019, the number of protocols reviewed by CONEP in 2020 increased by 94.45%.⁵ Between February 17, 2020 and February 5, 2022, CONEP approved 970 protocols related to coronavirus and/or COVID-19 that had been submitted by 97 institutions.⁶ Of these, 366 were interventional/experimental and aimed at enrolling 198,392 participants. 192 (52.5%) of the interventional/experimental protocols were submitted by public institutions and 170 (47.5%) by private entities.

Throughout the COVID-19 pandemic, clinical trials have been suspended, study arms interrupted, and CONEP has identified ethical irregularities in implementing COVID-related research protocols. Although CONEP does not report the number of studies that have been disapproved, suspended or interrupted, it was made public that a protocol involving proxalutamide was interrupted due to irregularities,⁷ and the arm of the Chloro-COVID-19 trial that studied the use of hydroxychloroquine (HQC) was discontinued⁸ because the dosages of HQC were too high and potentially toxic to patients.

Upon publishing the preliminary results of the Chloro-COVID-19 trial, the authors were attacked on social media with messages that exhibited the strong ideological bias of people who defended the use of HQC.⁹ It is worth remembering that the Bolsonaro government defended HQC at all costs, and this drug remains a symbol of Jair Bolsonaro's political struggle.¹⁰

The politicization of the COVID-19 response has been particularly alarming in Brazil,¹¹ but also in the USA.¹² In Brazil, this politicization led the Federal Senate to set up the Pandemic CPI,¹³ a Parliamentary Inquiry

Commission (CPI in Portuguese) to investigate the Federal Government's irregularities in managing this health crisis, in addition to dozens of other issues. One of the cases that drew attention and was highlighted in the CPI's final report¹⁴ was the research conducted by Prevent Senior, a Brazilian health insurance company specialized in assisting the elderly. The company implemented an intervention to prevent the worsening of COVID-19 patients using a combination of HQC and azithromycin (AZ), among other products. The CPI report called for the indictment of the company executives, as well as the physicians who participated in the study due to omissions in disease notification, ideological falsehood, endangering the life and health of others, and manipulating medical records and data from scientific experimentation, which was conducted without obtaining the participants' informed consent. In addition, CONEP suspended the protocol because the intervention was initiated before obtaining authorization, among other ethical problems,¹⁵ and on September 30, 2021, São Paulo City Council approved a specific CPI to investigate problems related to Prevent Senior, which is ongoing.¹⁶

This case study is based on analysis of the following documents: Prevent Senior's report of the clinical study,¹⁷ the information included in the Brazilian and USA clinical trial registries, Plataforma Brasil and clinicaltrials.gov, respectively, the Federal government's CPI report,¹⁸ and on the information reported by the media and on government websites. Our analysis focuses on the scientific validity of the study and the ethical problems related to its implementation, and on how Prevent Senior used a questionable protocol to improve its reputation, obtain government support and possibly reduce the number of its beneficiaries who required hospitalization due to a COVID-19 infection.

2 | CONTEXT AND ACTORS

2.1 | Prevent Senior, Jair Bolsonaro, the Ministry of Health, and the Federal Council of Medicine

Prevent Senior designed and financed the study, which recruited its own beneficiaries and was managed by Azidus, a Contract Research Organization (CRO).¹⁹

⁴Comissão Nacional de Ética em Pesquisa. (2020). Informe à sociedade. Brasília. Retrieved March 16, 2022, from http://conselho.saude.gov.br/images/comissoes/conep/documentos/CARTAS/Informe_Conep_sobre_2019-nCoV.pdf

⁵Comissão Nacional de Ética em Pesquisa. (2020). 2020 Portfólio. Brasília. Retrieved March 16, 2022, from http://conselho.saude.gov.br/images/comissoes/conep/documentos/Portfólio_Conep_-_2020.pdf

⁶CONEP. (2022). Observatório Plataforma Brasil. Retrieved March 16, 2022, from <https://observatoriopb.cienciasus.gov.br>; Comissão Nacional de Ética em Pesquisa, op. cit. note 5.

⁷Conselho Nacional de Saúde. (2021). NOTA PÚBLICA: CNS elucida à sociedade brasileira fatos sobre estudo irregular com proxalutamide. Retrieved March 16, 2022, from <https://conselho.saude.gov.br/ultimas-noticias-cns/2095-nota-publica-cns-elucida-a-sociedade-brasileira-fatos-sobre-estudo-irregular-com-proxalutamide>

⁸Borba, M. G. S., Val, F. F. A., Sampaio, V. S., Alexandre, M. A. A., Melo, G. C., Brito, M., et al. (2020). Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Network Open*. 3(4), e208857. <https://doi.org/10.1001/jamanetworkopen.2020.8857>

⁹ABRASCO (2020). Em respeito à ciência! Contra os ataques aos pesquisadores do estudo CloroCovid-19. Retrieved March 16, 2022, from <https://www.abrasco.org.br/site/noticias/posicionamentos-oficiais-abrasco/em-respeito-a-ciencia-contra-os-ataques-aos-pesquisadores-do-estudo-clorocovid-19/47055/>; Sociedade Brasileira de Medicina Tropical. (2020). Nota de repúdio ao ataque a sócios da SBMT em busca do tratamento para a COVID-19. Retrieved March 16, 2022, from <https://www.sgmt.org.br/portal/nota-de-repudio-ao-ataque-socios-da-sgmt-em-busca-do-tratamento-para-covid-19/>

¹⁰Caponi, S., Brzozowski, F. S., Hellmann, F., & Bittencourt, S. C. (2021). O uso político da cloroquina: COVID-19, negacionismo e neoliberalismo/The political use of chloroquine: COVID-19, denialism and neoliberalism. *Revista Brasileira de Sociologia - RBS*. 9(21), 78–102. <https://doi.org/10.20336/rbs.774>

¹¹Duarte, A. de M., & César, M. R. de A. (2020). Negação da Política e Negacionismo como Política: pandemia e democracia. *Educação & Realidade*. 45(4), 1–10. <https://doi.org/10.1590/2175-6236109146>

¹²Hart, P. S., Chinn, S., & Soroka, S. (2020). Politicization and Polarization in COVID-19 News Coverage. *Science Communication*. 42(5), 679–697. <https://doi.org/10.1177/1075547020950735>

¹³Senado Federal. (2021). Relatório Final. Comissão Parlamentar de Inquérito da Pandemia (Instituída pelos Requerimentos nos 1.371 e 1.372, de 2021). Brasília. Retrieved March 16, 2022, from <https://www6g.senado.leg.br/sdleg-getter/documento?dm=9031799%26>

¹⁴Ibid.

¹⁵Herdy, T., & Schmitt, G. (2020, April 20). Conep suspende estudo da Prevent Senior sobre uso de cloroquina para Covid-19. *O Globo*. Retrieved March 16, 2022, from <https://oglobo.globo.com/brasil/conep-suspende-estudo-da-prevent-senior-sobre-uso-de-cloroquina-para-covid-19-24384110>

¹⁶Câmara Municipal de São Paulo. (2022). CPI Prevent Senior. Retrieved March 16, 2022, from <https://www.saopaulo.sp.leg.br/comissao/comissoes-parlamentares-de-inquerito-cpis/cpi-prevent-senior/>

¹⁷Esper, R. B., Silva, R. S. da, Oikawa, F. T. C., Castro, M. M., & Razuk-Filho, A. (2020). Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine. Semantic Scholar, Corpus ID: 218687909. São Paulo. Retrieved March 16, 2022, from <https://drive.google.com/file/d/1fs7f6qX-iUYbRAGLBeDtWt8sNXjmjSxn/view>

¹⁸Senado Federal, op. cit. note 13.

Prevent Senior is Brazil's seventh largest private health insurance company and its health service network consists of 41 units, including eight hospitals and four emergency centers (totaling 614 beds), Advanced Medical and Diagnostic Centers and other specialized and accredited networks.²⁰ It employs 9,000 persons, including about 2800 physicians.²¹ Total revenues in 2019 amounted to 3.6 billion Reais and a net income of 432.1 million Reais²² (1USD = R\$4.20). Most network units are in the state of São Paulo, but also in Rio de Janeiro, the Federal District, and two other southern Brazilian state capitals: Curitiba and Porto Alegre. At the beginning of 2020, 7 of the 13 hospitals and emergency centers located in the municipality of São Paulo were operating without the necessary municipal license.²³

Prevent Senior has more than 548,000 beneficiaries:²⁴ 76% are elderly with an average age of 66.6 years, compared to a sector average of 14.2% and 35.8 years of age, respectively.²⁵ It is, therefore, an insurance scheme that needs to charge high premiums to cover expenses, since the elderly tend to be heavy users of health care services. The company was accused of concealing the first case of COVID-19 in Brazil and the city of São Paulo documented overcrowding, disorganization in the flow of care, and insufficient staff.²⁶ By March 19, 2020, the city of São Paulo had recorded five COVID-19 deaths, all of them patients treated at Prevent Senior facilities.²⁷ Consequently, the company's reputation suffered.

To restore its image, among other measures, Prevent Senior treated ambulatory patients with early symptoms of COVID-19 with HCQ and AZ. At that time this treatment was controversial, lacking evidence of effectiveness and safety and running counter to WHO recommendations. It was supported by politicians and influential people. About that time, Didier Raoult, a French physician, published an anecdotal study that was widely disseminated on social media by well-known businessmen, such as Elon Musk. Ultra-right populist media and governments, such as Fox Network and Donald Trump in the USA and Jovem Pan radio network and Jair Bolsonaro in Brazil defended the study.²⁸ According to Bolsonaro, "those on the right take chloroquine, those on the left, tubaína," a traditional Brazilian soft drink.²⁹

During March and April 2020, the Ministry of Health (MOH) disagreed with the expressed positions of the Federal Government and the Ministry of the Economy. For example, while the Minister of Health, Luiz Henrique Mandetta, was recommending social isolation,³⁰ the Federal Government launched the 'O Brasil Não Pode Parar' campaign, opposing isolation measures and restricting quarantine to the elderly.³¹ Similarly, while Mandetta cautioned about the indiscriminate use of HCQ and restricted its use to critically ill hospitalized patients with COVID-19,³² Bolsonaro promoted HCQ as a curative treatment for COVID-19.³³ The disagreements between Bolsonaro and Mandetta were blatant.

Mandetta also had harsh words for Prevent Senior,³⁴ especially for its Sancta Maggiore hospital, where 80 of the 136 COVID-19 deaths recorded in the city of São Paulo had occurred and suggested that Prevent Senior's hospitals should be investigated. Concurrently, the Public Ministry of the State of São Paulo opened an investigation on the underreporting of deaths by Prevent Senior.³⁵

Prevent Senior, under pressure from the media, the Public Ministry of the state of São Paulo, São Paulo City Council, and the Ministry of Health, sought communication with the Presidency of the Republic. The relationship between Bolsonaro and Prevent Senior is evident and undeniable. Jair Bolsonaro and his sons (also politicians) Flávio and Carlos praised the operator, criticized the Brazilian Public Health System, and defended the use of HCQ and the drugs included the Covid-Kit³⁶ to treat COVID-19.³⁷ For example, on March 25, 2020, Bolsonaro posted a message on Twitter which, without naming Prevent Senior, referred to the results of the intervention it had conducted:

The treatment of COVID-19, based on Hydroxychloroquine (CIS) and Azithromycin, has proven effective in the patients currently being treated. In the coming days, these results may be presented to the public, bringing the necessary atmosphere of tranquility and serenity to Brazil and to the world.³⁸

noticias.uol.com.br/ultimas-noticias/agencia-estado/2020/05/20/quem-e-de-direita-toma-clo-roquina-quem-e-de-esquerda-tubaina-diz-bolsonaro.htm?cmpid=copiaceola

³⁰Benites, A. (2020). Mandetta apela por isolamento para evitar colapso do sistema de saúde no final de abril. *El País Brasil*. Retrieved March 16, 2022, from <https://brasil.elpais.com/brasil/2020-03-20/mandetta-apela-por-isolamento-para-evitar-colapso-do-sistema-de-saude-no-final-de-abril.html>

³¹CNN Brasil. (2020, March 27). Governo lança campanha 'Brasil Não Pode Parar' contra medidas de isolamento. *CNN Brasil*. Retrieved March 16, 2022, from <https://www.cnnbrasil.com.br/politica/governo-lanca-campanha-brasil-nao-pode-parar-contra-medidas-de-isolamento/>

³²Mellis, F. (2020, March 25). Ministério autoriza clo-roquina para casos graves de covid-19. *R7*. Retrieved March 16, 2022, from <https://noticias.r7.com/saude/ministerio-autoriza-clo-roquina-para-casos-graves-de-covid-19-25032020>

³³O Globo. (2020, March 29). 'Deus é brasileiro e a cura tá aí', diz Bolsonaro sobre remédio ainda em teste contra Covid-19. *O Globo*.

³⁴Junqueira, C. (2021, September 23). Mandetta alertou Planalto sobre Prevent Senior.

³⁵Senado Federal, op. cit. note 13, p. 892.

³⁶Kit-Covid is the name used in the media and by CPI for the set of drugs for the treatment of COVID-19, mostly in off-label use. Although the main drugs were HCQ and AZT, this kit could also contain ivermectin, flutamine, dexamethasone, prednisone, zinc, and vitamin D.

³⁷O Globo. (2021, September 17). Bolsonaro e os filhos defenderam estudo da Prevent Senior sobre o uso de clo-roquina; veja. *O Globo*.

³⁸Bolsonaro, J. M. (2020). O tratamento da COVID-19, a base de Hidroxicloroquina e Azitromicina. Retrieved March 16, 2022, from <https://twitter.com/jairbolsonaro/status/1242881753162940419>

¹⁹Azidus. (2022). Azidus The Trusted CRO. Retrieved March 16, 2022, from <https://www.azidus.com>

²⁰Prevent Senior. (2022). Quem Somos. Retrieved March 16, 2022, from <https://preventsenior.com.br/quemsomos.php>

²¹Koike, B. (2020, April). Prevent Senior rebate críticas de Mandetta sobre ação na pandemia. *Valor Econômico*.

²²Ibid.

²³Ibid.

²⁴Benefícios RH. (2022). 9 maiores operadoras de planos de saúde para 2022. Retrieved March 16, 2022, from <https://www.beneficiosh.com.br/maiores-operadoras-planos-de-saude/>

²⁵Carranço, T. (2021, July 28). Prevent Senior: como plano de saúde investigado cresceu como 'única alternativa' para idosos. *BBC News Brasil*. Retrieved March 16, 2022, from <https://www.bbc.com/portuguese/brasil-58714986>

²⁶Moreira, M., Watanabe, P., & Saldaña, P. (2020, March 19). Prevent Senior, em SP, tem cinco mortes por novo coronavírus; Brasil soma sete. *Folha de São Paulo*. Retrieved March 16, 2022, from <https://www1.folha.uol.com.br/equlibrioesaude/2020/03/prevent-senior-tem-cinco-mortes-por-novo-coronavirus-em-sp-brasil-soma-sete.shtml>

²⁷Ibid.

²⁸Caponi, et al., op. cit. note 10, pp. 78–102.

²⁹Estadão Conteúdo. (2020, May 20). 'Quem é de direita toma clo-roquina, quem é de esquerda, Tubaína', diz Bolsonaro. *UOL Notícias*. Retrieved March 16, 2022, from <https://>

In less than a month, Prevent Senior, which had been criticized for its poor management and high COVID-19 mortality rates, began to be portrayed in the media as a success story. It was said that the intervention had resulted in decreased mortality rates and hospital admissions.³⁹ Bruna Morato, the lawyer representing 12 of the doctors who denounced Prevent Senior, reported to the CPI of the Pandemic:

So, Prevent Senior was sure that it would not be inspected by the Ministry of Health or other organs linked to the Ministry of Health. In fact, it was this security that motivated them to start an experimental protocol, knowing that they would not be duly investigated or investigated by the Ministry.⁴⁰

On April 5, 2020, Jair Bolsonaro and the director of Prevent Senior, Pedro Batista, appeared in a live-broadcast to talk about the benefits of the early treatment of COVID-19 with HCQ.⁴¹ On April 16, 2020, Mandetta was fired and the Federal Council of Medicine (CFM) approved the Opinion 4/2020,⁴² which was signed by its president Mauro Luiz de Brito Ribeiro, and authorized physicians to prescribe HCQ and AZ to treat COVID-19 patients with mild and unconfirmed symptoms of the disease or with moderate symptoms. This treatment had already been approved by the MOH to treat severe COVID-19 cases. The day after the promulgation of CFM Resolution 4/2020, Prevent Senior held a press conference to present the results of its intervention, which would support the use of HCQ in association with AZ for the “early treatment” of COVID-19.

On April 23, 2020, the CFM opinion 4/2020 was presented by its president, Mauro Ribeiro, during a meeting at the Presidential Palace attended by Jair Bolsonaro and the new Minister of Health, Nelson Teich.⁴³ Although the CMF Opinion 4/2020 warned that there was no robust evidence to support the use of drugs such as HCQ and AZ it ended up recommending the use of both drugs, especially HCQ, for all COVID-19 cases. To justify its conclusion, the CFM used the principle of “physician's autonomy” and concluded that “in view of the exceptionality of the situation during the declared pandemic period, a physician who uses chloroquine or hydroxychloroquine” in patients with COVID-19 would not commit an ethical infraction.⁴⁴

The controversy surrounding HCQ and other controversial treatments led to the resignation of Nelson Teich, less than 30 days

after becoming Minister of Health.⁴⁵ He was replaced by Eduardo Pazuelo, a Brazilian Army general with no background in health care or medicine.⁴⁶ Soon HCQ was incorporated into the official protocol of the Ministry of Health for treating all cases of COVID-19.⁴⁷

2.2 | The design of the study conducted by Prevent Senior

As mentioned, Prevent Senior released, during a press conference held on April 17, 2020, a paper entitled “Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed through telemedicine”⁴⁸ which presented the results of a research study that had been submitted for publication in the journal PLOS Medicine.⁴⁹ As seen in Table 1, the results of the study were released three days after CONEP approved the research protocol and registered its details in Plataforma Brasil (Number 30586520.9.0000.0008).⁵⁰ The study was registered in ClinicalTrials.gov as NCT04348474.⁵¹

The registration of the study on Clinicaltrials.gov occurred after the data collection and violates Article 35 of the Declaration of Helsinki, which clearly states that all research involving humans must be registered in a publicly accessible database before recruiting the first subject.⁵² The Brazilian National Council of Health Resolution 466/2012⁵³ was also violated because the intervention was initiated before receiving approval from CONEP.

Moreover, the information that appears in the registries and in Prevent Senior's unpublished article contains discrepancies in dates and in study design (see Tables 1 and 2). For example, according to ClinicalTrials.gov, only patients with a confirmed diagnosis of COVID-19 would receive treatment and the unpublished article says that patients suspected of having the disease were included, since “Laboratory swab testing was not mandatory and chest CT scan was performed according to physician judgment”.⁵⁴ Similarly, the number of participants also

⁴⁵Agência Senado. (2021, May 5). Teich diz que deixou cargo por falta de autonomia e por não aceitar cloroquina. *Agência Senado*. Retrieved from March 16, 2022, from <https://www12.senado.leg.br/noticias/materias/2021/05/05/teich-diz-que-deixou-cargo-por-falta-de-autonomia-e-por-nao-aceitar-cloroquina>

⁴⁶Caponi, et al., op. cit. note 10, pp. 78–102.

⁴⁷Ministério da Saúde. (2020). Orientações do Ministério da Saúde para manuseio medicamentoso precoce de pacientes com diagnóstico da Covid-19. Brasília. Retrieved March 16, 2022, from <https://www.gov.br/saude/pt-br/centrais-de-conteudo/arquivos/orientacoes-manuseio-medicamentoso-covid19-pdf>

⁴⁸Esper, et al., op. cit. note 17.

⁴⁹Desidério, op. cit. note 39.

⁵⁰CONEP. (2022). Plataforma Brasil. Retrieved March 16, 2022, from <https://plataformabrasil.saude.gov.br/login.jsf>

⁵¹Azidus. (2020). NCT04348474, History of Changes for Study: Efficacy and Safety of Hydroxychloroquine and Azithromycin for the Treatment of Ambulatory Patients With Mild COVID-19. Retrieved March 16, 2022, from <https://clinicaltrials.gov/ct2/history/NCT04348474?A=1%26B=2%26C=merged#StudyPageTop>

⁵²World Medical Association. (2013). WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. Fortaleza, Brazil. Retrieved March 16, 2022, from <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

⁵³Conselho Nacional de Saúde. Resolução N 466, de 12 de Dezembro de 2012 (2012). Brasil. Retrieved March 16, 2022, from <https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf>

⁵⁴Esper, et al., op. cit. note 17, p. 7.

³⁹Desidério, M. (2020, April 17). Hidroxicloroquina precoce reduziu mortes em 60%, diz Prevent Senior. *Exame*. Retrieved March 16, 2022, from <https://exame.com/negocios/hidroxicloroquina-precoce-reduziu-mortes-em-60-diz-prevent-senior/>

⁴⁰Senado Federal, op. cit. note 13, pp. 890–891.

⁴¹Essa tal rede social. (n.d.). 6 vezes em que Bolsonaro defendeu o estudo da Prevent Senior. Retrieved March 13, 2022, from <https://essatalredesocial.com.br/2021/09/16/seis-vezes-em-que-bolsonaro-defendeu-o-estudo-da-prevent-senior/>

⁴²Conselho Federal de Medicina. Processo-Consulta CFM Nº8/2020-Parecer CFM nº 4/2020 (2020). Brasil. Retrieved March 16, 2022, from <https://sistemas.cfm.org.br/normas/visualizar/pareceres/BR/2020/4>

⁴³Planalto. (2020). Bolsonaro e CFM discutem uso da hidroxicloroquina em pacientes com Covid-19. Retrieved March 16, 2022, from <https://www.gov.br/planalto/pt-br/acompanhe-o-planalto/noticias/2020/4/bolsonaro-e-cfm-discutem-uso-da-hidroxicloroquina-em-pacientes-com-covid-19>

⁴⁴Conselho Federal de Medicina, op. cit. note 42.

TABLE 1 Chronology of key dates of the Prevent Senior study

Event	Date
Bolsonaro announces that positive results of research with HQC and AZT in the treatment of Covid-19 would be released soon	March 25, 2020
Data collection period according to the Prevent article	March 26 to April 4, 2020
Submission of research to CONEP	April 6, 2020
Approval of the study by CONEP	April 14, 2020
Registration of the study on ClinicalTrials.gov	13 April 2020
Publication of study results by Prevent	17 april 2020
Cancellation of the study by CONEP	20 april 2020
Changes in the ClinicalTrials.gov records	21 april 2020
Period of data collection as registered in CONEP	April 06 to June 28, 2020
Data collection period as registered in ClinicalTrials.gov	April 20 to July 31, 2020

Source: Produced by the authors, 2022.

differs: 636, according to the article (412 in the treatment group), well above the 200 listed in both registers.

One could think that they referred to different studies. However, the Prevent Senior article clearly linked its study to these two registries. Only when CONEP halted the study, after learning in the media about the research⁵⁵ did Prevent Senior change its narrative, stating that the manuscript widely disseminated by its press office had been leaked without authorization, and another study would be initiated.⁵⁶ CONEP rejected this argument.

2.3 | The results of the study conducted by Prevent Senior

According to the article released by Prevent Senior, the average age of the participants was 62.5 ± 15.5 years: 400 (64%) were female;⁵⁷ 85 (13.4%) had Type 2 diabetes mellitus, 168 (26.5%) had a history of hypertension, and 49 (7.7%) were obese. Clinical characteristics were similar between the groups, except for a higher rate of diabetes, prior stroke, dyspnea, and influenza-like symptoms in the treatment group than in the control group. During the follow-up, when only patients with dyspnea were evaluated, the patients in the treatment group experienced a greater improvement than the entire group of participants in the treatment group (13.5% vs. 5.8%).⁵⁸

⁵⁵Estadão, C. (2020, April 21). Prevent Senior testa hidroxicloraquina sem aval e estudo é suspenso. *Exame*. Retrieved March 16, 2022, from <https://exame.com/brasil/prevent-senior-testa-hidroxicloraquina-sem-aval-de-comite/>

⁵⁶Vidale, G. (2020, April 27). Conep suspende estudo da Prevent Senior com hidroxicloraquina. *Veja*. Retrieved March 16, 2022, from <https://veja.abril.com.br/saude/conep-suspende-estudo-da-prevent-senior-com-hidroxicloraquina/>; Estadão, op. cit. note 55;

Herdy & Schmitt, op. cit. note 15.

⁵⁷Esper, et al., op. cit. note 17.

⁵⁸Ibid: 11–12.

No serious side effects were reported for patients treated with HQC in combination with AZ. Two patients in the treatment group died during the follow-up period, one suffered an acute coronary syndrome and the other had metastatic cancer.⁵⁹

The results were reported as being very promising, with the need for hospitalization being 1.9% in the treatment group vs 5.4% in the control group (2.8 times higher), which represents an Absolute Risk Reduction of 3.5% and 28 patients had to receive treatment to avoid one hospitalization (Number Need to Treat [NNT] = 28). When stratifying the analysis according to the number of days those participants had experienced symptoms prior to receiving treatment, the patients treated prior to the 7th day of symptoms needed fewer hospitalizations than those who received the treatment after the 7th day (1.17% vs 3.2%). 23 patients had to receive treatment prior to the 7th day of symptoms to avoid one hospitalization (NNT = 23).⁶⁰

The document concluded that “empirical treatment with hydroxychloroquine associated with azithromycin for suspected cases of COVID-19 infection reduces the need for hospitalization”.⁶¹

2.4 | The scientific value of the study

Article 21 of The Declaration of Helsinki states that medical research with human subjects must conform to widely accepted scientific principles.⁶² National and international experts questioned the

⁵⁹Ibid: 12.

⁶⁰Ibid: 11–12.

⁶¹Ibid: 17.

⁶²World Medical Association, op. cit. note 52.

TABLE 2 Comparison of the study design disclosed by Prevent Senior with the records in ClinicalTrials.gov and Plataforma Brasil.

	Documento Prevent Senior	ClinicalTrials.gov	Plataforma Brasil
Title of the document	Empirical treatment of suspected cases of COVID-19 with hydroxychloroquine and azithromycin. Follow-up was done by telemedicine	Open Label, Multicentric, Non-Randomized, Exploratory Clinical Trial to Assess the Efficacy and Safety of Hydroxychloroquine and Azithromycin for the Treatment of Mild Acute Respiratory Syndrome (COVID-19) Caused by SARS-CoV-2 Virus Efficacy and Safety of Hydroxychloroquine and Azithromycin for the Treatment of Ambulatory Patients with mild COVID-19	A concept, open-label, non-randomized clinical trial to evaluate the efficacy and safety of oral administration of hydroxychloroquine in combination with azithromycin in the treatment of mild acute respiratory illness (COVID-19) caused by SARS-CoV-2 virus.
Principal Investigator/ Corresponding Author	Rodrigo Barbosa Esper	Rafael Souza	Rafael Souza da Silva
Date research begun	March 26, 2020	April 20, 2020	April 6, 2020
Date research project ended	April 4, 2020	July 31, 2020	June 28, 2020
Objective	To assess whether the empirical prescription of hydroxychloroquine and azithromycin to patients with suspected COVID-19 decreases the need for hospitalization.	To demonstrate a decrease in hospital related complications among ambulatory patients with mild COVID-19 by treating them with HCQ and AZ on top of standard care, compared to patients who receive standard care only.	
Description of the study	A telemedicine team evaluated suspected COVID-19 outpatients with flu-like symptoms, if no contraindications were detected, treatment with hydroxychloroquine and azithromycin was prescribed after obtaining consent from subjects. Using telemedicine, patients were monitored daily [...] until the fifth day of symptoms, after that, patients were contacted twice a day (sic*) until the fourteenth day of symptoms. Hydroxychloroquine and azithromycin were delivered to the home of the patients who who consented to home visits and to the use of medication. *Probably should read twice a week.	Exploratory study to evaluate the efficacy of hydroxychloroquine and azithromycin to treat mild ambulatory COVID-19 patients. Ambulatory patients who on day 3 have symptoms and a confirmed diagnosis of COVID-19 will receive the treatment. Study Type: Interventional. Primary Purpose: Treatment. Study Phase: Early Phase 1. Interventional Study Model: Single Group Assignment. Number of Arms: 1. Masking: None (Open Label). Allocation: N/A. Enrollment: 200 [Anticipated]	see above (Title cell)
Intervention group	Outpatients with persistent flu-like symptoms (suspected COVID-19 infection), persisting for equal of longer than 2 days, were first evaluated by the telemedicine team or by the emergency physician. Patients received hydroxychloroquine 800 mg on the first day and 400 mg for 6 days, and azithromycin 500 mg once daily for five days. Patients in the treatment group consented to the treatment with hydroxychloroquine plus azithromycin.	Ambulatory patients on day 3 of symptoms and with confirmed diagnosis of COVID-19 will receive the treatment. All patients included in the study will receive HCQ (400 mg BID on D1 and 400 mg/day on D2 to D7) for 7 days, and AZ 500 mg per day for 5 days.	

TABLE 2 (Continued)

	Documento Prevent Senior	ClinicalTrials.gov	Plataforma Brasil
Control group	The control group was composed of patients who refused and did not sign the informed consent to receive hydroxychloroquine and azithromycin.	Patients who do not fulfill the inclusion/exclusion criteria or who are not willing to participate in the study will be invited to consent to use their data as part of the "control" group.	
Outcome Measures	<p>To evaluate whether the empirical prescription of Hydroxychloroquine plus Azithromycin to outpatients decreases the need for hospitalization.</p> <p>To evaluate the difference in the rate of hospitalization among patients treated before and after the seventh day of symptoms.</p> <p>The main hospitalization admission criteria were:</p> <ul style="list-style-type: none"> • Worsening general condition • Oxygen Saturation < 90% <hr/> <p>Breathing pattern was evaluated during videoconference</p> <p>It was considered that the patient had dyspnea when s/he referred "a subjective experience of breathing discomfort consisting of qualitatively distinct sensations that varied in intensity". The improvement in dyspnea during follow-up was defined as the total improvement in dyspnea symptoms reported by the patient.</p> <p>The swab diagnostic test was not mandatory and chest computed tomography was performed on selected patients according to medical judgment.</p> <p>Lung injury criteria for COVID-19 were determined based on tomography scans displaying the presence of opacities in multiple lung lobes with bilateral predominance and peripheral localization (which may evolve to the central region).</p> <p>All patients were followed daily by telemedicine consultations until the fifth day of symptoms, after that, patients were contacted twice a day until the fourteenth day of initial symptoms.</p>	<p>Primary</p> <p>Change in Clinical Condition [Time Frame: 28 days]</p> <p>Ordinal scale (7 points ordinal scale that measures illness severity over time)</p> <p>Secondary</p> <ol style="list-style-type: none"> 1. Hospitalization 2. Time for normalization of body temperature 3. Time for normalization of respiratory rate 4. Time for cough relief 5. Rate of mortality within 28-days 6. Change in Clinical Condition related to comorbidity <p>Time Frame: 28 days</p>	
Number of participants	636 (412 experimental group, 224 control group)	200	200
Inclusion criteria	Patient over 18 years old and flu-like persistent symptoms > 3 days, with a probable diagnosis of COVID-19 and no immediate indication for hospitalization.	<ol style="list-style-type: none"> 1. Informed consent from patient or legal representative. 2. Male or female, and: <ol style="list-style-type: none"> a. aged ≥ 70 years; or aged $< 70 \geq 18$ with associated risk factors (chronic obstructive pulmonary disease; heart failure, immunosuppressed, obesity [BMI ≥ 35] uncontrolled diabetes and 	

(Continues)

TABLE 2 (Continued)

Documento Prevent Senior	ClinicalTrials.gov	Plataforma Brasil
	uncontrolled systemic arterial hypertension)	
	3. One or more mild symptoms characteristic of COVID-19 for 3 days, such as fever, cough, and signs of respiratory distress, which did not require hospitalization.	
Exclusion criteria	<ol style="list-style-type: none"> 1. Severe related retinopathy 2. Severe liver disease 3. Myasthenia Gravis 4. Known QT enlargement 5. Pregnant 6. Severe renal failure 	<ol style="list-style-type: none"> 1. Participation in another RCT in the last 12 months 2. Known allergy to HCQ or chloroquine 3. Any contraindication to HCQ or AZ, including retinopathy and prolonged QT, 4. Severely reduced LV function 5. Severely reduced renal function 6. Pregnant or breastfeedingAny other clinical condition which, in the opinion of the principal investigator, would not allow safe completion of the protocol and safe administration of the investigational products
Consent	<p>The consent form was electronically sent to the patient and signed online, during telemedicine call or presently when the first evaluation was done in the emergency room.</p> <p>Control group consisted of patients that refused and did not sign the informed consent.</p> <p>All patients were informed that the efficiency (sic) of AZ and HQC in treating COVID-19 remains to be determined. They were also informed about the safety profile of the drugs and their potential side effects.</p>	

Source: Produced by the authors using the referenced documents.¹¹⁷

scientific validity of the study soon after the results were released,⁶³ and highlighted the following problems: (1) lack of randomization, which, as we have seen, resulted in significant differences between the experimental and control groups; (2) inadequate control group; (3) open label; (4) the use of subjective diagnostic criteria and biased measurements; (5) violations of the inclusion and exclusion criteria; (6) large differences in the drugs included in the Covid-Kit, and (7) data manipulation.

It was the patients themselves who chose, or were led, to be part of the treatment group. The control group, on the other hand, was composed of those who supposedly refused to take the “early

treatment”. Experts considered that the study was inadequately controlled because it did not use a placebo, which would have been appropriate since there was no proven effective drug to treat or prevent COVID-19. Being an open label (unblinded) study, both investigators and participants could affect the implementation and the results of the study by influencing treatment adherence or the reporting of results, which in this case included subjective impact measures, or by altering the analysis plan and ultimately biasing the results.

The primary endpoint was the need for hospitalization, and it was assessed remotely (telemedicine). The researchers did not confirm the diagnosis for COVID-19, but rather they recruited elderly patients with flu-like symptoms. Although some patients were swabbed and underwent chest CT scans, these tests were not performed in a standardized manner, as it is unclear whether they were obtained before, during, or after the research.

⁶³Pasternak, N., & Orsi, C. (2020, April 18). Uma aula de como não se deve testar um medicamento. *Questão de Ciência*. Retrieved March 16, 2022, from <https://www.revistaquestaodeciencia.com.br/questao-de-fato/2020/04/18/uma-aula-de-como-nao-se-deve-testar-um-medicamento>

The study did not respect the inclusion and exclusion criteria. According to Prevent Senior's unpublished article and ClinicalTrials.gov, patients with certain health conditions, including some cardiovascular problems, should have been excluded. HQC and AZ are generally safe and widely used, but they have a multitude of adverse effects that can increase the risk of heart problems or death.⁶⁴ However, research participants' cardiovascular conditions were not assessed prior to enrolling them in the intervention. According to the CPI of the Pandemic report, the lawyer representing doctors who denounced Prevent Senior stated that the medical practice at the company was to prescribe HQC even without performing an electrocardiogram, therefore without evaluating the QT interval.⁶⁵ It should be noted that hypertension is associated with prolonged QT interval⁶⁶ and 26.5% of the participants who took these drugs had a history of hypertension. In addition, hepatitis and neutropenia are clinical manifestations of COVID-19, and liver and bone marrow dysfunctions can be aggravated by the off-label use of these drugs.⁶⁷

Moreover, the content of the Covid-Kits delivered to the homes of Prevent Senior customers was not always the same. Bruna Morato, in testimony to the CPI, said that "it got to such a pitiful point, in my opinion, that this kit was composed of eight items" including ivermectin.⁶⁸

The dossier submitted to the CPI of the Pandemic by doctors working for Prevent Senior shows that the company manipulated patient data, including omitting the cause of death in the medical records of people treated with the so-called Covid-Kits, so that the hospital discharge rates and COVID-19 mortality rates would be favorable to the intervention.⁶⁹ The study authors only mentioned two deaths in the treatment group as unrelated to the drug and to COVID-19, but it has been reported that at least 9 patients died during the research project.⁷⁰ Of these, 6 were in the treatment group, two were in the control group, and there was one patient whose group was not identified.⁷¹ The coordinator of CONEP, Jorge Venâncio, affirmed that some of the deaths that occurred during the implementation of the research protocol were not reported,⁷² as required by the Brazilian regulations.⁷³

This dossier reported that two days after the release of the scientific article at the press conference, Rodrigo Esper, director of Prevent Senior

and first author of the study, sent an audio message to a group of doctors at Prevent Senior providing guidance on how to review the data of the 636 participants,⁷⁴ implying that such data had not been reviewed in depth prior to reporting the results to the media. In the audio, Esper states that the data needs to be "assertive" and "perfect" so that there are no disputes:

[...] we need to review this data by tomorrow at the latest, including all patients, [...] we are reviewing all 636 patients in the study. We already have about 140 reviewed, but we need the taskforce to finish this by tomorrow. We need to look at everything. If there was electro (electrocardiogram) or not, if there was alteration in the QT interval or not, if the Covid swab was done yes or no. [...] and then we will establish the criteria and we will think about the table, and we will establish the criteria, and everyone will collect the data, and with about six people, it is like 100 patients each, [...] but the data must be assertive and perfect, because the world is looking at us, ok? This data will change the trajectory of medicine in the coming months in the entire world, okay? I contacted Didier Raoult yesterday, he mentioned our work on Twitter, I answered him, and so we need to be perfect, the data need to be perfect, okay? Even the President of the Republic quoted us. This audio must stay here, it cannot leave. So, let's meet at five o'clock today, in a videoconference, everybody, so we can adjust the screws and everybody will speak the same language and will have a perfect overview of the data⁷⁵.

The results of the study were revealed prior to being subjected to scientific scrutiny. The study was described in a PDF document in the form of an article,⁷⁶ and was not published in a peer-reviewed scientific journal. Instead of reporting the results in scientific circles, Prevent Senior released its findings at a press conference.⁷⁷ To date, no articles from Prevent Senior have been published in a peer-reviewed journal.

3 | MORE ETHICAL PROBLEMS

3.1 | Informed consent and pressures on doctors

Prevent Senior's leaked article claimed that the consent of the participants had been obtained, but throughout 2020 there were a

¹¹⁷CONEP (op. cit. n. 50). Available at: <https://plataformabrasil.saude.gov.br/login.jsf> [Accessed 16 March 2022] Azidus (op. cit. n. 51). Available at: <https://clinicaltrials.gov/ct2/history/NCT04348474?A=1%26B=2%26C=merged#StudyPageTop> [Accessed 16 March 2022] Esper, Silva, Oikawa, Castro, Razuk-Filho (op. cit. n. 17)

⁶⁴Kalil, A. C. (2020). Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. *JAMA*, 323(19), 1897–1898. doi:10.1001/jama.2020.4742

⁶⁵Senado Federal, op. cit. note 13, p. 934.

⁶⁶Festa, A., D'Agostino, R., Rautaharju, P., Mykkanen, L., & Haffner, S.M. (2000). Relation of systemic blood pressure, left ventricular mass, insulin sensitivity, and coronary artery disease to QT interval duration in nondiabetic and type 2 diabetic subjects. *American Journal of Cardiology*, 86(10), 1117–1122. [https://doi.org/10.1016/S0002-9149\(00\)01170-X](https://doi.org/10.1016/S0002-9149(00)01170-X)

⁶⁷Kalil, op. cit. note 64, pp. 1897–1898.

⁶⁸Senado Federal, op. cit. note 13, p. 934.

⁶⁹Senado Federal, op. cit. note 13.

⁷⁰Balza, G. (2021, September 16). EXCLUSIVO: Prevent Senior ocultou mortes em estudo sobre cloroquina, indicam documentos e áudios. *Globo News e G1*.

⁷¹Ibid.

⁷²Estadão, op. cit. note 55.

⁷³Conselho Nacional de Saúde, op. cit. note 53.

⁷⁴Balza, op. cit. note 70.

⁷⁵Ibid.

⁷⁶Esper, Silva, Oikawa, Castro, Razuk-Filho (op. cit. n. 17)

⁷⁷Desidério (op. cit. n. 39) Giulia Granchi. (2020, April 17). Estudo da Prevent aponta menos internações para quem usou hidroxilcloroquina. *VivaBem*. Retrieved from <https://www.uol.com.br/vivabem/noticias/redacao/2020/04/17/estudo-da-prevent-aponta-menos-internacoes-para-quem-usou-hidroxilcloroquina.htm>

significant number of accusations that company hospital doctors were encouraged, even forced, to prescribe the so-called Covid-Kit or face dismissal.⁷⁸ Bruna Morato, the lawyer representing 12 doctors who denounced Prevent Senior, said:

He [the doctor] didn't have the autonomy to remove this item [ivermectin]. And the doctors on duty, at least as they explained it to me, took the kit and gave it to the patients saying: "Look, I have to give it to you, because if I don't give you this kit, I can be fired; but my advice to you is that if you are going to take anything from here, take only the proteins or the vitamins. Because the other drugs, in addition to not being effective, are very dangerous for this specific population."⁷⁹

There were also serious failures in obtaining informed consent, because the company instructed physicians not to inform patients and their families that they were taking part in a research project and were being treated with HQC and AZ.⁸⁰

There were also problems obtaining the informed consent from the control group. The leaked article stated that "The control group was composed of the patients who refused and did not sign the informed consent to receive HQC and AZ".⁸¹ In other words, the data of the control group participants were used without their consent.

It should be noted that the research participants were elderly persons with flu-like symptoms compatible with COVID-19. They were, therefore, people of greater vulnerability. In that regard, the lawyer representing doctors at Prevent Senior, Bruna Mendes Dos Santos Morato, in testimony to the CPI of the Pandemic said:

Because, you see, the elderly patient is extremely vulnerable. So, for them to understand what was happening, the doctor would tell the elderly patient that there was a good treatment that was going to start being used - that patient was the telemedicine patient. They would tell the patient, "Look, you are going to go through a treatment. It is a very effective treatment; it is a new treatment. If you want to participate in this treatment, you must give the o.k.". And they would give this o.k., but they are a vulnerable population. They didn't know they were going to be guinea pigs; they knew they were going to get a drug. These are different things.⁸²

All indications are that, in addition to not obtaining informed consent, the physicians in the study appear to have deliberately led participants to believe that they were receiving treatment, reinforcing the therapeutic misconception,⁸³ in violation of current ethical standards.

The qualifications of the physicians involved and whether they had completed a course on good clinical practice and research ethics, as required by national and international regulations, are unknown. The testimony of one of the authors of the leaked article, Fernando Teiichi Costa Oikawa, clinical director of Prevent Senior, indicates that authorship rules were violated. Oikawa said that his name appears on the document because the patients observed were from telemedicine - the area in which the doctor worked, but he did not participate in the research project.⁸⁴

4 | CONSEQUENCES OF THE PREVENT SENIOR STUDY

Despite the lack of scientific integrity, the Prevent Senior study had an impact on public health in Brazil. The prescription of medicines at the onset of the symptoms compatible with COVID-19, without confirming the diagnosis, became public policy.

On May 20, 2020, the official MOH protocol for treating COVID-19 patients was released (39) and was very similar to the protocol used in the Prevent Senior study: the same dosages of HQC (D1: 400 mg 12/12 h = 800 mg, D2 to D5: 400 mg 24/24 h) + AZ (500 mg 24/24 h) for 5 days. The only difference was that the Prevent Senior had treated patients with HQC during two additional days.⁸⁵

The CFM opinion 4/2020 and the Prevent Senior study constituted the basis for the "Health Ministry Guidelines for early drug management of patients diagnosed with COVID-19".⁸⁶ Moreover, the text of the MOH guidelines includes excerpts from CFM opinion. In June 2020, the WHO dropped the HQC arm of the Solidarity trial and on June 15, 2020 the US FDA revoked the emergency use of chloroquine to treat COVID-19.⁸⁷ In contrast, the Brazilian MOH expanded the use of HQC and AZ to treat children and pregnant women on June 18, 2020.⁸⁸

In December 2020, the WHO made a strong recommendation against the use of HQC in patients with COVID-19, regardless of

⁷⁸Nathalia Galvani. (2021, September 28). Advogada diz que médicos da Prevent eram obrigados a prescrever Kit-Covid. *Estado de Minas*. Retrieved March 16, 2022, from https://www.em.com.br/app/noticia/politica/2021/09/28/interna_politica,1309631/advogada-diz-que-medicos-da-prevent-eram-obrigados-a-prescrever-kit-covid.shtml

⁷⁹Senado Federal, op. cit. note 13, p. 935.

⁸⁰Ibid: 931

⁸¹Esper, et al., op. cit. note 17, p. 10.

⁸²Senado Federal, op. cit. note 13, p. 929.

⁸³Henderson, G. E., Churchill, L. R., Davis, A. M., Easter, M. M., Grady, C., Joffe, S., Zimmer, C. R. (2007). Clinical trials and medical care: Defining the therapeutic misconception. *PLoS Medicine*. 4(11), 1735–1738. <https://doi.org/10.1371/journal.pmed.0040324>

⁸⁴Câmara Municipal de São Paulo. (2021, November 18). Ex-médica da Prevent Senior afirma que havia orientação para prescrição do Kit Covid. Retrieved March 16, 2022, from <https://www.saopaulo.sp.leg.br/blog/ex-medica-da-prevent-senior-afirma-que-havia-orientacao-para-prescricao-do-kit-covid/>

⁸⁵Prazeres, L. (2021, September 23). Ministério da Saúde citou Prevent Senior em recomendação de 'kit covid'. *BBC News Brasil*. Retrieved March 16, 2022, from <https://www.bbc.com/portuguese/brasil-58670735>

⁸⁶Ministério da Saúde, op. cit. note 47.

⁸⁷U.S Food and Drug Administration. (2020). Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. *FDA News Releases*. 1–2. Retrieved March 16, 2022, from <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and>

⁸⁸Agência Saúde. (2020). Ministério da Saúde amplia orientações para uso da cloroquina.

severity.⁸⁹ In February 2021, a Cochrane review concluded that HQC has no clinical benefit in the treatment of COVID-19; on the contrary, compared to placebo it triples the number of adverse events, although few of them are serious⁹⁰. In March 2022, the website of the Brazilian MOH included its COVID-19 early treatment guidelines, which still includes HQC.⁹¹

Although we have not discussed the role of the CFM in this article, the final report of the CPI of the Pandemic mentions that “[...] the opinion of CFM 4/2020 served as the basis for many of the actions taken by the Federal Executive, which practically throughout the pandemic defended and prioritized the early treatment with HQC + AZ as the main tool to combat COVID-19”.⁹² The CFM report, in light of the uncertainty about the efficacy and safety of COVID-19 treatments, based its recommendation on the principle of medical autonomy, and stated that physicians who prescribe the ineffective drugs for COVID-19 patients will not violate ethics principles, “the Council transferred the responsibility for prescribing these drugs to physicians, even though they were aware of the ineffectiveness of the treatment”.⁹³ The report also points out that:

The concept of physician's autonomy, noble in its original sense, was transformed by the opinion of the Council signed by its president, who assumed the duties of rapporteur, granting doctors permission to do anything, especially providing the early treatment defended by President Jair Bolsonaro without any scientific basis. In the specific case of Prevent Senior, such autonomy served as justification for encouraging the widespread use of early treatment.⁹⁴

Mauro Ribeiro, President of CFM, who in a video shared by Jair Bolsonaro classified the CPI as “toxic and shameful”,⁹⁵ confessed in another video that the CFM 4/2020 opinion was adopted improperly: “We, in an unusual decision, quite outside of our standards, ended up unleashing the use of HQC”.⁹⁶ In a new video, the Vice -President of the CFM, Emmanuel Fortes, said that those who do not prescribe HQC would have more problems than those who do: “We have to tell those who prescribe [chloroquine] that their safeguard is much greater than that for those who do not prescribe it”.⁹⁷ Emmanuel Fortes appears with two other CFM counselors in a third video that

discusses the legal basis for the prescription of HCQ and strategies to promote it.⁹⁸ In the latter, the counselors admit, amid laughter, that they are going against the medical code of ethics, therefore acting criminally, as described in this excerpt:⁹⁹

“This cannot be made public, among other things because I am in charge of Codame, [the area that disciplines medical advertising and publicity in Brazil]. I myself wrote what I can't do”, said the CFM's third vice-president.

“And you have to be very careful with your words. Stop and think, I am here, Doctor Emmanuel, Doctor Annelise, Doctor Graziela... There are people from the Council here and this would generate an even bigger problem. Just imagine, us, involved [in the promotion of chloroquine]?”, said another CFM Counselor.

The CFM position of allowing the off-label prescription of drugs for COVID-19 cases became increasingly obsolete as time passed and new robust papers showing the ineffectiveness and harmful effects of HQC and AZ for COVID-19 were published. However, the CFM top leadership was filled with names linked to Bolsonarism,¹⁰⁰ and there is no doubt that they defended “early treatment” to avoid contradicting Jair Bolsonaro. Maintaining the ideological alignment of CFM managers with Bolsonaro's ideology has led to sustaining the CFM opinion until today (March 2022), which serves as a legal safeguard for Prevent Senior using the Covid-Kit and the prescription of ineffective drugs against SARS-CoV2 by private health plans such as Hapvida, Unimed, Prevent Senior, and even the Ministry of Health itself.¹⁰¹

In addition, Prevent Senior intended to generate an impact and change the company's public image by revealing the results of the study in a press conference. This strategy backfired due to the quality of the study and the ethical problems unveiled in the aftermath of the release. When CONEP interrupted the study, Prevent Senior reappeared in the media and was accused of research fraud and other questionable practices. However, the ties to Bolsonarism remained, and those who insist on “early treatment” continue to pave the way for the Federal Government and Prevent Senior's decisions. A major symbol of the Government's commitment to early treatment and off label use of drugs for COVID-19 treatment was Bolsonaro's

⁸⁹World Health Organization. (2020). Therapeutics and COVID-19. *Living Guideline*. (17 December). Retrieved March 16, 2022, from <https://apps.who.int/iris/handle/10665/337876>

⁹⁰Singh, B., Ryan, H., Kredt, T., Chaplin, M., & Fletcher, T. (2021). Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database of Systematic Reviews*. 2021(2). <https://doi.org/10.1002/14651858.CD013587.pub2>

⁹¹Ministério da Saúde, op. cit. note 47.

⁹²Senado Federal, op. cit. note 13, p. 150.

⁹³Ibid.

⁹⁴Ibid: 897.

⁹⁵Bolsonaro, J. M. (2021). O Presidente do CFM (Conselho Federal de Medicina), Dr. Mauro Ribeiro, classifica a CPI como tóxica e vergonhosa. Retrieved March 16, 2022, from <https://fb.watch/bNYyQj4v1A/>

⁹⁶Metrópolis. (2021). Investigado pela CPI, presidente do CFM disse em live que órgão apoia @jairbolsonaro. Retrieved March 16, 2022, from <https://twitter.com/Metropoles/status/1446491070184009732?s=20>

⁹⁷The Intercept Brasil. (2021). Vice-presidente do CFM fala sobre a prescrição da cloroquina em reunião do gabinete paralelo. Retrieved March 16, 2022, from https://www.youtube.com/watch?v=le-Yc8N_kY

⁹⁸The Intercept Brasil. (2021). Conselheiros do CFM defendem cloroquina no gabinete paralelo. Retrieved March 16, 2022, from <https://www.youtube.com/watch?v=z91YrNJRn1I%26t=3s>

⁹⁹Frente Pela Vida. (2021). Frente pela Vida cobra apuração criminal dos atos praticados pelos conselheiros do Conselho Federal de Medicina. Rio de Janeiro. Retrieved March 16, 2022, from https://www.abrasco.org.br/site/wp-content/uploads/2021/10/nota_video_CFM_final.pdf

¹⁰⁰JUCÁ, B. (2021, October 15). Como o Conselho de Medicina silenciou diante do negacionismo de Bolsonaro e abraçou a cloroquina. *El País Brasil*.

¹⁰¹Caponi, et al., op. cit. note 10, pp. 78–102.

speech at the opening of the UN General Assembly on September 21, 2021:

Since the beginning of the pandemic, we have supported physician's autonomy in prescribing early treatment, following the recommendation of our Federal Council of Medicine. I myself was one of those who received early treatment. We respect the doctor-patient relationship in deciding the medication to be used, even off-label use.¹⁰²

Currently, in addition to the investigation conducted by the CPI of the Pandemic at the Federal level, Prevent Senior continues to be investigated on different fronts: a criminal investigation filed by the Public Prosecutor's Office and the State Department of Homicide and Personal Protection of the Civil Police of São Paulo; an administrative investigation of Prevent being carried out by a CPI of the City Council of São Paulo; a labor investigation by the Public Prosecutor's Office of Labor; and a civil investigation by the Federal Public Prosecutor's Office of São Paulo.¹⁰³

5 | DISCUSSION

At the onset of the COVID-19 pandemic, the unprecedented health threat and uncertainty about appropriate treatments, using different interventions in clinical practice and in patient care could have been justified under Article 37 of the Helsinki Declaration.¹⁰⁴ Considering that HQC and AZ are inexpensive and easily available, and their general side effects are well-known, a well-designed observational study would be considered acceptable. Prevent Senior's proposal had value, so much so that CONEP approved the research protocol. However, Prevent Senior's research intended to evaluate the efficacy and safety of these drugs, and could only have been achieved by conducting a robust multicenter, double-blind, placebo-controlled clinical trial.

Given the level of emergency and the ambiguity surrounding the possible containment of COVID-19, and treatment methods, it is easy to understand CONEP's decision to approve the study. However, the flaws evidenced during its implementation highlights the need for regular and closer oversight of approved protocols, especially those that might be of high risk to the participants.

What cannot be accepted is that, despite it being a methodologically weak observational study, with significant implementation problems, Prevent Senior emphatically concluded that the "empirical treatment" for COVID-19 with HQC and AZ led to "a strong decrease in the need for hospitalization" when prescribed during the first days of symptoms.¹⁰⁵ Only the lack of scientific rigor and integrity, such as

the "making up" of information,¹⁰⁶ could have led them to that conclusion. One could easily conclude that the company did not design this study to advance science, but to improve its image and ingratiate itself with the Bolsonaro government, which, at a time, was in the crosshairs of criticism and investigations.

Analyzing the risk-benefit ratio of this study is crucial to understanding the seriousness of the case. Although Prevent Senior's research design was based on a potential benefit to participants and society, it was not without risks. COVID-19 patients treated with HQC had three times more side effects than the placebo group.¹⁰⁷ AZ and the other drugs included in the Covid-Kit cause other side effects, and presumably, some the elderly users did not even have COVID-19.

The undue positive publicity of the Covid-Kit provided a false sense of security to the Brazilian society, and many might have taken greater risks believing that there was an effective early treatment. This was exactly what the Bolsonaro government intended:

There is no point in running away from it, running away from reality. We must stop being a country of sissies. [We have to face it with all our energies, ready to fight. What kind of generation is this one?]

We are facing a real problem: the virus is there. We have to face it, but face it like a grown man, not like babies. Let's face the virus for what it really is. It is life. All of us will die one day.¹⁰⁸

These lines from the Brazilian President's speech, besides being sexist and homophobic, go against the restrictions on mobility recommended by the WHO and other experts. Unfortunately, the endorsement of Prevent Senior's study, the support of CFM and the successive changes at the helm of the MOH generated an "environment of tranquility and serenity in Brazil".¹⁰⁹ All this might have worsened the effects of the pandemic. The mortality from these drugs could be considered low, but many people infected with COVID-19 might have taken these drugs without seeking health services in a timely manner. Or, they might have reduced their adherence to effective protective measures, such as wearing a mask or social distancing. Data from the "DETECTCoV-19" study showed that SARS-CoV-2 infection was 50% higher among those who self-medicated with prophylaxis for COVID-19 (25% of the study sample) and supports this thesis.¹¹⁰ Still, most municipalities that supported

¹⁰⁵Esper, et al., op. cit. note 17, pp. 16–17.

¹⁰⁶Russo, M. (2014). Ética e integridade na ciência: Da responsabilidade do cientista à responsabilidade coletiva. *Estudos Avancados*. 28(80), 189–198. <https://doi.org/10.1590/S0103-40142014000100016>

¹⁰⁷Singh, et al., op. cit. note 90.

¹⁰⁸BBC News Brasil. (2020, November 11). Coronavírus: 'país de maricas' e outras 8 frases de Bolsonaro sobre pandemia que matou 162 mil pessoas no Brasil. *BBC News Brasil*. Retrieved March 16, 2022, from <https://www.bbc.com/portuguese/brasil-54902608>

¹⁰⁹Bolsonaro, op. cit. note 38.

¹¹⁰Lalwani, P., Salgado, B. B., Filho, I. V. P., da Silva, D. S. S., de Moraes, T. B. do N., Jordão, M. F., ... Lalwani, J. D. B. (2021). SARS-CoV-2 seroprevalence and associated factors in Manaus, Brazil: baseline results from the DETECTCoV-19 cohort study. *International Journal of Infectious Diseases*. 110, 141–150. <https://doi.org/10.1016/j.ijid.2021.07.017>

¹⁰²Senado Federal, op. cit. note 13, p. 63.

¹⁰³Leite, I. (2022, February 10). Caso Prevent Senior: investigações dependem de novos depoimentos, laudos e documentos para serem concluídas neste ano. *GloboNews*.

¹⁰⁴World Medical Association, op. cit. note 52.

Bolsonaro, where science denialism among the population was strongest, had the worst COVID-19 mortality rates.¹¹¹ And perhaps this explains why Brazil was among the ten countries in the world with the highest COVID-19 mortality rate (per million inhabitants),¹¹² at least until before the launch of vaccination in the country.

The emergence of COVID-19 was followed by a flurry of low-quality studies that were justified by the idea that a health crisis requires exceptions and action needs to be taken before science can recommend the best quality standards supported by scientific studies that respect research ethics principles.¹¹³ This appears to have been the thinking of the authors of the study, who justified the proposed protocol as "It was implemented in a special context".¹¹⁴ CFM used the same argument when affirming that their opinion took into account "the exceptionality of the situation during the declared period of the pandemic".¹¹⁵

Finally, although the conduct of the Senate CPI has been criticized, its initiative and extensive and exhaustive investigative work must be commended. It unveiled the strategies of the Bolsonaro government that ended up increasing the spread of COVID-19 in Brazil and contributed to the regretful number of more than 650,000 COVID-19 deaths in Brazil.¹¹⁶ The CPI was conducted by a political entity, and it had its limits, but it managed to produce a report that names those who should be subject to a criminal investigation procedure. However, there could be many other developments that will need to be researched in future studies. It is the role and obligation of competent bodies to hold to account those responsible for these abuses.

6 | CONCLUSION

The case of the Prevent Senior's scientific fraud and its political-ideological bias is an unfortunate chapter in a recent history of transgression of ethics and integrity of research in Brazil. For Prevent Senior, the fallacy of "early treatment" was a strategy to improve the company's image and for the Federal Government it was a populist measure to avoid supporting social distancing.

The urgent need to respond to a pandemic, far from serving as an excuse to conduct research of low scientific and ethical quality, increases the responsibility of those involved in research. After all, even in case of emergencies, science and ethics should guide the

actions required to reduce uncertainties in decision-making and to avoid using human beings as guinea pigs.

It is necessary to learn from the experiences of this pandemic. There is a need to boost public institutions and their accountability, by strengthening the National Health Council and its National Research Ethics Evaluation System (Sistema CEP/CONEP). The entire health system needs to embrace research ethics, so that future atrocities can be avoided, and in future pandemics the decisions that affect the lives of thousands of people are more prudent and scientifically sound.

CONTRIBUTIONS

Fernando Hellmann wrote the first and subsequent versions of the manuscript. Núria Homedes revised and commented on the first and subsequent versions of the manuscript. Both authors approved the final version.

FUNDING

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to disclose.

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¹¹¹Xavier, D. R., Silva, E. L. e., Lara, F. A., Silva, G. R. R. e., & Oliveira, M. F. (2022). Involvement of political and socio-economic factors in the spatial and temporal dynamics of COVID-19 outcomes in Brazil: A population-based study. *The Lancet Regional Health - Americas*, 1–16. <https://doi.org/10.1016/j.lana.2022.100221>

¹¹²Ritchie, H., Mathieu, E., Rodés-Guirao, L., Appel, C., Giattino, C., Ortiz-Ospina, E., et al. (2020). Coronavirus Pandemic (COVID-19). Retrieved March 16, 2022, from <https://ourworldindata.org/coronavirus>

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¹¹⁴Conselho Federal de Medicina, op. cit. note 42, p. 15.

¹¹⁵Ibid.

¹¹⁶Ventura, D. de F. L., Aith, F. M. A., & Reis, R. R. (2021). The timeline of the Federal Government's strategy to spread Covid-19. São Paulo. Retrieved March 16, 2022, from <https://cepedisa.org.br/wp-content/uploads/2021/08/LexAtlas-C19-Brazil-The-Timeline-of-the-Federal-Governments-Strategy-to-spread-Covid-19.pdf>.

How to cite this article: Hellmann, F., & Homedes, N. (2022). An unethical trial and the politicization of the COVID-19 pandemic in Brazil: The case of Prevent Senior. *Developing World Bioethics*, 1–13. <https://doi.org/10.1111/dewb.12363>