Note from the Brazilian Society of Bioethics and the entities listed below in REPUDIATON to the damages to participants for non-compliance with ethical standards in research that used the drug proxalutamide and in SUPPORT of the National Health Council-CNS/CONEP for the investigation of the facts by the Brazilian Attorney General's Office (PGR)

The Brazilian Society of Bioethics, the Brazilian Association of Collective Health (Abrasco), the Brazilian Center for Health Studies (Cebes), the United Network, the Brazilian Association of Physicians and Physicians for Democracy (ABMMD) and the National Network of Physicians and Popular Physicians STRONGLY REPUDIATE the conduct of research involving human beings[1], with non-compliance with ethical requirements emanated from the CNS Resolution 466/2012, which included unauthorized modifications to the protocol and to the Informed Consent Form initially approved.

The fact on screen, detailed in the CNS Public Note [2] and in the CONEP's representation [3] to the PGR, filed on September 3, 2021, refers to the double-blind trial with Proxalutamide, a nonsteroidal antiandrogen, initially developed for the treatment of breast and prostate cancer and not registered for other uses, in patients severely affected by SARS-CoV 2 infection.

The entities associate themselves with CONEP's representation to the PGR "*for the investigation of 200 reported deaths, as well as, in that case, any other causes that lead to damages resulting* from the research in comment."

THEY also SUPPORT CONEP's decision to permanently suspend the study due to "the presence of evidence of *irregularity*" in its conduct, *"to protect the dignity and other guarantees of the participants of said research".*

Considerations on this note are as follows:

For scientific proof of any therapeutic measure, it is necessary to conduct clinical trials scientifically and ethically approved. It should be reiterated that the Brazilian guidelines related to ethics in research involving human beings (Resolution CNS 466/2012) are exemplary in the defense of the rights of participants[4] and require that all research to be initiated, must be first evaluated, and approved by an institutional Research Ethics Committee (CEP), part of the CEP/CONEP system. Both CNS and the Brazilian Medical Ethics Code (2019) still require that the patient/participant has the right to receive clear and adequate information, based on scientific evidence, to decide on procedures or medications prescribed to him/her. [5]

[1] Proxalutamide for patients hospitalized by COVID-19. The Proxa-Rescue AndroCoV Trial, registered nthe Brazil Platform under the number CAAE 41909121.0.0000.5553.

2 PUBLIC NOTE: CNS elucidates to Brazilian society facts about an irregular study with proxalutamide-15 2021 http://conselho.saude.gov.br/ultimas-noticias-cns/2095-nota-publica-cns-elucida-a-sociedade-brasileira-fatos-sobre-estudo-irregular-com-proxalutamida

3 Oficio 829/2021/CONEP/SECNS/MS on the research project "Proxa-Rescue AndroCoV Trial" http://conselho.saude.gov.br/ultimas-noticias-cns/2095-nota-publica-cns-elucida-a-sociedade-brasileira-fatos-sobre-estudo-irregular-com-proxalutamida

4 CNS Resolution 466/2012 - https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf

5 Code of Medical Ethics 2019 - CFM Resolution No. 2,217 of September 27, 2018, as amended by CFM Resolutions No. 2,222/2018 and 2,226/2019 - https://portal.cfm.org.br/images/PDF/cem2019.pdf

The project, *The Proxa-Rescue AndroCoV Trial*, initially approved by CONEP, was a double-blind study, aiming at recruiting a defined number of possible participants, with a free and informed Consent Form with clear information about all the details of the research and to be carried out in a single research center.

The Public Note of the National Health Council (October 15, 2021) and the representation to the PGR point to violations of the rights of participants in the various stages of the study, including an increase in the number of participants, the unauthorized expansion to other research centers and the non-clarification of the cause for a large number of participants who died during the project.

It is unacceptable unauthorized expansion to other research centers, and it must be noted the inclusion of Manaus in the study, a city with a population already very vulnerable in its sanitary condition, with insufficient ICU beds, shortage of medicines and especially hit by the lack of hospital oxygen for severe cases.

It is also unacceptable the decision to increase the number of participants, which was only requested to CONEP when the study was already completed. And, furthermore, the disclosure that the necessary independent scientific committee to monitor the study included people linked to the sponsors, which, at the very least, characterizes conflict of interest.

However, the most serious fact is related to the death of 200 participants, and the researcher's decision to maintain recruitment and continuation of the study with the use of proxalutamide or placebo despite knowledge of increasing number of serious adverse effects and deaths. From an ethical standpoint, it is mandatory to open the blinding and immediately communicate to CONEP, when there is an occurrence of excess deaths. This is to verify whether the deaths were occurring due to the use of the experimental drug itself or, if concentrated in the control group these participants would be harmed without benefiting from the supposed efficacy of the drug under test. CONEP was not notified, and blinding opening never occurred during the research and thus, if proxalutamide would have been effective (as claimed by the researchers), the fact is that people were PASSIVELY seen to die without adoption of the appropriate measures described above

In summary, the known facts, detailed by the CNS and by CONEP clearly show situations of disrespect to the National and International guidelines on human research ethics and the Brazilian Code of Medical Ethics.

Agreeing with the CNS, which stated that "Throughout *the history of the National Health Council, there* has never been such disrespect in the country to ethical standards and research participants" and with a recent manifestation of *the Red Latinoamericana y del Caribe de Bioethics,* this episode can be characterized as one of the most serious attacks on the human rights of participants in research, involving the suspicious death of 200 people. It is worth adding that these facts also point to the disrespect to the directives of UNESCO's Universal Declaration of Bioethics and Human Rights (UDBHR)[6], to which Brazil is a signatory. The UDBHR proclaims the protection of Human Dignity and Human Rights, the indispensability of Consent, the protection of Human Vulnerability and Individual Integrity.

We express our support and solidarity with bereaved families and the vehement REPUDIATION of the facts detailed above.

[6] The Universal Declaration of Bioethics and Human Rights (DUBDH) was approved by acclamation in 2005 191 countries present at the General Assembly of the United Nations Educational, Science and Culture - UNESCO, in Paris.

We associate ourselves with the CNS and CONEP in the request for URGENT investigation by the PGR and if confirmed the facts, all those involved including the research team, the participating institutions and sponsors must be held legally accountable, making sure that a conduct like is never repeated.

And it must be EMPHASIZED that there is no health emergency that justifies any disrespect of the dignity and human rights of research participants.

Brasilia, 18 October 2021

Sociedade Brasileira de Bioética
Associação Brasileira de Saúde Coletiva (Abrasco)
Centro Brasileiro de Estudos de Saúde (Cebes)
Rede Unida
Associação Brasileira de Médicas e Médicos pela Democracia (ABMMD)
Rede Nacional de Médicas e Médicos Populares