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SOCIAL CONTROL, TRANSPARENCY, ACCOUNTABILITY AND SCIENTIFIC INTEGRITY IN MEDICAL RESEARCH

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Abstract

The CEP/CONEP System, submitted to social control, is responsible for the ethical approval of research in Brazil to protect research participants. The Informed Consent Form (ICF) is the public document that enforces the protection of participants. This paper presents two cases of medical research in the Amazon region on malaria and the use of chloroquine for treating COVID-19. The participants were uninformed in the ICF on relevant aspects of the two studies, with serious health risks. For the sake of increasing transparency and social control, it is proposed that there should be mandatory publication of the ICF in studies supported by public funds, presentation of an objective summary of the study at the beginning of the ICF, publication of central elements of the protocol of clinical trials in open access Brazilian virtual platforms, and promulgation of a dedicated law to improve scientific and ethical integrity in Brazilian medical research.

Keywords: Ethics, Research. Human experimentation. Informed consent. Consent forms. Formal social control. Scientific Misconduct. Ethics Committees, Research

Introduction

Since the publication of the [Nuremberg Code](#)¹ in 1947, international norms and guidelines for conducting research involving human beings have been consensual in determining respect for the dignity and self-determination of the participants, embodied in the adequate obtaining of free and informed consent. In Brazil, the first three resolutions on the ethical regulation and protection of participants in research involving human beings - [CNS Resolution 01/1988](#)², [CNS Resolution 196/1996](#)³ and [CNS Resolution 466/2012](#)⁴ - primarily regulated biomedical research. They were followed by [CNS Resolution 510/2016](#) for research in the human and social sciences⁵.

In 1996, the National Commission for Research Ethics (CONEP), subordinated to the National Health Council (CNS), was established to coordinate the local activities of Research Ethics Committees (CEP)

nationally, forming the CEP/CONEP System. It is their responsibility to appreciate the research protocol, guided by the principles of impersonality, **transparency**, reasonableness, proportionality and efficiency, aiming to **strengthen the special protection of research participants** and **stimulate popular participation in the social control initiatives** of research involving Human Beings. CNS resolutions - norms of relative imperativeness - regulate it. The CEP/CONEP System imposes **complete secrecy** on research documents for its members - including user representatives - which conflicts with public access to information norms provided in [Law No. 12,527/2011](#), hindering effective social control.

The Free and Informed Consent Form (ICF) is the primary document for the special protection of participants, classified as public by [CNS Operational Norm 001/2013](#), clarifying the purpose, procedures and foreseeable risks and benefits⁶ to potential participants. Clinical studies display an apparent asymmetry between researchers - who draft the protocol and ICF - and participants, mainly if conducted in Brazilian Unified Health System (SUS) patients with aggravated or enhanced vulnerability. After reviewing two paradigmatic cases, focusing on ICFs applied to vulnerable populations in the northern region of Brazil, this article advocates for greater transparency and the expansion of social control, with proposals for the diffuse empowerment of society and the enhancement of protection for citizens involved in medical research, in line with the central mission of the CEP/CONEP System.

CASE 1: Human baits for mosquitoes in Amapá: A deceptive ICF from the CEP/CONEP System with payment to quilombolas and sending blood samples abroad with foreign funding in 2003^{7,8}

From 2003 to 2005, a group of ten residents from the community of São João do Pirativa, Amapá, participated in the collection and feeding of malaria-transmitting mosquitoes (carapanãs) with their blood in a project with a budget of one million dollars sponsored by the University of Florida (U.F.) and the United States National Institutes of Health, in collaboration with Fundação Oswaldo Cruz (FIOCRUZ). The community's inhabitants were quilombolas (descendants of runaway slaves), with an average monthly family income of R\$300.00 (approximately 60 U.S. dollars), mainly from fishing and domestic agriculture. There was no basic sanitation. Most adults could barely write their names. The nearest health center was in Santana town, an hour and a half away by boat.

The objective was to "determine whether the type, presence and abundance of mosquitoes can be used to monitor and improve malaria prevention and control," as stated in the ICF. To do so, volunteers would work nine nights a month in 6.5-hour shifts. The ICF, bearing the U.F. emblem on the first page⁹, stated in English that it was "*approved for use*" from 10/16/2003 to 10/15/2004 by the U.F. Health Center's *Institutional Review Board* (IRB), including two paragraphs in English about communication of discomforts or new information obtained during the study, mixed into the Portuguese text. Describing the procedures, it clarified that "you will aspirate mosquitoes (those responsible for malaria transmission) from an exposed leg; above the knee, before the mosquitoes bite, using a plastic

vacuum cleaner, placing the mosquitoes [in] containers modified to accommodate mosquitoes. The procedure will be done for nine consecutive nights each month. You will be asked as ***a volunteer to feed 100 mosquitoes*** on your arm or leg for mark-recapture studies. This will occur twice during the year." Among the risks, it is described that "***you may contract malaria,***" which could be minimized "if you have only one leg exposed above the knee, then you **can collect mosquitoes before they bite**", adding that "in the mark-recapture study ***the risk is minimized by allowing feeding of only 100 mosquitoes*** and the use of chemoprophylaxis recommended by the Ministry of Health for this region of Brazil" (emphasis added). Item 10 of the ICF stated that "you will receive a normal salary and participation per day in the study," totaling R\$108.00 per month (R\$12.00 per night of work). The minimum wage in 2003 was R\$240.00. Ten interested individuals quickly signed an "Informed Consent for the Collectors to Participate in the Research". Volunteers who did not meet the goal of capturing the 100 mosquitoes due to pain and intense itching received no payment, which was made against receipt. The ICF was not read to the riverine inhabitants. A one-week course was taught, with theoretical and practical classes on the correct capture and handling of mosquitoes. The same procedures were followed in two other nearby communities.

During the research, **all participants in Pirativa contracted malaria**, in addition to another **twelve** from the two riverside communities, and the spread to other residents was unusual. From 2003 to 2005, FUNASA also stopped spraying repellents in the area to collaborate with the research, going against CONAMA Resolution No. 268/2001, according to a complaint by the Amapá Public Prosecutor's Office, also sent to the Commission on Human Rights and Participative Legislation of the Federal Senate and the CNS. One of the participants had complications from the disease and was hospitalized without receiving medical assistance or compensation.

Blood from quilombolas was sent to the United States in the bodies of 120 female mosquitoes. However, the original project had planned to feed the mosquitoes with blood from domestic animals kept in cages. FIOCRUZ, in an official note, explained that the research protocol approved by its CEP did not mention payment for the study participants or that they would be used as human feeders for the mosquitoes. However, a sentence in the original English text anticipated using volunteers as human feeders¹⁰. After pressure from the Federal Senate and the media, the CNS ordered the research to be halted on 12/14/2005, which was definitively suspended on 02/09/2006 by [CNS Resolution 357](#)¹¹. In addition to requesting the Federal Public Prosecutor's Office to file a compensation lawsuit for the research participants, the CNS recommended that articles with the research results should not be published in scientific journals. In 2013, however, the article was published in [Malaria Journal](#)¹², with the co-authorship of the Brazilian researchers involved, in addition to citing the ethical approval of the project by CONEP (No. 1280/2001). The CNS was notified of this irregularity.

CASE 2: CHLOROQUINE OVERDOSES IN HIGHLY VULNERABLE AND CRITICALLY ILL PATIENTS HOSPITALIZED IN A PUBLIC HOSPITAL FOR THE TREATMENT OF COVID-19: An ICF non-conforming with the research protocol in a clinical trial conducted with public resources in 2020, in the city of Manaus.

The CloroCovid-19 clinical trial was planned in a context of significant scientific uncertainty and apprehension by Brazilian and international health authorities - in addition to abusive politicization - about the efficacy and safety of chloroquine as an antiviral therapy for COVID-19. It was proposed by researchers from the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado and carried out at the Delphina Aziz Hospital (HDA), at the time the exclusive reference for COVID-19 hospitalizations in the Unified Health System (SUS) in Manaus. The technical director of the HDA, a candidate for Ph.D. under the supervision of the Principal Investigator, was the first author of the paper, which the JAMA Network Open later published.

The first aim of the research was to investigate the efficacy and, secondarily, the safety **of chloroquine diphosphate (CQ)** as adjuvant treatment of patients over 18 years of age hospitalized with severe acute respiratory syndrome (SARS) and suspected SARS-CoV-2 infection, to assess whether it would reduce mortality in the study population by 50%, compared to placebo. The research project was electronically inserted into Plataforma Brasil on 03/20/2020 and approved three days later, with immediate admission of participants. In a short time, the control group with placebo was replaced by another therapeutic schema of CQ, less toxic, which would be proposed on 03/27/20 by the Ministry of Health (MoH). An inclusion criterion was also adopted - not described in the [protocol](#) or [article](#) published in JAMA Network Open (JNO) but mentioned in the registration made on the ClinicalTrials.gov database - that would only allow the inclusion of participants with SARS if over 51 years of age or with at least one known risk factor for COVID-19 progression.

The changes in the original protocol were not incorporated into the ICF applied to participants or legal guardians. They led to a change in the primary purpose of the CloroCovid-19 study. Instead of assessing efficacy, the main target became evaluating the safety of two disparate doses of chloroquine in patients with SARS and suspected COVID-19. Chloroquine tablets manufactured by Farmanguinhos/FIOCRUZ were used, with 150 mg chloroquine base equivalent to approximately 250mg of CQ. No exclusion criteria were established. At least 40 vulnerable participants were over 50 years old. Two women were pregnant. Others had severe cardiovascular, liver or kidney diseases - including AIDS and tuberculosis - and all over 75 years old were randomly selected to use the toxic high doses.

Without considering the criterion of clinical equipoise, the participants were randomized into two groups for oral administration of *Farmanguinhos cloroquina* tablets, in addition to the standard therapy defined by the hospital (azithromycin, ceftriaxone and, optionally, oseltamivir). The **high-dose group** received 600mg of chloroquine base (4 tablets) twice daily for ten days (total dose of 12g, equivalent to CQ 20g). The **low-dose group** followed the dosing schedule indicated by the Brazilian

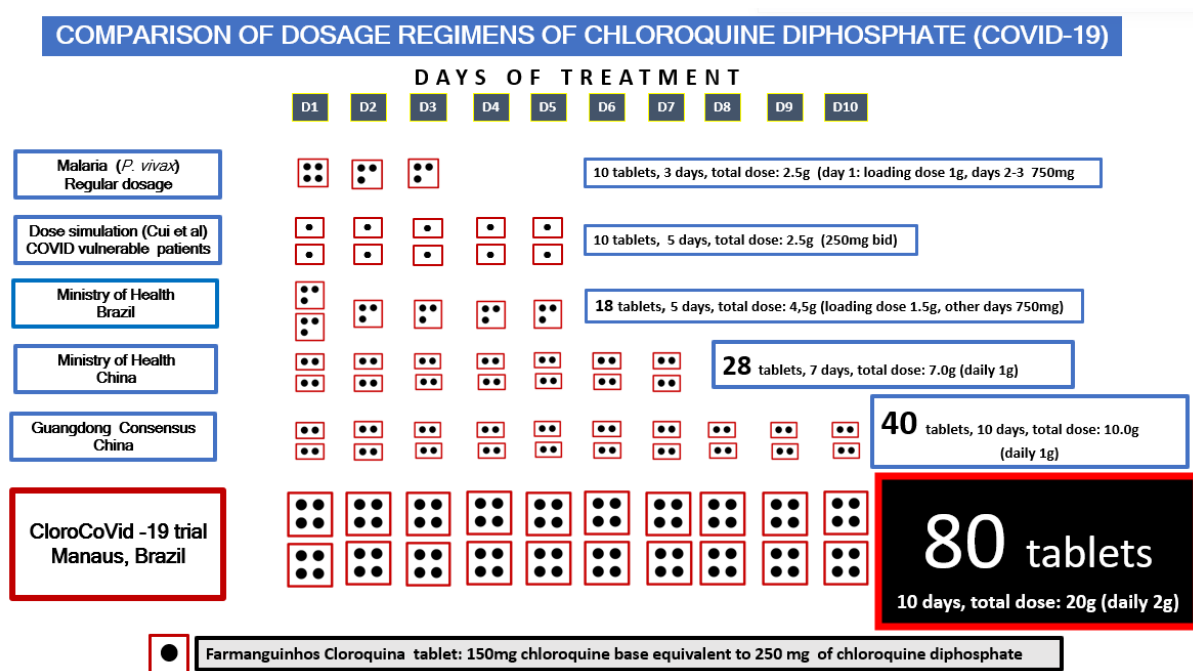
MoH, taking three tablets twice a day on the first day and then only once per day until the fifth day (total dose of 2.7g of chloroquine base or 4.5g of CQ). In [the protocol](#) and [article](#) published in the JNO, the numerical values of the doses were **mistakenly** described as if they were referring to chloroquine base (lower values than those equivalent to chloroquine diphosphate). However, the title directly cited chloroquine diphosphate¹³ as the interventional drug. The protocol was published in English on the [clinicaltrials.gov](#) database. It was not disclosed in Portuguese on the Brazilian Registry of Clinical Trials (ReBEC) platform or submitted to Anvisa, the Brazilian drug regulatory agency.

The authors estimated in the protocol an average annual lethality of 20%. Already in the first week, 7 participants in the high-dose group died against 4 in the other group. In the second week, there were nine more deaths among the 34 survivors in the high-dose group, with an overall lethality rate of 39%, against only two deaths in the other group, which had a 15% lethality rate. Given the significantly higher incidence of adverse events and deaths, the high-dose group was terminated after two weeks, switching to the dose indicated by the MoH to complete the ten days. The primary outcome was absolute death on day 28, and later information showed that 26 patients (63.4%) died in the high-dose group.

The recommended total dose in the *Farmanguinhos cloroquina* [package insert](#) for the treatment of uncomplicated malaria in adults is 25 mg/kg (10 tablets), spread over three days, with a loading dose of 4 tablets on the first day, and then three tablets for two days. The World Health Organization (WHO) recommended 10mg base/kg or 600mg base as the maximum single dose for adults. The ingestion of a single dose of 1,500mg base can be fatal within a few hours, and there is still uncertainty about the safety of CQ in pregnant women. In a [technical note](#) for the use of chloroquine in COVID-19, FIOCRUZ warned of the prohibition of concurrent use with various drugs and the need to verify normal levels of electrolytes (potassium, sodium, chlorine), blood sugar, and liver and kidney function in short-term clinical trials.

The participant in the high-dose group, if completing the study, would have ingested 4.4 times more chloroquine than the total dose recommended by the Brazilian MoH, having taken in the first three days a CQ dose 2.4 times higher than the maximum recommended by [the drug package insert](#) and medical literature. According to the [principal investigator](#) (PI) of the CloroCoVid-19 study¹⁴, the high dose would be similar to that suggested in a publication by the [regional consensus](#) of Guangdong¹⁵, which advised using the attack dose for malaria (600mg base or 1,000mg CQ) divided into two daily doses of CQ 500mg. It was claimed that the dose was increased from 500 to 600mg to avoid partitioning the tablet, even though two tablets of *Farmanguinhos cloroquina* already contained 500mg of CQ. In the CloroCoVid-19 trial, patients in the high-dose group were to receive two loading doses of chloroquine, used to treat malaria, daily for ten days, twice as much as recommended by the Guangdong consensus, as shown in Figure 1. None of the participants in the high-dose group completed the entire 10-day treatment cycle. The error was later acknowledged in an interview by the PI with the journal [Science](#)¹⁶.

Figure 1. Comparison of Dosage Regimens of Chloroquine Diphosphate in Malaria and COVID-19



Sources: Articles published in the literature ([Cortegiani A et al.](#) and [Cui C et al.](#)), Informative Note [No. 05/20](#) of DAF /SCTIE/MS and [Malaria Treatment Guide in Brazil](#).

No prior pharmacokinetic simulation was conducted to choose a potentially effective and safe posologic schema. [A dose-modeling pharmacokinetic study](#)¹⁷, using data from young French people in attempts of suicide with CQ, suggested that the high dose of the CloroCovid-19 study could potentially be lethal on its own. Nineteen patients ingested chloroquine without laboratory confirmation of COVID-19, resulting in three (16%) deaths. In the paper's conclusion, the authors did not recommend the use of high-dose chloroquine combined with azithromycin and oseltamivir to treat very severe cases of COVID-19. The study attracted significant media attention, leading to the early suspension or cancellation of other clinical trials using chloroquine to treat COVID-19, along with [another paper](#) published in *The Lancet* that was quickly retracted for possibly fabricated data¹⁸.

CONEP denied requests for copies of the protocol and the ICF through the Access to Information Law under additional claims of respect for copyright or industrial property. It was also argued that the ICF would be a substantially private document under the custody of CONEP/CNS, contradicting CNS Operational Norm 001/2013. The full ICF was obtained after filing a [writ of mandamus](#) in a pioneering judicial precedent, which has been adjudicated and is now publicly available¹⁹.

The 11-page ICF provided by CONEP/CNS assured that **there would be no complications from using chloroquine in the study** due to the short duration of the treatment, without mentioning the uncertainty regarding its safety for pregnant women and fetuses. It informed that participants would be randomized to receive **either chloroquine or a placebo**, stating in the title that the study would be **placebo-controlled**. It did not inform the patient or legal guardian that two dosage regimens of chloroquine would be tested **in addition** to the conventional hospital treatment for severe acute

respiratory syndrome (SARS) or the concurrent use of other potentially cardiotoxic drugs, which could pose additional risks to participants. It did not include vomiting and diarrhea among the common and uncomfortable effects when describing the risks under the heading "treatment with chloroquine/placebo." It failed to mention that a new dose of CQ would be administered within 30 minutes in case of vomiting or rejection. It did not specify criteria for participant withdrawal after drug intolerance, risking dehydration or severe metabolic disorders, hard to correct in elderly or very debilitated patients. It omitted the predictable incidence of more adverse reactions in one of the groups due to accumulation and the narrow safety margin of chloroquine (Table 1).

Table 1. Inconsistencies between the protocol (version 2.0) and the ICF of the CloroCovid-19 study

Item	ICF	PROTOCOL
Title	Placebo-controlled study	No mention of placebo as a control
Objective	"Evaluate whether the use of chloroquine helps reduce the number of deaths caused by the new coronavirus (COVID-19)."	To evaluate if the therapeutic scheme of group 1 reduces mortality by 50% in the study population compared to group 2.
Interventions	"If you enter the study, you will be randomly assigned to receive either chloroquine or placebo." Use of study drug (chloroquine or placebo) in a dose of four tablets twice a day for ten days orally or by nasogastric tube.	High dose: Chloroquine [Base] 600mg (4 tablets), twice/day for ten days; Low dose chloroquine [Base] 450mg (3 tablets) daily for five days, with loading dose (900mg) on the first day. Use of placebo for study blinding.
Safety	It is a medication used for malaria since 1930 and is safe for use in pregnant women. "The complications of chloroquine are related to the prolonged use of the medication, which will not occur in this study, as the treatment will be carried out over a period of 10 days."	For malaria treatment, few doses are used in safe concentrations. CQ can deposit in tissues, mainly ocular, causing retinal toxicity associated with prolonged use and high doses.
Risks and Adverse Effects	Headache, stomach pain, nausea, itching, changes in your heart, vision, mood and blood test (liver enzymes). "These discomforts are not common, but to minimize them, you will periodically have electrocardiograms and physical and blood tests for follow-up."	Among toxic manifestations, it cites cardiovascular changes (hypotension, vasodilation, myocardial function suppression, cardiac arrhythmias, cardiac arrest), blurred vision, corneal opacity, headache, fatigue, nervousness, gastrointestinal irritation, nausea and vomiting, among others.
Dose Repetition	The ICF does not mention administering a new dose in case of vomiting or rejection by the patient.	"If the patient vomits or rejects the treatment during the 30 minutes, the same dose will be given again. (...) All measures will be taken to ensure that patients receive treatment following the protocol."

Sources: ICF provided by CONEP/CNS in Writ of Mandamus 5021329-93.2020.4.03.6100; Protocol in English disclosed on the clinicaltrials.gov database platform and published in the supplement to the JNO article.

No cases of withdrawal or voluntary exit were reported. The ICF stated that participants would be regularly informed about information that could affect their decision to continue involved in the study. Only two potential participants (2.4%) refused to enter the study. CONEP and the CNS were notified of the ethical discrepancies. The trust of patients (or their families) in the researchers and involved institutions, the impossibility of being admitted to another SUS hospital, and the situation of great uncertainty and risk of death, combined with a high economic and socio-educational vulnerability, may have influenced the decision of participants (or legal guardians) to consent, in the hope that the principles of human dignity, good faith, autonomy, beneficence, non-maleficence and justice would be respected.

NEED FOR GREATER TRANSPARENCY AND EFFECTIVE DIFFUSE SOCIAL CONTROL OF CLINICAL RESEARCH IN BRAZIL

The two cases illustrate the possibility of deceiving medical research participants through flawed ICFs that the CEP/CONEP System approved. They also reveal situations of fallibility in the ethical regulation of research in Brazil²⁰, focusing on the CEP/CONEP System's performance, which should balance the objectives of researchers and sponsors and the need to minimize risks and maximize possible benefits for participants. They also show the limited supervisory capacity of the CEP/CONEP System in monitoring studies involving socially vulnerable individuals and communities carried out by public bodies and conducted in environments with low inhibition of the researchers' freedom of action. They reinforce the inseparability of scientific and ethical justification in analyzing protocols and ICFs of biomedical studies, requiring *scientific expertise* to make ethical and technical judgments²¹. They point to the powerlessness of CONEP/CNS, in the absence of legal sanctioning support, to stop the publication, in international journals, of articles resulting from research that had its ethical authorization suspended in Brazil.

The described facts are indicators of the Brazilian reality regarding the deficient qualification of clinical research participants and apparent flaws in the ethical review process by the CEP/CONEP System. Although scarce, empirical studies on the profile of participants in clinical studies in Brazil, mainly conducted in units linked to the SUS, indicate a high degree of vulnerability and social inequality. Participants show low understanding or ignorance of the procedures, risks and adverse effects of the treatment to be tested and believe that the study would be based on their needs and interests²², leading to the conclusion that *research priorities might be taking precedence over the individual needs of the patient*²³. Patients recruited from the SUS for clinical research generally have vulnerability aggravated or potentiated by socioeconomic and educational factors, with a significant incidence of functional illiteracy. They often face serious illnesses, therefore being considered hypervulnerable²⁴, as in the case of the CloroCoVid-19 study. The situation worsens when the ICFs of the studies are lengthy and difficult to read²⁵, which may lead patients to decide to participate in the research before reading the document, as occurred with 94% of older adults in a study conducted in Rio Grande do Sul²⁶.

Participant adherence to medical research relies on the good faith and trust placed in researchers and institutions, endorsed by the CEP/CONEP System, following the ethical evaluation of research protocols. Poverty and low educational levels may have facilitated immediate study consent, exacerbated by the health emergency during the CloroCoVid-19 trial. Manaus was the metropolitan region with the highest index of social vulnerability²⁷, according to a [study](#) by the Institute of Economic and Applied Research (IPEA). It is significant to note that the refusal rate for participation in the CloroCoVid-19 study was 2%, whereas, in São Paulo, it was 35% in an [observational study](#) of elderly individuals with suspected COVID-19 treated at home with the use of hydroxychloroquine and azithromycin²⁸.

The cases also exemplify discretionary and contradictory behaviors of CONEP/CNS, with ethical authorization being revoked and notifying the Public Prosecutor's Office in the Amapá study while maintaining strict silence on the CloroCoVid-19 study despite widely publicized critical comments^{29,30} regarding the use of a potentially lethal toxic dose of chloroquine in clinically unstable or very debilitated patients without scientific and ethical justification. Despite multiple warnings of methodological and ethical inadequacies – including a [public retraction request](#)³¹ – CONEP and CNS have yet to officially comment on potential irregularities in the study. Regarding other clinical studies on COVID-19, CONEP/CNS [withdrew authorization](#) for conducting studies³², issued public notes on methodological and ethical irregularities in studies on the CNS internet portal^{33,34}, and filed a complaint in the Chamber of Deputies³⁵ with the full report sent to the Attorney General's Office for initiating a public civil action³⁶.

The ongoing corruption of informed consent in medical research in the United States³⁷ seems even more critical in countries or regions with lower Human Development Indexes associated with exploiting or manipulating vulnerable participants. Volunteers from both studies were recruited from highly vulnerable categories of Brazilian citizens, SUS users, in places with critical indicators related to health conditions, age, economic income, employment, and access to health and education services. The deterioration in the quality of information provided to research participants in Brazil can be seen by comparing the guidelines in the [2015](#)³⁸ and [2020](#)³⁹ versions of the *Research Participant's Guidebook* edited by CONEP/CNS, with a reduction in emphasis on the potential participant reading the ICF in detail and asking for further clarification of remaining doubts.

PROPOSALS FOR THE EXPANSION OF SOCIAL CONTROL AND TRANSPARENCY IN CLINICAL RESEARCH

Society demands that clinical research be founded on sound scientific and ethical practices. **To be ethical, regulations in biomedical research must first be transparent**, providing broad access to documents – particularly the protocol, ICF, and research results – that are of interest to everyone and that pertain to the health of citizens. In recent decades, social, technological, and structural transformations have demanded changes in Brazil's centralized and opaque practices regulating clinical research, claiming more public and patient engagement.

Fifty-five years ago, Beecher warned that, in the role of researcher, it is doubtful that, in all situations, the physician will always choose the best treatment for the patient⁴⁰. With increasing competition, there is a need to prevent fraud and scientific misconduct caused by inappropriate ambition, stardom, haste and the pursuit of academic or economic power by researchers, in addition to more subtle factors of conviction or political-ideological direction⁴¹. In a debate on the ethical aspects of research in psychiatry, Elizaldo Carlini⁴² warned in 2001 against centralizing control of research control in a central body linked exclusively to the CNS, excluding the sanitary surveillance agency from decisions, which could introduce ideological elements into ethical decision-making.

In clinical trials, the ICF can juridically be understood as a *sui generis* contract, semi-standardized, unilaterally written by the PI, and submitted for ethical review by the CEP/CONEP System as a participant protection body. It describes both patrimonial (compensation clause for damages resulting from the research and treatment costs, as well as the non-onerous delivery of effective post-trial medication) and non-patrimonial obligations (permission for medical conduct established in the research protocol and communicated in the ICF, with a revocability clause at any time). Despite the recommendation for it to be written as an invitation, by signing it, the participant (or legal representative) declares to be duly informed and aware of the procedures and risks to be undertaken. After protocol approval, the CEP or CONEP/CNS becomes co-responsible regarding the ethical aspects of the research, as per item X.3.9 of CNS Resolution No. 466/2012.

Informed consent obtained under oppression or without adequate information is legally null and void. Professor William Saad Hossne - a pioneer in the ethical regulation of research involving human beings in Brazil - warned that the ICF is not a drug leaflet, nor does it serve as proof of legal exemption from responsibility by researchers⁴³. His warning aligns with the World Medical Association's [Declaration of Helsinki](#). Commenting on the minimum information proposed by the WHO in 2008 for clinical trial registration, Yazici⁴⁴ suggested incorporating the ICF among the mandatory documents for public registration of clinical trials and maintaining any amendments to it in the database. He argued that the transparency proclaimed in the ethical regulation system of research is very limited and short-term, merely by having a societal member present. Along with the disclosure of the ICF, articles resulting from randomized clinical trials should transparently describe the circumstances under which participants were informed and consent obtained⁴⁵.

With the implementation in 2018 of the revised version of the [United States federal policy for the protection of research participants](#)⁴⁶, new rules to improve the protection of human beings involved in research were enacted, including the mandatory posting of the ICF on a public electronic portal for clinical trials conducted or supported, in whole or in part, by a government agency or department, excluding commercially confidential information and other information that should not be publicly available. As of September 28, 2022, the [clinicaltrials.gov](#) database contained 72 files with ICFs and 626 clinical trial protocols involving Brazil, of which 8 ICFs and 34 protocols were specific to COVID-19. Additionally, starting in 2026, all peer-reviewed publications funded by federal resources in the United States will be freely available to the public. In Brazil, the provisions of [Federal Decree No.](#)

[10.228/2020](#), which created the Public Service Users Councils and allowed for voluntary, non-selective citizen participation as advisors in relevant areas related to public service provision, including human research, still seem to be under-applied.

In line with public transparency and efficiency, a [2004 proposal](#) to create electronic journals with free access articles in Portuguese, in major knowledge areas, with an editorial body of researchers linked to graduate programs supported by public funding agencies, was ignored⁴⁷. It is estimated that concrete governmental measures could help reverse the [trend](#) of Brazilian health researchers, funded with public resources, publishing topics of more interest to international journals or those less related to solving our health problems⁴⁸.

The following proposals are based on the guiding principles of Public Administration in Brazil and on ethical guidelines or norms for research involving human beings, designed to expand effective social control by citizens.

Proposal 1: Full disclosure of the ICF templates of clinical trials after their approval by the CEP/CONEP System: The approved ICF models (and their amendments) for clinical trials are public documents and should be published on free access portals on the Internet, such as the Plataforma Brasil or the ReBEC portal, managed by Fiocruz and created to provide transparency to national studies. Their availability would allow real-time knowledge of clinical trials in development in a particular city or geographic region, similar to what occurs on WHO and the U.S. government platforms. It could contribute to better recruiting potential participants, widening social control and participant protection while assisting CONEP/CNS in fulfilling its mission and demonstrating transparency.

Proposal 2: Informative summary as the first and prominent mandatory item of the ICF: This summary should contain the minimum information with the maximum value for a potential participant's overall understanding of the study, highlighting the main points for making an informed decision. If the participants find the study interesting, they can deepen their knowledge by reading the full ICF. Considering the usual standard of research participants in Brazil, it should have a short title with simple terms, followed by the central question of the study (maximum of 25 words), the reason for the research, objective, procedures, benefits, risks and alternatives if they choose not to participate. It should be written in short sentences and commonly used words by the population where the research will be conducted, thus being easy to read. For example, the following is a summary of the CloroCovid-19 trial according to what was described in the article and the protocol attached in JNO.

Table 2. Model Summary for mandatory inclusion in ICFs of clinical trials

CLINICAL STUDY TO EVALUATE THE EFFECTS OF CHLOROQUINE ON COVID-19
<p>QUESTION: Can chloroquine, added to standard hospital treatment, reduce deaths in hospitalized patients with severe respiratory problems and clinical suspicion of COVID-19?</p> <p>REASON FOR RESEARCH: There is uncertainty about whether chloroquine acts as an antiviral and what the safe dose is against the virus that causes COVID-19.</p> <p>OBJECTIVE: To assess whether there is a reduction in deaths in two groups of patients suspected of having COVID-19 with severe respiratory problems after using two different doses of chloroquine in addition to the treatment adopted in the hospital to treat respiratory discomforts.</p> <p>PROCEDURES: Participants will be assigned by chance to two groups, who will use the treatment for ten days. One group will receive the dose the Ministry of Health indicated for COVID-19 (18 tablets, supplemented by placebo). The other group will use a higher dose (80 tablets) to combat the coronavirus.</p> <p>BENEFITS: Benefits may occur if the medication shows antiviral action, inhibiting disease progression and reducing deaths.</p> <p>RISKS: Chloroquine is a very safe drug; its effects depend on the amount of the dose ingested and the duration of use. It can produce unpleasant effects such as nausea, vomiting, diarrhea, abdominal pain, headache, visual problems, nervousness, and itching. The joint use of other medications for treating respiratory problems can lead to changes in cardiac function, which the research team will monitor.</p> <p>NON-PARTICIPATION OPTIONS: The treatment commonly adopted in the hospital for severe respiratory problems will be administered.</p>

Proposal 3: Disclosure of crucial elements of the clinical research protocol in Portuguese:

Mandatory disclosure in Portuguese, partially or preferably in full, of clinical research protocols funded with public resources – or, in foreign projects, with collaboration from public service employees – would contribute to increasing transparency and social control. The disclosure could be done on a separate site in Plataforma Brasil or the ReBEC platform. All produced and approved versions for the study would be registered, allowing a quick comparison of their changes over time. Contrary to recent CONEP/CNS guidelines for conducting clinical trials⁴⁹, the protocol should be *mandatorily* (and not preferentially) registered on ReBEC in Portuguese. The disclosure could also be helpful for counseling, by their attending physicians, of interested participants in the study.

Proposal 4: Legal standardization on scientific integrity in biomedical research:

The international trend seems to be evolving from the current voluntariness to normative imperativeness that reinforces the protection of clinical trial participants and enhances social control, as has been the case in France since 1988 (Huriet Law). The regulatory gap regarding the responsibilities – in the administrative, civil and criminal planes – of those involved in clinical trials, without a clear definition of sanctions, generates legal uncertainty and disinhibits questionable or harmful scientific practices. It may also undermine societal trust, hindering the desired, safe, and orderly progress of medical research in Brazil. The enactment of a specific law on the ethical regulation of clinical research in Brazil

- with the definition of a coordinating body comprising governmental organs or departments interested in promoting research involving Brazilian citizens - should consider including specific sanctions in case of norms violation- including fines, deprivation of liberty and suspension or revocation of professional practice or public office - to be applied independently of the judgment of professional councils, universities, funding agencies or public institutions involved in research.

The current system of user representation in the CEP/CONEP System, chosen by imprecise criteria and generally with minimal familiarity with complex scientific methods or central ethical issues (such as equipoise in randomized clinical trials), seems inefficient. In order to reduce corporate biases, the ethical review of clinical trial protocols could be implemented by another accredited CEP that is not linked to the proposing institution, contrary to what was established in paragraph 2 of article 16 of [CNS Resolution 506/2016](#)⁵⁰. Without good faith, transparency and trust, there is no sustainable mutual commitment between the parties involved in regulating ethical research in Brazil.

FINAL CONSIDERATIONS

Popular participation leverages administrative transparency and must be fueled by valid, useful and reliable information. The higher the degree of administrative transparency, the closer it will be to a fully democratic regime, especially in the case of conducting clinical research with drugs that may endanger participants' lives. The universal disclosure of ICFs and protocols may stimulate cooperative investigation of common problems and help precisely direct scientific actions with more significant social impact in Brazil, privileging the most vulnerable and providing answers to our most relevant and urgent problems.

All entities involved in conducting clinical trials - sponsors, regulatory agencies, researchers, research institutes and universities, public research funding agencies, medical journals, professional societies, patient associations, and health authorities - must fulfill their roles and responsibilities to ensure the utmost respect for human dignity, acting with transparency and impartiality. Researchers and sponsors have an inalienable responsibility for the ethical and legal aspects of the research, just as physicians have for the patients under their care, particularly in clinical trials. The claims - in poorly designed and dangerous clinical studies to the participants' health - that approval by the research regulatory body and the signing of the ICF by the participant/legal guardian make the study's ethics or legality unquestionable do not deserve to prosper.

In a country with low health literacy, it is possible that Brazilian citizens with evident socioeconomic and psychosocial vulnerabilities - who see research as a way to have more agile medical follow-up and treatment with drugs provided by researchers - are being used merely as a means to achieve the priority interests of researchers or sponsors. The work of medical scientists must serve the participants of research and society, requiring the adoption of new legal instruments to prevent the misuse of Brazilian citizens as objects - and not subjects - of clinical research, particularly those served within the SUS.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest in preparing this article.

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