Remuneration of participants in clinical research

Remuneration of participants in clinical research: reflections based on the Constitution

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Abstract

While Resolution CNS 466/2012 establishes the possibility of the participants in Phase I clinical research or bioequivalence receiving payment, the Federal Constitution of 1988 absolutely prohibits the commercialization of the human body. This ethical and legal study aims to analyze the unpaid participation of individuals in research in the light of an international theoretical framework and the Brazilian Constitution. We conclude that there is no international consensus on what payment would represent "undue inducement", especially if we consider that there are people who live on the margins of the poverty line, particularly in Brazil. Considering the constitutional rule concerning the prohibition of all kinds of commercialization of the human body, this text supports the ethical and legal inadequacy of the device Resolution CNS 466/2012.

Keywords: Research. Payment. Resolution 466/12. Federal Constitution.

Resumo

Remuneração dos participantes de pesquisas clínicas: considerações à luz da Constituição

A Resolução CNS 466/2012 do Ministério da Saúde estabelece a possibilidade de se ofertar quantia financeira a participante de pesquisas clínicas de fase I ou de bioequivalência, e a Constituição Federal de 1988 assenta a vedação absoluta de comercialização do corpo humano. Esta pesquisa, de cunho ético-jurídico, analisa a participação não gratuita de indivíduos em pesquisa à luz do tratamento teórico internacional do tema e do arcabouço constitucional brasileiro. Conclui que não há consenso no mundo acerca do que seja pagamento que caracterize "indução indevida", mormente quando se considera que há pessoas que vivem à margem da linha de pobreza, o que, particularmente no Brasil, é um problema crucial. Tendo em conta a vedação constitucional de qualquer tipo de comercialização do corpo humano, este texto sustenta a inadequação ética e legal do dispositivo da Resolução CNS 466/2012.

Palavras-chave: Pesquisa. Remuneração. Resolução 466/2012. Constituição federal.

Resumen

Remuneración de los participantes de investigaciones clínicas: consideraciones a la luz de la Constitución

La Resolución CNS 466/2012 establece la posibilidad de ofrecer una cuantía financiera a los participantes de investigaciones clínicas de Fase I o de bioequivalencia y, la Constitución Federal de 1988 determina la prohibición absoluta de la comercialización del cuerpo humano. Esta investigación de naturaleza ético-jurídica, analiza la participación no gratuita de los individuos en investigaciones a la luz del tratamiento teórico internacional del tema y del marco constitucional brasilero. Se concluyó que no existe un consenso internacional acerca de lo que es un pago que caracterice el "incentivo indebido", principalmente si tenemos en cuenta que hay personas que viven en el margen de la línea de pobreza, lo cual se exhibe particularmente en Brasil como un problema importante. Teniendo en cuenta la prohibición constitucional de todo tipo de comercialización del cuerpo humano, este texto es compatible con la insuficiencia ética y legal del dispositivo de la Resolución CNS 466/2012.

Palabras-clave: Investigación. Remuneración. Resolución 466/2012. Constitución federal.

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Declaram não haver conflito de interesse.

On the 12th of December 2012, the Ministry of Health, through the Conselho Nacional da Saúde (the National Health Council - CNS), published Resolution CNS 466[1], which contains guidelines and regulatory standards for research involving humans in Brazil. The aim of this update was to complete the provisions of the previous standard, CNS Resolution 196, dated October 10, 1996[2], which recognized the contextual character of this type of regulation and the requirement for periodical revision. These updates must be in accordance with ethical and technoscientific needs, always seeking to better ensure the rights and duties of the scientific community, participants in research projects and the state.

The free availability of tissues, organs and parts of the human body, whether alive or post-mortem, for use in transplants and treatment, is regulated by Law 9.434, dated February 4, 1997[3], which does not refer to research.

Among the alterations addressed in CNS Resolution 466/2012, one of the most notable is the admission of paid participation in phase I or bioequivalence clinical studies, item II.10: *participant in the research – an individual who receives the necessary clarification, or after authorization from their parent(s)/guardian(s), volunteers to take part in the study. Participation should be freely given, with the exception of phase I or bioequivalence clinical studies*[1].

This demands profound reflection, given the specific nature of Brazilian society and the contents of article 199, paragraph 4, in the Constitution of the Republic: *the law shall dictate the conditions and requirements that govern the removal of human organs, tissues and substances for use in transplants, research and treatment, as well as the collection, processing and transfusion of blood and its derivatives, for which all types of commercialization are prohibited*[4]. This text is regulated in Law 10.205 dated March 21, 2001[5], which addresses the collection, as well as the protection of the donor and the recipient – prohibiting payments for donations –, as well commercialized collection, processing, storage or transfusion of blood and its components/derivatives. These hemotherapeutic activities may be necessary in some studies.

Thus, the resolution has an infra-legal status and is edited by a collective organ of social participation, which established the possibility of a perceived financial amount for participating in phase I or bioequivalence studies, while the Federal Constitution absolutely prohibits the commercialization of the human body.

The aim of this exploratory literature review was to analyze the paid participation of individuals in studies in light of the theoretical international treatment of the topic and the Brazilian constitutional framework, thereby providing a relevant contribution to the debate that began in Brazil upon the approval of CNS Resolution 466.

This article was structured in two parts. The first part addresses the goals of the research and analyzes international literature on the payment of participants in studies. The aim of this section was to expose the complexity of the topic and the controversy surrounding the ethical adequacy of these payments. The second part examines the constant forecast in CNS Resolution 466 based on the Brazilian constitutional precept.

Payment of participants in clinical studies: current panorama

The payment of participants in clinical studies is a controversial topic. Some have called it improper, exploitative and morally reprehensible, whereas others have highlighted its importance when seeking to gather a sufficient number of individual participants[6]. Although the USA, Switzerland and the UK have legalized payment for participation in clinical, biostatistical and legal research, people's opinions within those countries still differ concerning the ethical and legal aspects related to the payment of a financial value to a person so that they will take part in a clinical study.

Indeed, even in the United Sates, where there is a long tradition of paying participants in clinical studies, there are inconsistencies in relation to when, how much and how to pay. The U.S. Food and Drug Administration (FDA) stipulated that payment should be a recruitment incentive, and not a benefit, thereby clarifying (for ethics review committees) that the value, method and duration of payment should ensure that no *coercion* or *undue inducement* occurs[7].

Regardless of an assessment of whether these payments are ethical or legal, an appreciation of the payment in each case should always be based on the perspective of exploitation of the participant, rather than just another integral aspect of the free and informed consent form[8]. Likewise, Aschcroft[9] indicated that the payment affects the quality of the informed consent and represents a circumstance that is favorable to the exploitation of the participant.

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As reported by Slomka and others [10], in the USA, it is normal to offer payment in order to recruit individuals to participate in studies. However, questions related to its conception, methods and the amount to be paid remain controversial. This is especially relevant when recruiting individuals classified as poor or vulnerable. There are very few empirical studies on the effects of payment on this participation.

Ethical debates about paying participants in clinical studies often revolve around the issue of *undue* or *coercive inducement,* which is defined as the provision of positive incentives in values that are high enough to undermine the individual´s ability to act in their own best interests, thereby increasing the risk of being subjected to serious harm [8]. Indeed, high payments could hinder assessments of the eventual harm caused by the research to the participants, particularly when dealing with people who live below the poverty line.

In these cases, Lemmens [8] stated that the ethics review committee should analyze if the amount of the payment represents *undue inducement*, always considering the financial situation of the participant, as well as their level of education and if their consent was provided by a legal representative [11]. The remaining issue is the value of the payment and at what point it can be considered *undue inducement*. Concerning the analysis of the ethics review committees, it is important to highlight that a number of authors have classified them as patronizing or capable of undue interference in the autonomy of the individual [12].

It has been argued that *undue inducement* could invalidate the participant´s informed consent, particularly when the patient lives below the poverty line. In these cases, it is undeniable that the money offered can distort human reason. Consequently, there are laws that prohibit the commercialization of organs and tissues, the sale of neonates and the use of the human body in certain situations [13]. Informed consent, which is the expression of an individual´s autonomy, is not enough to validate paid participation in clinical studies, and as such, other protective measures should be adopted to protect the individual, particularly their physical and mental integrity.

Thus, *undue inducement* is incompatible with informed consent, given that it eliminates the characteristic of voluntariness, while also affecting the capacity of the participant to learn about eventual harm caused by the clinical study [6]. In general, those who are most susceptible to a financial offer are also those who have less cognitive and technical awareness of the risks the research represents for their health. A study conducted by Bentley and Thacker [6] stated that high payments make a study more attractive, even if the health risks are significant. The same authors asserted that more studies should be analyzed to determine whether these payments represent *undue inducement*. Similarly, Dickert, Emanuel and Grady [7] also indicated that more studies and debate are required to understand when the payment is inadequate, as well as its impact on the selection of participants and the integrity of the research.

In the USA, Slomka and collaborators [10] conducted an empirical study on HIV prevention with Afro-American drug users. They confirmed that, although some individuals had agreed to participate altruistically, the majority signed up because they would get paid, which contributed to their adherence. The researchers believed that individuals who live below the poverty line may participate in clinical studies simply as a form of sustenance, as a result of the payment offered. Thus, the participation in studies could be seen by these individuals as an alternative to other risky activities. Another conclusion from this study is that the payment could represent an integral activity in the informal economy of low-income areas.

Other empirical studies have demonstrated that several healthy participants did not consider the payment the main reason for taking part, claiming that economic gains were rarely the main reason for their participation. However, other studies have shown that the payment has a significant influence on the decision of healthy participants [6].

Concerning the phases of clinical studies, they must first be synthesized and then discussed. Phase I involves the initial assessment of the tolerance of healthy volunteers, between 20 and 100 participants, to drugs, taking note of the following aspects: the highest tolerable dose; the lowest effective dose; the dose/effect ratio; the duration of the effect and side effects. In summary, new active principles or new formulae are tested on healthy individuals, in order to *establish a preliminary evolution of the safety of the pharmacokinetic profile and, whenever possible, the pharmacodynamic profile.* [14] In phase II, or the therapeutic pilot study, the first controlled studies are conducted with patients – i.e., unhealthy individuals –, between 100 and 200 participants, to demonstrate the potential effectiveness of the medication. Phase III involves multicentric trials with different populations of patients (at least 800 people) to test the effectiveness and safety of the drug [14].

According to Moreno [15], participation in phase I or bioequivalence clinical studies is paid because adherence to these studies generally sustains the hope for a cure, or at the very least, a palliative for the illness in question. However, in phase I, the participants are healthy, which would, in theory, deviate from the explanations for their voluntary adherence and the fact that the drug being tested could have a positive effect on a patient´s illness. Nevertheless, similar to the manner in which voluntary blood, organ and tissue donors do not make any profit from their actions, participants in this type of study should be recruited for reasons other than financial gain. Essentially charitable actions can be referred to as *bodily gifts for strangers,* as a result of feelings of empathy and solidarity [16].

The assertion that the payment of participants in clinical studies is necessary for their recruitment has no scientific grounds and is detrimental to bonds of solidarity. It could even lead to the promotion of the commercialization of the human body as just another commodity in our consumer society. In studies that involve a great risk to the health of the participant, the offer of large sums of money can have a direct effect on the evaluation capacity of vulnerable individuals, sometimes leading to irreversible damage. Conversely, some researchers who are against the idea of payment have accepted its use in cases in which the risk to the participant would be minimal [17].

Further problems arise in cases that involve the participation of children or people whose autonomy or civil capacity is restricted. It is important to consider that, even when dealing with homogeneous cohorts, the tolerance to a test substance may differ between the participants, which prevents or hinders the definition of parameters of an unequivocally generalizable risk. This differentiation must be taken into consideration by researchers, as well as legal guardians, since it promotes reflection on the role of financial payments in studies containing incapable individuals [16]. These clinical studies should not be paid for, since there is a probability that the participant would not benefit from the value received, which would be collected by the guardian/parent/caregiver. In order to avoid this type of participant becoming a product, their legal guardians must not be paid [9].

Even those who state that the payment of participants is not unethical believe that it can become problematic when the protection of the participant is inadequate [6]. The idea that the payment can compensate them for eventual risks to their physical integrity or life must be rejected [8]. Consequently, most of the theories that defend the ethical adequacy of payment advocate that it should be restricted to studies in which the risk of damage is low [18].

From a strictly legal point of view, there is disagreement about the nature of the bond between the participant in the research and the person who pays them. Lemmens [8] characterized this bond as a working relationship, which should be subject to labor laws in order to increase the protection provided for the participant. Resnik [18] made similar claims, asserting that if the main reason for the individual´s participation in the study is the payment, the bond with the researcher, or paying sponsor, is a labor bond, in which informed consent is seen as the working contract. Similarly, Wilkinson and Moore stated that participation in clinical studies is a normal job, an argument that McNeill [12] disputes, claiming that ordinary jobs do not entail the health risks involved in the performance of this type of research.

The disclosure of the payment of participants in clinical studies is also a concern for those who support the idea: commercials stress the financial aspect of participation and omit the onus of investigations, thereby creating an atmosphere that is supposedly conducive to study and influencing the assessment of the eventual participant. Thus, even those who do not consider these payments unethical *per se*, believe that ensuring the availability of adequate information and appropriate recruitment policies are essential to the ethical acceptance of payment. Therefore, payment, despite its legality in certain countries, is only ethically plausible in contexts that involve an effective protection system for the participant [12].

Reame [19] stated that it is important to reassess the assertion that financial incentives, despite their value, are the best way to recruit volunteers for clinical studies. Payment induces people to submit to health risks, which affects their individual autonomy, given that the state and society are obliged to protect citizens from behavior that is damaging to their health. In addition, in order to create a caring society and promote *beneficial relationships,* the provision of payments for blood, organ and tissue donors, as well as participants in clinical studies, is a practice that should be rejected.

Legal and bioethical regulatory frameworks in research involving humans in Brazil

Research involving humans in Brazil is not regulated by a specific law, although the activity is

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undoubtedly covered by the normative principles established in the country's constitution, particularly the section related to human dignity, a foundation of the republic and the democratic state of law (art. 1, III).

Dignity is an intrinsic or inherent value of the human person. From an ethical point of view, it is one of the central values in the law, and according to many authors, it represents the moral justification of human and fundamental rights. In the legal field, it has become a constitutional principle, producing relevant consequences [20]. Dignity leads to the right to physical integrity, which includes the prohibition of torture, slave labor, forced labor, cruel punishment and a guarantee of protection related to clinical studies, eugenics, the sale of organs and human cloning. Human dignity can be broken down into two commands: personal empowerment, which assigns the ethical obligation to respect one´s individual capacity to make free choices; and the limits of self-determination, in that the state restricts the activities of humans in order to protect their dignity [21].

Resolution 466 was edited by the Conselho Nacional de Saúde (National Health Council -CNS), which approves ethical guidelines for research involving humans. The council is predominantly ethical, although it also plays an administrative role, although without the force of law. This does not diminish its importance, particularly when one considers the recognized legitimacy of the CNS on this subject, nor does it remove it from the incidence field of constitutional guidelines, since it is included in the regulatory power of the administration. The bioethical principles of autonomy, non-maleficence, beneficence, justice and equity were expressly adopted as directives, the ethical aspects that must be observed by researchers were also described [1]. The foundations of the resolution include respect for human dignity and special protection for the participants of scientific studies, which must respect the dignity, liberty and autonomy of humans.

International documents addressing human rights were also adopted as references, including: the *Nuremberg Code* (1947); the *Universal Declaration of Human Rights* (1948); the *Helsinki Declaration* (1964) and its updated versions (1975, 1983, 1989, 1996 and 2000); and the *Universal Declaration on Bioethics and Human Rights* (2005), among others. However, these pillars of recognition and confirmations of the dignity, liberty and autonomy of humans were mentioned as "protocol", without giving them the due emphasis. An affirmation, or even a requirement, that researchers observe the contents of these documents, which go beyond the above-mentioned principles, would be useful.

Nevertheless, the researcher´s duty to observe the bioethical and legal regulations in the Resolution is clear, since this ensures the complete protection of participants in studies.

Paid participation in studies: a "limitation" of questionable constitutionality

Although the link between CNS Resolution 466 and ethical and legal principles is clear, and despite further confirmations that participation in studies should not be paid, a limitation was created for phase I or bioequivalence clinical studies, allowing: *paid participation for individuals who, voluntarily and with a full understanding, or with the understanding and authorization of their legal guardian(s), agree to take part* (definition provided by the resolution for "participant in a study", an expression that was adopted in place of "subject of a study", which was previously used).

A number of clarifications, based on CNS Resolution 466 [1], are required in order to better understand the payments for these examinations. According to item II, the fee in question cannot be confused with "indemnity", defined as *material coverage to repair damage caused by the research to the participant* (sub-item II.7), nor as the "provision of previous material", which is *material compensation, exclusively for the participant's transport and food costs, as well as those of their companions, when necessary, prior to participation in the study* (item II.18), or "repayment", defined as *material compensation, exclusively for the expenses of the participant and their companions, when necessary, including transport and food* (sub-item II.21).

Phase I clinical studies are those involving humans and new drugs, medications, vaccines or diagnostic tests. These are governed by the specific regulations of CNS Resolution 251/1997 [22], as well as the CNS, according to which phase I *is an initial study with small groups of human volunteers, usually healthy, the object of which is a new active principle or a new formula. These studies propose to establish a preliminary evolution of safety, the pharmacokinetic profile and when possible, the pharmacodynamic profile* (sub-item II.1).

Based on these definitions, it is possible to conclude that CNS Resolution 466 authorizes payments to participants in phase I studies. Thus, the initial study of

a new active principle or formula can pay its (usually healthy) participants, in order to establish *a preliminary evolution of safety, the pharmacokinetic profile and when possible, the pharmacodynamic profile* [14].

Sub-item II.10 states that the limitation also affects people who are classified as incapable, given that their participation is defined as follows: *individuals who, voluntarily and with a full understanding, or with the understanding and authorization of their legal guardian(s), agree to take part*. CNS Resolution 466 does not provide for differentiated treatment or specific care for this hypothesis, as stipulated, although minimally, in CNS Resolution 251, which established that, when dealing with people who do not have a normal capacity for self-determination, as well as a legal guardian, it is necessary to take into account the expression of the subject themselves, even if they are civilly incapable.

The participation of incapable (underage or interdicted) individuals, who are defined as vulnerable, does not seem reasonable in phase I, particularly as the individuals taking part should be healthy. Depending on the type of risk involved, with exceptions in some cases, and depending on the proof of the eventual benefit to be obtained, legal authorization will be required, since the legal guardian does not have the power to make the incapable individuals body available.

The limitation related to payments in CNS Resolution 466 is surprising. Since 1993, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, created by the Council for International Organizations of Medical Sciences (Cioms), in collaboration with the World Health Organization (WHO), have led to the revision of previous guidelines, rejecting the *undue inducement of possible participants to consent to take part in a study, against their better judgement* [23]. Payments made in money, goods or prizes for participation in studies are considered unacceptable as they could persuade the individual to take undue risks, or endanger their capacity to freely express their wishes, thereby invalidating their consent.

In bioethical terms, payment represents a regression in the protection of participants in studies in Brazil, given that the types of studies in which payments can be made are *designed to determine the toxicity and safety of drugs in healthy individuals, without offering any benefit. Only risks and damage are foreseen for the health of those who participate* [24].

The legal situation is even more complex. The terms of § 4 in article 199 of the Federal Constitution determine the disposition of human organs, tissues and substances for the purposes of transportation, research and treatment. Law 9.434/1997 regulates the removal of organs, tissues and parts of the human body for the purposes of transplants. Law 10.205/2001 governs the collection, processing, storage, distribution and use of blood, its components and derivatives. Both of these laws are clear in relation to gratuities for the provision of the human body parts mentioned, and fulfill the constitutional determinations that prohibit *all types of commercialization*, an expression which should provide a broad interpretation in order to address any and all types of payment in exchange for human material. As a middle income country that has not yet been able to control the poverty of a section of its population, greater care must be taken to protect the human rights of more vulnerable groups in Brazil, since these people are more likely to accept payment to participate in studies. In Brazil, there is no law that regulates the activities of studies involving humans, and the constitutionality of sub-item II.10 in CNS Resolution 446/2012 is questionable.

The bioethical legitimacy of this item is equally questionable, in that there is no direct benefit for the participants in phase I studies, a period which involves high risks. This is clearly contrary to the principle of non-maleficence. Unpaid participation, for altruistic reasons, is ethically acceptable and is supported in the Universal Declaration on Bioethics and Human Rights (2004), according to which *solidarity between humans and international cooperation should be encouraged* (art. 13) [25].

Final Considerations

Considering that the participation of healthy individuals in phase I clinical studies often requires them to suspend their normal activities, submit to invasive procedures and remain within the hospital environment for a period of time, one can support the idea of using payments to recruit participants. However, Grady [26] stated that there is no empirical proof of the real effect of payment on the recruitment of participants for clinical studies. In other words, they suggest a range of motivations for the adhesion of healthy individuals to this type of study.

Issues related to the pressure to participate when payment is offered, particularly among people with low incomes, as well as the ratio between the payment offered and the risks involved in the research and the weakening of bonds of solidarity

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have occupied bioethicists who deal with this issue. Furthermore, there is no consensus concerning what a payment that represents *undue or coercive inducement* actually is, particularly when considering that there are people who live on or below the poverty line. In Brazil, this problem is particularly significant and impels the prohibition of payment for participation in clinical studies.

Another undeniable point of relevance is the whether the nature of the payment represents an incentive to participate, a repayment for expenses incurred by the participant (no profit made), compensation for any common occurrences related to the research, or a payment for the time and effort the participant put into the study [27]. In Brazil, payment is not confused with other types of reimbursements for expenses incurred in CNS Resolution 466/2012.

The debate surrounding the ethicality of paying participants to take part in clinical studies remains controversial in the bioethical field, with a lack of widely disseminated ethical and legal benchmarks. Offering money to people who are classified as poor is a serious ethical and legal issue that cannot be neglected, particularly in Brazil, where the debate should be conducted in light of the Federal Constitution.

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