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The process of informed consent in research on sickle cell disease

Luis Felipe Siqueira Valêncio [1], *Claudia Regina Bonini Domingos* [2]

Abstract

Sickle cell disease is a term that refers to a group of hemoglobinopathies associated with the presence of hemoglobin S. Occurring primarily in black population, and affecting mainly the most vulnerable, the homozygous form of the disease, sickle cell anemia, is considered an important public health problem in Brazil. Understanding scientific research as essential to promote health and improve the quality of life of people with sickle cell disease, the informed consent process should be done to overcome, as far as possible, the vulnerabilities which people with sickle cell disease are exposed to. The use of recreational resources, the transmission of collective information, the protection provided by patient associations and the continuous training of ethics in research by the professionals involved in the agreement are shown as tools for the optimization of this process.

Keywords: Anemia, sickle cell. Informed consent. Ethics, research.

Resumo

O processo de consentimento livre e esclarecido nas pesquisas em doença falciforme

Doença falciforme diz respeito a grupo de hemoglobinopatias associadas à presença da hemoglobina S. Sendo majoritária na população negra, e acometendo em sua maioria vulneráveis e vulnerados, a forma homozigota da doença – a anemia falciforme – é considerada relevante problema de saúde pública no Brasil. Entendendo a pesquisa científica como essencial para a promoção da saúde e para melhorar a qualidade de vida dos pacientes, o processo de consentimento livre e esclarecido deve ser aplicado para superar, na medida do possível, vulnerabilidades a que as pessoas com doença falciforme estão expostas. Recursos lúdicos, transmissão coletiva de informações, proteção conferida pelas associações de pacientes e a formação permanente em ética em pesquisa por parte dos profissionais que aplicam o consentimento são indicados como ferramentas para otimizar esse processo.

Palavras-chave: Anemia falciforme. Consentimento livre e esclarecido. Ética em pesquisa.

Resumen

El proceso de consentimiento informado en investigaciones sobre la enfermedad de células falciformes

La enfermedad de células falciformes es un término que se refiere a un grupo de hemoglobinopatías asociado con la presencia de la hemoglobina S. La forma homocigótica del gen de la enfermedad se presenta sobre todo en la población negra y se considera un problema importante de salud pública en Brasil, que afecta sobre todo a vulnerables y vulnerados. Entendiendo a la investigación científica como esencial para la promoción de la salud y para el aumento de la calidad de vida de las personas con enfermedad de células falciformes, el proceso de consentimiento libre e informado debe ser aplicado para superar, en la medida de lo posible, las vulnerabilidades a las que las personas con la enfermedad de células falciformes están expuestas. El uso de los recursos recreativos, la transmisión de información colectiva, la protección que ofrecen las asociaciones de pacientes y la formación continua en ética en investigación por parte de los profesionales que aplican el consentimiento son señaladas como herramientas para la optimización de este proceso.

Palabras clave: Anemia de células falciformes. Consentimiento informado. Ética en investigación.

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The hemoglobins are proteins present inside the erythrocytes (red cells) of the blood. Sickle cell disease (SCD) that corresponds to a number of diseases of genetic origin in which the presence of hemoglobin S (Hb S) predominates. There are three most common genotypic forms of the disease: sickle cell anemia (Hb SS); Hb S/beta thalassemia; and double heterozygosity, s such as Hb SC and Hb SD [1]. Among them, the homozygous form of Hb S - sickle cell anemia (SCA) - is the most clinically severe. The heterozygous for Hb S in association with normal adult hemoglobin (Hb A) is, in turn, called "sickle cell trait" (Hb AS) and does not manifest any of the clinical symptoms, leaving only referral for genetic/educational guidance [2].

Autosomal recessive FA is the most commonly monogenic hereditary disease in Brazil, particularly affecting the Afro-descendant population, and is mainly distributed in the North and Northeast states [3.4]. This population distribution is associated with the likely evolutionary origin of the disease in Africa, where the high frequency of hemoglobin S is attributed to the adaptive advantage of the heterozygote (Hb AS) in the interaction with the protozoan *Plasmodium falciparum*, the causative agent of malaria [2]. The large migratory flow of Africans to Brazil, enforced during the period of slavery, heightened the frequency of the disease in Brazil.

The Hb S polymerizes inside the erythrocyte in a condition of hypoxia, dehydration or acidosis, forming polymer beams that disrupt the binding of the erythrocyte membrane with cytoskeletal proteins, modifying the architecture and the flexibility of the cell, passing from a biconcave to a "sickle" shape [5.6]. This condition results in two main pathophysiological events of FA, hemolysis and vaso-occlusion, which, associated with genetic and environmental factors, modulate the diversity of clinical manifestations that people may present: anemia, episodes of pain crisis, acute chest syndrome, pulmonary hypertension, stroke, priapism, osteonecrosis, leg ulcers, and multiple organ failure [7.8].

Scientific research in the sphere of health can increase knowledge of the disease, as well as promote the discovery of new techniques, procedures and medications, responsible for improving the quality of life of people living with FA. However, as it happens with clinical studies on any other illness, the conduct of the proceedings should be safeguarded, basing them on ethics, aimed to promote the safety of research participants.

The concept of harmful effects stems from the imperative *primum non nocere* – which defines "do no harm" as the first obligation of those who are dedicated to finding a cure [9]. This notion remains to the present day as a fundamental reference for the conduct of health. The beneficence of health is usually associated with the relief of suffering, hygiene, prevention of possible pain, illness and disability [10].

To meet these primary health goals the informed consent process is essential, as both the harmful and the beneficial effects will be known by those involved. The need to know the procedures to which one will be subjected to, and to consent with their realization, are fundamental processes for medical practice. Likewise, clinical research does not obviate these process. According to Article 4 of the *Universal Declaration on Bioethics and Human Rights* (UDBHR), called "Benefit and harm", *the direct and indirect benefits to patients, research patients and other affected individuals should be maximized and any possible harm to such individuals should be minimized* [11]. Furthermore, Article 5 of Resolution 466 of the Brazilian National Health Council (*Conselho Nacional de Saúde* - CNS), called "*Dos Riscos e Benefícios*" (Regarding risks and benefits), assigns to the CEP/CONEP System the monitoring and responsibility regarding the weighting of the risks and benefits, and makes provision for the admissibility of clinical research cases [12].

Historically, transgressions that occurred in the field of human rights and of scientific research generated concerns about the proper conduct of the knowledge construction process in the field of life sciences [13]. Bioethics, which is a field of human knowledge that has developed from the 1970s in response to the pioneering thinking of the American oncologist Professor Van Rensselaer Potter, was initially proposed as a bridge between the humanities and life sciences - according to the author, the latter develop methods and technologies more quickly than the capacity of critical reflection about possible impacts created by this new knowledge [14]. Thus, it would be up to bioethics to promote the reflection, not by preventing the scientific progress or the standardization of behavior, but rather their best possible use [15].

The bioethical context of sickle cell disease can be analyzed both in the microbioethics context, which considers the genophenotypic dimension (bodies, organizations, behavior and beliefs), and within the macrobioethics (which focuses on the dimension of social logic and power relations in the sphere of hygiene), bringing multiple and necessary approaches to the understanding of the complex

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relationship between health and disease [16]. We resort here to the historical significance of health as defined by the World Health Organization (WHO) for "research ethics" as *a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity* [17], and contemporary approaches to the concept of health, guided by quality of life and transcendent to biomedical reductionism.

It is proposed in this paper thought be given to the main topics that should be considered to obtain free, prior and informed consent in the context of research on FA, which can be taken as a persistent problem in bioethics due to the old and recurrent picture of vulneration [15] . There is a scarcity of studies that address the issue of informed consent with regard to this disease. Therefore, we intend to contribute to the debate on the subject and encourage critical reflection by researchers and health professionals, as well as to raise awareness among people living with FA. The analysis employed is based on two legal documents, one international and one national: the UDBHR from 2005 [11], and CNS Resolution 466 of 12 December 2012 [12], chosen because of their importance as protection mechanisms for research participants and their adaptation to the social context of developing countries.

The vulnerability in sickle cell disease

"Vulnerability" can be defined as a potential wound or trauma that a particular social group or individual is subject to. On the other hand, "vulneration" refers to trauma or injury that a particular social group or individual has suffered [18]. In the context of public health, the distinction between the two terms is relevant considering that the first concerns capacity and the second, to act.

Finitude and mortality are inalienable aspects of life, and, in accordance with Article 8 of UDBHR, *in applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account* [11]. Thus, any and every life can be considered vulnerable. However, vulnerability is not present in an equitable manner throughout the multiplicity of life forms, since these are subjected to many different factors such as their biological, social and cultural conditions [19]. Thus, the complexity of each of these aspects should be analyzed with greater caution and depth by researchers.

For people living with FA, biological vulnerability is evident in several clinical implications imposed by the disease. The possibility of living with severe pain, recurrent interventions (surgical and non-surgical), the need for continuous treatment, and constant hospitalizations are examples of the materialization of these adverse conditions. For people with anemia, social vulnerability can be considered a product of biological vulnerability because the damage to the physical body can undermine their mental health and, consequently, their social relations.

Frequently, patients with the disease complain of depressive symptoms. In many cases, they report having suffered from prejudice and stigmatization since childhood, which can lead to lower academic achievement [20-23]. Lack of knowledge about the disease causes children and adolescents embarrassing situations due to yellow eyes (clinically known as jaundice), short stature and frail appearance, which patients often feature. In adulthood, some psychological issues persist related to the family unit, in which problems often arise from difficulties related to the provision of financial support, the care for the anemic person, and their sex life. Moreover, women and men experience anxiety due to the imminent failure of the execution of work tasks and sport activities [24-26].

Considering the work activities, the great advancement of technology, process automation and computer ubiquity are attributed to the Third Industrial Revolution, differentiating it from the preceding stages because of the prioritization of "intellectual capital". Thus, companies seek to select intelligent, creative and motivated professionals in order to generate new knowledge for the organizational culture [27]. Thus, the worst levels of education and socioeconomic development of the black population [28], and, in particular, of people with FA [29] place them in a particularly vulnerable situation in the context of the labor market, in both the "physical" and skilled labor aspects of work.

Another aspect of the labor market related to FA pertains to genetic screening and the selection process of labor recruitment: there are reported cases of exclusion of people with sickle cell trait (asymptomatic) for job positions in 1970 in the US [27]; in Brazil, there was a high-profile case in which a player was removed from the Brazilian national volleyball team because she carried the sickle cell trait [30]. Although occasional, the referred cases were widely discussed because no benefit for the safety

of workers could be obtained from these analyzes and, through this process, these people had their rights violated in relation to the secrecy and confidentiality of their genetic data.

Although it does not constitute a rule, the people affected by FA are mostly black. Thus, it can be deduced that the cultural vulnerability is also present in their lives, as well as social and economic vulneration factors. Religion is part of the culture of a population [29,31], and religions of African origin, as well as their music and customs, are constantly flouted and depreciated. Therefore, it can be deduced that interpersonal and institutional racism also interfere in the pursuit of health, as it excludes the development of desirable human potential for people living with the disease [32-34].

Another aspect relates to regional customs, such as the use of teas, potions and other traditional practices. These features should preferably be used in situations where people are sufficiently informed about the potential risks and benefits produced. Low education of the population about the disease, added to the difficulties of the users of the health system in primary care due to the unpreparedness of health professionals [35], generate the need for these practices to be integrated into the established conventional treatment, so that they do not produce damage [36].

In view of these aspects of vulnerability, Article 8 of UDBHR stresses the need for contemplation of the individual in their entirety, in order to protect vulnerable groups. Under the epistemological perspective of bioethics, this is achieved through its transdisciplinary characteristic, which cannot be restricted to a determined disciplinary paradigm, as it is committed to understanding the concrete totality [37]. This view is in line with the *Portaria 1391* [Decree 1391] from the Brazilian Ministry of Health, which establishes the guidelines of the *Política Nacional de Atenção Integral às Pessoas com Doença Falciforme e Outras Hemoglobinopatias* [National Policy for Integral Attention to People with Sickle Cell Disease and other Hemoglobinopathies], prevailing in the country since 16 August 2005 [38]. Also in relation to vulnerabilities, it is emphasized that people who have FA should be evaluated with caution by the professionals involved in the informed consent process. They should understand the biological, social and cultural aspects as existing factors, without stigmatizing or without reducing these people to their genotype or socioeconomic status, and always consider the uniqueness of each.

Autonomy, capacity, responsibility and willingness

The term "autonomy" is of Greek origin and was originally used to characterize the self-management and self-government exercised in the city-states in ancient times. Since then, the term has been extended to individuals and may have different meanings, such as: the right to liberty, privacy, individual choice, freedom of will, be the engine of their own behavior, belonging to himself/herself, among others [39]. According to Article 5 of UDBHR, the *autonomy of persons to make decisions, while taking responsibility for those decisions and respecting the autonomy of others, is to be respected* [11].

Immanuel Kant argues that respect for autonomy stems from the intrinsic unconditional value of all people. Thus, if this value is violated, the person will be treated merely as a means, not as an end in themselves. Thus, the interests of other people are prioritized in relation to the interests and objectives of oneself [40]. This concept is constituent of Kant's ethics theory called categorical imperative [41].

For someone to be considered able to consent to a certain procedure or participation in a study, it is necessary that the professional conducting the procedure or research assess the person's capacity to consent. By definition, capacity is the ability to perform a task [42]. Then, situations involving some kind of permanent (severe brain damage) or temporary (fainting or coma) harm of participants' capacity compromise the proper performance of the task and, in the context of scientific research, the autonomous decision [10].

The autonomous decision-making requires awareness to act appropriately based on certain commitments, or, in short, requires responsibility. Thus, the person who participates in an autonomous form of research should be responsible for the consequences of their free decisions and not violate the autonomy of others, evoking the common sense knowledge that their autonomy ends where the autonomy of others begin [43]. Therefore, in research where there are no differences between groups of children and adolescents with FA and adults with FA, priority should be given to participation of the latter, who have the greatest level of autonomy.

In the reality of research on FA, the vulnerabilities listed above may impair the ability to

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directly assess the situation, hindering autonomous choice. Thus, people invited to participate in scientific studies tend to suffer external influences to their will and coercive pressures from health workers or researchers. In other words, the difficulty in understanding the situation alienates and takes the role of decision-making from these people, subverting them and putting them at potential risk of abuse. Moreover the difficulties in access to health care of the most vulnerable population should be considered, a factor that may also lead to participation in a clinical study in the expectation of receiving differentiated and better quality health care .

When the researcher identifies a situation of vulnerability in a research participant, the researcher should strengthen their intent to act with kindness and ethical responsibility, empower the research participant in order to protect them and leave them free of controlling and paternalistic influences. This approach, from the perspective of bioethics' call for protection, implies that the power relations and vulnerabilities affecting both parties are unequal and, therefore, researchers need to be attentive, and committed to the principle of equity [18]. With this approach, the researcher ensures that research participation is voluntary, considering that, by accepting or declining the invitation to participate in the study, the person is acting of his own free will.

The free, prior and informed consent process

The process of free, prior and informed consent is composed of a series of steps through which the person invited must go to participate in a research project in Brazil, as explained in Article 4 of CNS Resolution 466 [12].

Quoted in national and international documents, the process of free, prior and informed consent is considered essential to the ethicality, good conduct of a research project, and respect for human rights. Through it, the research participants expresses their verbal and written consent to participate in a given project, after being informed about the study characteristics, potential risks and expected benefits. All clinical research involving human subjects must first be evaluated and approved by the relevant committee, which may, depending on the type of study, be a research ethics committee or even the National Research Ethics Commission Comissão Nacional de Ética em Pesquisa (CONEP), as provided in Article 8 of the before mentioned resolution. In the case of research involving people with FA, it is recommended that a health professional specialized in the field of hematology and a person with FA (preferably a representative from the patients association) participate in the consideration of the project.

The resolution is currently responsible for regulating scientific research involving human beings in Brazil. Section 2 presents an extensive list of terms, with great practical value, given the variability of connotations and meanings attributed to the usual research ethics terms that can be found in the literature. Thus, the document has the role to prevent dubious or misleading interpretations that add additional risks in conducting the research.

According to section 4, subsection 1, which provides for the steps of the free, prior and informed consent process, the first action of the researcher in relation to the potential participant should be clear and accessible explanation of the specifics of the research project. The researcher should clarify any doubts, consider the specifics of the person invited, and give them time to make their decision and consult their family or other people they trust, if deemed necessary. Then, as stated in subsection 2, the potential participant, or legal guardian, must read and understand the free, prior and informed consent (FPIC) form, which should be provided in two copies by the main researcher.

It is emphasized that the FPIC form is one of the steps of the free, prior and informed consent and cannot, therefore, be considered synonymous or even the most important part of the participant's consent process. The document must contain all the procedures to be performed and that involve the person invited, as well as the risks and benefits that they will be submitted to if they accept. It should also include information about the leading researcher, the sponsor of the research, specify the measures in case of compensation, as well as highlight the contact numbers, all arranged concisely and in accessible language.

There are also situations where it is difficult, or even impossible, to obtain the consent of the research participant due to problems relating to their ability to consent. In such cases, as stated in Article 7 of UDBHR called "Persons without the capacity to consent", the authorization for the research can only be granted in cases that directly benefit the referred participant, which should, as far as possible, be involved in the

decision-making. Thus, although legally deemed unable to give consent, their wishes must be taken into account and respected.

Another aspect to be considered by the researcher is the need to explain to the person invited that their participation is not bound to the continuity of the treatment of the disease, diagnosis or drug supply, particularly if the invitation is done in an environment designated to health care services. Making this aspects known is very important to ensure the willingness of participants, especially of those violated. Although research involving vulnerable groups should only be carried out in cases in which there are possibilities of benefits for these groups, it is important to emphasize that the possibility of benefits increases the groups' vulnerability, especially those whose vulnerability is initiated by problems of a physical nature.

Brazilian studies raise questions about the actual validity of the application of the FPIC form in developing countries because of the vulneration of part of the participating population, given that the proper understanding of the term is associated with higher levels of education, familiarity with reading and internet access [44]. These indicators are interpreted in some work as being directly related to the functional illiteracy of the country [45,46] and, therefore, affect the efficacy of the implementation of the FPIC form in developing countries. Thus, education in ethics in scientific research has an important role to educate researchers regarding the steps of the informed consent process, and the risks and damage to the consent when it is reduced only to the FPIC form. Awareness contributes decisively to professionals taking pains to ensure the rights of participants and minimize their vulneration. It is necessary that professionals and other research collaborators respect the privacy and confidentiality of research participants, so that no one else is aware they are participating in the study because they are carriers of the FA.

Final considerations

The considerations elucidated in this update evoke the following question: how can we overcome the challenges of the informed consent process applied in the context of vulneration of the population, considering specifically research on FA in the country?

The selection of study participants, regarding color, must be balanced with the frequency of the disease found in the population, and, also, carried out among people who already have been diagnosed with the disease, thus preventing a search being carried out in the community, which would generate stigmatizing actions.

Some tools are proposed to improve the level of understanding regarding the informed consent process, such as the use of playful resources - for example, explanatory drawings and videos [47]. These tools contextualize the essential information in the context of the everyday life of those invited to participate in the research, allowing them a more appropriate view of the study and, therefore, empowering them. The inclusion of information regarding the rights of people participating in scientific studies in explanatory booklets about the disease and self-care can help in popularizing this information.

Another tool suggested to increase the level of understanding by those invited to participate is their collective communication of the information [48]. This resource consists of explaining the research information of interest to the team, seeking to foster disinhibition and decreased embarrassment, and helping to clarify doubts and particularities. However, it should be noted that the resource cannot replace the individual step of the informed consent process, since the collective can somehow cause embarrassment to those who do not wish to participate in the study. Just as with the use of playful resources, professionals who opt for the inclusion of collective communications in the informed consent process should consider aspects related to available resources and physical space.

In Brazil, FA patients associations are protagonists in the fight for the rights of people with the disease [49], as well as for the health of the black population in general. Therefore, as long as these representative bodies have trained human resources and knowledge in the area of ethics in research and bioethics, a structure similar to an ethics committee can be formed. Thus, members can enjoy an additional protection factor, since the decisions in these situations tend to be more assertive, considering the effort spent by the collective. One option for the training of ethics in research for entities protective of the interests of people participating in research are the Bioethics Permanent Education Program (*Programa de Educação Permanente em Bioética*) courses offered online, with the possibility of full scholarships, by the Latin America and the Caribbean Bioethics Network (Redbioética), UNESCO.

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This also addresses the importance of the continued education of ethics in research by the professionals involved in the informed consent process, considering the importance of their social role in promoting health and proper compliance with the professional ethics codes. Once the quality of consent is associated with the experience of professionals in this practice [50], it is advisable that young researchers, still in training, follow the work of their tutors to perfect their skills in relation to the informed consent process. We also recommend the development of feedback in an accessible language that briefly reports the results and conclusions found by the research, in order to maximize benefits and contribute to the quality of information about the participant's disease, which may even improve their self-care.

Finally, although these are not an exclusive aspect of clinical research in health, but rather mechanisms aimed at eliminating vulneration and promoting emancipation and social empowerment, constant improvement and deepening of public policies aimed at social equity and the promotion of full citizenship for all citizens of the country are recommended as a key measure to health.

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