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CONSENT OF CLINICAL RESEARCH PARTICIPANTS: FREE AND ENCOURAGED?

Talita Garcia do Nascimento de Castro
Nurse. Doctor in Nursing. Process Coordinator at CTO - Cancer Treatment Center
Ribeirão Preto, São Paulo, Brazil
https://orcid.org/0000-0002-1758-1628

Lina Domênica Mapelli
Nurse. Master's Student of the Nursing Graduate Program in Public Health at the Institution's Ribeirão Preto School of Nursing: Universidade de São Paulo
São Sebastião da Grama, São Paulo, Brasil
https://orcid.org/0000-0002-3744-8154

Thais de Oliveira Gozzo
Nurse. Doctor in Nursing. Associate Professor at the Maternal-Child and Public Health Department at the Institution's Ribeirão Preto School of Nursing:Universidade de São Paulo
Ribeirão Preto, São Paulo, Brazil
https://orcid.org/0000-0002-7687-9459

Abstract: Objective: to evaluate the consent process of clinical research participants. **Method:** descriptive study with prospective collection. **Results:** after the descriptive analysis of the data and comparison between the variables through univariate analyses, of the 70 participants who composed the sample, 83% were women; with a mean age of 46.7 years; 55.7% were white; 45.75% had a partner; 52.9% low schooling; 49.3% economically active. Of the participant, research and Free and Informed Consent Term: 35.7% were unaware of the type of study they participated in (Observational, Surgery, Medicine); information about the risks or discomforts that could be experienced while participating in the research was received by 51.4%, while 62.3% were informed of the benefits; 62.7% had no information on indemnities; 66.2% confirmed that they did not read the entire document before signing; about the form and content of the document, 86.8% of the participants reported that the ICF was easy to read, 62.2% found the document long, and 71.1% reported that the words in the document were easy to understand. **Conclusion:** it is pertinent to encourage national studies that assess perceptions of research participants regarding their rights, as well as the construction of instruments that allow this verification in the Brazilian population.

Keywords: Personal Autonomy, Bioethics, Free and Informed Consent, Confidentiality, Research Ethics.

INTRODUCTION

In the post-World War II world, the bioethical precepts of beneficence, non-maleficence, autonomy and justice apply on condition: *sinequa non* with regard to research involving human beings. The historic demarcations of the Nuremberg Court (1947) and the Declaration of Helsinki (1964) deliberated conducts for clinical research designed for researchers and participants (SILVA; CONCEIÇÃO, 2020)[1].

Respect for the participant's autonomy is ensured via informed consent, which provides clarification about procedures, treatments and/or health research, in addition to informing benefits, risks and implications of interventions. The effectiveness of informed consent depends on the precise, objective and clear sharing of the aforementioned elements and it is up to the researcher to pay attention to the language accessible to the receiver (participant) so that he/she understands the contents, the finalAges of what is being presented and uses these explanations to to consent or not to consent (CORDEIRO; SAMPAIO, 2019)[2]. In view of the seriousness of this document, reaching informed consent can be a challenge in practice (CORDEIRO; SAMPAIO, 2019).[2]

Among its ethical and legal foundations, informed consent must have three constituents: voluntary participation; provision of appropriate information; apprehension and agreement, aiming to respect, promote the participant's autonomy and protect him/her from any type of damage/damage. Obtaining written informed consent from research participants, prior to enrollment in a study, is nationally and internationally recommended (GARBIN et al., 2021; COSAC, 2017).[3,4]

When the potential participant is invited to take part in the research, he/she is exposed to the Free and Informed Consent Term (FICT). This is characterized by being an explanatory document, in written format, in which information regarding the research project is addressed, in order to guarantee the individual's voluntariness. The qualAge of this term is linked to the degree of understanding of it by the research subjects (COSAC, 2017; BRASIL, 2012) [4,5].

The informed consents in health research often pass as obscure to the general population, who are unaware of their existence and relevance. (GARBIN et al., 2021) [3]. To certify that the participant absorbs the content of the informed consent and proves their willingness to make voluntary decisions, the researcher must confirm that it is in the participant's language and meets the participant's cultural, psychological and social requirements. The information must be true, cover all relevant aspects and no facts must be omitted, if any of the items is not met, the consent is invalid and unclear (GARBIN et al., 2021; CASTRO et al., 2020(6)); BATISTA et al., 2018(7); MILLUM; BROMWICH, 2021 [8])[3,6-8].

However, barriers to its understanding are still observed, such as: inclusion of technical and specific health terms; use of words that are difficult to assimilate; barriers with the Portuguese language; areas with low levels of formal education; collection of signatures, without due clarification, by the professionals themselves due to lack of knowledge of the value of the document. The TCLE only makes sense in the eyes of ethics when these barriers are crossed (GARBIN et al., 2021; CASTRO et al., 2020(6); BATISTA et al., 2018[7])[3,6,7].

In Brazil, there is a lack of prospective studies that assess the degree of understanding of clinical research participants, therefore, the importance of the present study, which aims to evaluate the consent process of clinical research participants, is justified.

METHOD

This is a descriptive, cross-sectional study carried out in a hospital of national reference in the treatment of cancer patients. It was approved by the Research Ethics Committee.

The study was developed from July 2016 to January 2017. Participants in clinical research in the field of oncology, appreciated by CONEP, aged 18 years or older and who had already passed the consent process and signed the ICF in a previous visit. Potential participants who were unable to respond to the form could count on the participation of their legal representative.

The data collection instrument was prepared based on information from Resolution 466/12 of the National Health Council [5], considering the mandatory items of an informed consent. A pilot study was carried out with 10 participants and later adjustments were made in form and content, more specifically on the words used.

Based on the volume of clinical studies at that institution, a sample size of 100 participants was calculated. However, at the request of the service, the study was interrupted with the inclusion of 70 participants.

Data were obtained through interviews with clinical research participants and/or their legal guardians, and additional information was collected through consultation of medical records. The signatures of the TCLEs for participation in this study were collected after application of the form, in order to minimize methodological bias.

In data analysis, the concept of readability index was used, referring to the size, formatting of words and construction of sentences, as well as paragraph spacing and alignment and other elements of the textual presentation (SILVA et al., 2021; COSTA et al., 2021; COSTA et al. al., 2020)[9,10].

This index was originally proposed by Rudolf Flesch, and looks for a correlation between average sizes of words, sentences and the ease of reading. Such indices are mathematical models that evaluate the structure of a text in terms of its sentences, paragraphs and quantAge of word syllables. (SILVA et al., 2021[9]; COSTA et al., 2020[10]; LOBATO; CAÇADOR; GAZZINELLI, 2013[11]; MIRANDA et al., 2009[12]) [9-12]. The Flesch-Kincaid Readability Index (ILFK) has

been the most used to assess the readability of a text, and its result estimates the years of study necessary for proper understanding (LOBATO; CAÇAADOR; GAZZINELLI, 2013; FERREIRA et al, 2021) [11,13].

To assess the readability of the TCLEs, the teams provided a copy of them that were typed in the Microsoft Word 2010 software, organized in alphabetical order, according to the research title, and identified from 01 to 12. Afterwards, they were analyzed by the ILFK, method validated for the Portuguese language (LOBATO; CAÇADOR; GAZZINELLI, 2013; MIRANDA et al., 2009) [11,12].

The identification of the elements necessary for the calculation of this index was operated by Microsoft Word 2010 and Word Counter software, to analyze the number of words, number of sentences and number of syllables contained in each TCLE.

To obtain the ILFK, each of the ICFs analyzed, the formula was used: ILFK = [(0.39 x average of words per sentence) + (11.8 x average of syllables per word)] - 15.59. The result obtained with the formula estimates the years of study necessary for the text to be properly understood. The ILFK values considered most effective for a text are those between 6 and 10 (LOBATO; CAÇADOR; GAZZINELLI, 2013; MIRANDA et al., 2009(12); FERREIRA et al.,2021) [11-13].

The Flesh Reading Ease Index formula is as follows: IFLF = 206.835 - ((1.015 x average sentence length) + 0.846 x (number of syllables per 100 words) The Flesh Reading Ease Index can be interpreted using a percentage scale of 0-100, where the standard IFLF is between 60 to 70% (FERREIRA et al., 2021; FERREIRA et al., 2020)[13,14].

RESULTS

The descriptive analysis of the data and comparison between the variables through univariate analysis showed that, of the 70 participants who composed the sample: 82.9% were women; Ages ranged from 23 to 79 years with a mean of 46.7 years (DV ±13.99 years). As for color, 55.7% declare themselves as white; 52.8% had a partner; 52.9% low schooling; 47.2% economically active. Among those who reported being professionally active and/or who had income, the average income found was 1496.2 reais (SD ± 1229.50 reais), (Table 1).

Although 64.3% of the participants reported having knowledge about the type of research they were involved in, 52.9% did not know or did not remember about the research. It is noteworthy that 64.7% were not informed about other treatments besides the one proposed by the study, and 63.2% did not receive information about assistance in case of interruption of the research or its termination (Table 2).

Information about the risks or discomforts that could be experienced while participating in the research was received by 51.4%, while 62.3% were informed about the benefits and 65.7% were aware of the secrecy and confidentiality of their data. personal data (Table 2) Regarding the information that, even refusing to participate in the research, it would not harm the continuity of care at the health service, 75.7% confirmed the receipt of this information and 62.9% were informed that they could withdraw from participating in the research in any time and continue receiving care at the hospital. The guarantee of reimbursement of expenses to participate in the research was informed to 57.8% of the participants; 62.7% said they had not received information about compensation for possible damages related to their participation (Table 2).

The signature of the TCLE, agreeing to participate in the research, was attested by 91.4% of the participants, 58.6% indicated that, before signing the document, someone from

Variables		N	%
Gender	Female	58	82,9
	Male	12	17,1
Age	21 to 30 years	8	11,4
	31 to 40 years	21	30
	41 to 50 years	14	20
	51 to 60 years	13	18,6
	61 to 70 years	11	15,7
	71 to 80 years	3	4,3
Color	White	39	55,7
	Brown	24	34,3
	Black	6	8,6
	Yellow	1	1,4
Marital status	With partner	37	52,8
	Without partner	33	47,2
Education	Illiterate	4	5,7
	Incomplete Elementary School	27	38,6
	Complete Elementary School	6	8,6
	Incomplete high school	8	11,4
	Complete high school	16	22,9
	Incomplete Higher Level	2	2,8
	Complete Higher Level	7	10
Work activity	Active	33	47,2
	Unemployed	16	22,8
	Retired/Pensioner	13	18,6
	Health leave	3	4,3
	Others*	5	7,1

* Others: housewives, students

Table 1- Distribution of participants according to gender, age, color, marital status, education, work activity and type of study the individual was undergoing.

Questions	Options	Number	%
What kind of research do you participate in?	Observational	19	27,2
	Surgery	18	25,7
	Medicine	8	11,4
	The person does not know	25	35,7
Can you tell me about the research you are participating in?	Yes	22	31,4
	No	27	38,6
	Partially	11	15,7
	The person does not remember	10	14,3

Did the person receive information about the risks or inconveniences of participating in the research?	Yes	36	51,4
	No	29	41,4
	The person does not remember	5	7,2
Did the person receive information about the benefits of participating in the research?	Yes	43	61,4
	No	18	25,7
	The person does not remember	9	12,9
Did the person receive information about the confidentiality of the name and personal information during the research?	Yes	46	65,7
	No	17	24,3
	The person does not remember	6	8,6
	The form has not been filled	1	1,4
Did the person receive information about not accepting to participate in the research and continuing to be treated at the hospital?	Yes	53	75,7
	No	13	18,6
	The person does not remember	4	5,7
Did the person receive information about giving up participating in the research at any time and continuing to be treated at the hospital?	Yes	44	62,9
	No	19	27,1
	The person does not remember	7	10
The person received information that he would not have expenses and that his expenses for participating in the research would be covered?	Yes	37	52,9
	No	20	28,6
	The person does not remember	13	18,5
Did the person receive information about compensation for possible damages related to their participation in the research?	Yes	9	12,9
	No	42	60
	The person does not remember	13	18,6
	The form has not been filled	6	8,5
Before signing: did anyone from the research team read it?	Yes	41	58,6
	No	24	34,3
	The person does not remember	5	7,1
Did the person have the opportunity to ask questions with someone from the research team?	Yes	37	52,9
	No	31	44,2
	The person does not remember	2	2,9
Before signing: could you take the consent form home to read and talk to your family members?	Yes	18	25,7
	No	46	65,7
	The person does not remember	6	8,6
Before signing: did the person read the entire ICF?	Yes	22	31,4
	No	45	64,3
	The person does not remember	3	4,3
Did you sign the consent form before starting to participate?	Yes	64	91,4
	No	2	2,9
	The person does not remember	4	5,7

Table 2 - Research participant's understanding of the type of research, presentation and signature of the TCLE

Source: search database.

the research team read it and 52.9% declared that there was an explanation of the TCLE. Among the respondents, 52.9% reported the opportunity to clarify doubts with someone from the research team, 25.7% took the ICF home to read and talk to their families and 31.4% confirmed that they had read the entire document. before signing (Table 2).

A comparative analysis of the questions answered by the participants was carried out, according to the variables: age, gender and education and the statistically significant results are compiled in Table 3.

Among the participants in this study, 92.9% confirmed receiving a copy of the consent form, 73.9% said it was signed by someone from the research team and 94.2% said they had kept their copy of the term. As for the form and content of the TCLE, 86.8% of the participants reported that the TCLE was easy to read, 62.2% found the document long, and 71.1% reported that the words in the document were easy to understand. The ICF of 82% of the respondents did not present drawings and/or explanatory schemes.

The 70 participants were part of 12 clinical trials, of which 66.7% were international multicenter and 16.7% national multicenter, and the research involved clinical trials with drugs, tests of New therapeutic devices and radiotherapy treatment (Table 4).

In the readability analysis, it was noted that the TCLEs had a minimum of three and a maximum of 34 pages, with an average of 12.7 pages. After calculating the ILFK of each ICF, it was found that 100% of the ICFs evaluated had a value from 0 to 30, that is, very difficult reading, requiring higher education for understanding (Table 4).

DISCUSSION

Informed consent has become a critical component in the development of clinical trials. Only when this consent is truly informed and voluntary are the research results valid and reliable. Participants must receive sufficient and correct information about the study in order to feel secure about their participation. (CASTRO et al., 2020; MARINA; DUARTE; RICOU, 2020)[6,15].

Thus, the quality of informed consent is associated with the degree of understanding that research participants have about it. Which makes the voluntary and truly informed consent process a challenge to obtain (CORDEIRO; SAMPAIO, 2019; MARINA; DUARTE; RICOU, 2020)[2,15].

Cases of violations in the quality of the informed consent process are frequently described in studies carried out in developing countries, where Brazil is located. It can be considered that these countries have a large part of their population and possible research participants extremely vulnerable, due to low levels of formal education, social, cultural and economic conditions; in addition to little familiarity with biomedical research and limited access to health services (COSAC, 2017; CASTRO et al., 2020)[4,6].

In a study carried out with participants in clinical trials developed at a research center in Brazil, the following personal characteristics that can interfere with the understanding of informed consent were identified: low level of education, female gender and low socioeconomic level (AMORIM et al., 2018) [16]. Data corroborated in the present study, and may point out that potential research participants and their characteristics must be properly evaluated to identify factors that may negatively affect the quality of consent obtained.

When dealing with the analysis of understanding of the informed consent, one must consider the assessment of the readability of texts and terms used in clinical trials. When evaluating the TCLEs used in Brazil, it is important to consider the schooling

Quizz	Variables	Statistical test	p value
The person received information about compensation for possible damages related to their participation in the research	Education	Fisher's Exact Test	0,029
Before signing: someone from the family helped in reading the informed consent	Age	Fisher's Exact Test	0,024
Before signing: someone from the family helped in reading the informed consent	Gender	Fisher's Exact Test	0,01
Difficulty in reading the ICF	Age	Qui²	0,042
The person had the opportunity to ask questions with someone from the research team	Age	Fisher's Exact Test	0,05
The person signed the consent form before starting to participate	Age	Fisher's Exact Test	0,025

Table 3.

Source: study data.

ID TCLE	Type of research *	Research about	Number of Participants	Number of pages	ILFK
1	MN	Medicine	1	15	19,9
2	MI	Radiotherapy	9	12	16,6
3	MI	Medicine	1	13	15,5
4	MI	Medicine	1	21	21,6
5	EN	New devices	14	6	15,3
6	MI	Surgery	4	11	17,4
7	MI	Medicine	1	17	20,4
8	MI	Medicine	1	4	16,3
9	MI	Medicine	1	12	15,3
10	PE	New devices	29	5	15,8
11	MN	Observational	7	3	17
12	MI	Medicine	1	34	18,7

*MN: national multicenter; MI: international multicenter; PE: foreign participation; EN: national study

Table 4 - ILFK index according to the type of research, number of informed consent pages and number of participants.

profile of a large part of the population, in which a large portion of Brazilians are classified as having low formal education (LOBATO; CAÇAADOR; GAZZINELLI, 2013; FERREIRA et al., 2021).)[11,13].

In addition, attention must be paid to understanding the risks, benefits, confidentiality, continuity of care in case of refusal and the right to withdraw, the results observed in this study are corroborated by a meta-analysis of 103 studies (TAM et al., 2015) [17]. It pointed out that 75.8% of the participants understood about the freedom to withdraw consent at any time, 74.7% about the nature of the study, 74% about the potential benefits and 67% about the risks and side effects, 66, 2% on confidentiality and 64.1% on availability of alternative treatment.

The complexity of clinical research informed consents stems from the very nature of these investigations, which makes a detailed explanation of their methodological procedures necessary. Failure to include information may affect the understanding of the documents, since the methodology of these studies is unknown by research participants (LOBATO; CAÇADOR; GAZZINELLI, 2013) [11].

Laws, regulations and cultures contribute to the formulation of complex consent forms. Currently, only a few ethics committees are willing to address the complexity and length of these documents and ask researchers and sponsors to review them in order to make them understandable to potential participants (BLEIBERG et al., 2017) [18].

Several strategies have been adopted in an attempt to improve informed consent in clinical studies, including: written information (enhanced consent document, Yesplified language, use of illustrations and layout change); detailed verbal information; interventions with feedback testing; telephone interventions; computer-assisted programs; audiovisual interventions and medical communication training. However, most of these studies focused on the ICFs or their structural components, aiming to improve the presentation of information or the mode of delivery, and not the decision-making process. The focus on improving the provision of information is further reflected in the results of these studies, which show few significant improvements in knowledge and understanding among participants when analyzed together. (GILLIES et. al., 2015) [19].

Yesplifying the informed consent, by itself, does not always significantly improve the participants' understanding, since, after a survey, it was found that approximately 40% of the participants do not understand a Yesplified consent document. Among its reasons are: the precarious literacy skills; little knowledge about health-related issues; and a likely fear of asking for clarification on the information provided, even if they did not understand what the healthcare professional said (BLEIBERG et. al, 2017) [18].

Therefore, it is necessary to use documents that can be understood by a wider number of participants, considering their peculiarities. Once this is done, other approaches will be needed to evaluate the process, and eventually develop communication strategies (BLEIBERG et. al, 2017) [18].

Discussions around these issues contributed to a greater interest in evaluating the process of obtaining consent. Greater attention must be given to the strategies put in place by research groups to invite subjects to participate, inform them about the activities and purposes of the research, and obtain their final signatures on the consent form. (WESTFALL et al., 2017[20]; KRIEGER et al., 2017[21]; GRADY et al., 2017[22])[20-22].

The legitimacy of informed consent is directly related to the participant's ability to understand and record information about the

study, and is not guaranteed only by Yesply signing the informed consent. In this sense, it is suggested that the conduct of research with human beings follows ethical norms and guidelines, such as those that are also registered in good clinical practices. This document provides a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical studies, ensuring the credibility and accuracy of data and results, as well as the protection of the rights, integrity and confidentiality of the subjects of the study (GARBIN et al., 2021; CASTRO et al., 2020; BATISTA et al., 2018; MILLUM; BROMWICH, 2021)[3,6-8].

Although this study brings important contributions regarding the consent process of clinical research participants, it must point out limitations, such as the lack of an instrument for data collection and the request for the interruption of the research by the service.

CONCLUSION

Free and informed consent is a complex process, with the beliefs, values and culture of a human being at stake and, therefore, must be treated as the fundamental step of all research. When signing the document, its last step, it must be ensured that the individual has an accurate understanding of its content. It is then up to the professionals to ensure that the participant was not only informed of all the details of the research, but also clarified.

Faced with the need to establish standards that provide reliable, conscious and proper decision-making by potential participants, it can be stated that actions aimed only at Yesplifying the informed consent, in terms of its form, structure and language, would not significantly improve its understanding. In addition to essential the preparation of documents that can be understood by a greater number of individuals, the development of communication strategies, in accordance with the uniqueness of each individual, considering their educational level, their personal needs, expectations, beliefs and customs.

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