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HEALTH LITERACY AND UNDERSTANDING OF THE INFORMED CONSENT FORM IN CLINICAL RESEARCH

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ABSTRACT

Objective: To verify and analyze the Functional Health Literacy (FHL) test in 40 clinical research participants in view of the understanding of the Free and Informed Consent Term (FICT). **Method:** quantitative, observational, cross-sectional and descriptive research. A questionnaire containing specific questions and sociodemographic characterization was used to assess understanding of the FICT, and for the FHL, the validated instrument Brief Test of Functional Health Literary in Adults was used. Statistical analyzes were performed using the Stata® software, version 15.1. and considered statistically significant associations with p value <0.05. **Results:** 50% men, 65.5 years old on average, 40% did not know what the informed consent is, 19 people signed it without reading it, 60% did not know the meaning of placebo, 77.5% did not know the study period and 15% did not know that leaving the study had no implications, 55% attended incomplete elementary school. Gender, age and schooling were associated with the mean variation in the total FHL score. Women and more educated people had higher scores and increasing age was associated with a decrease in the average score (R^2 of the final model of 0.57). **Conclusion:** 52.5% had inadequate FHL. Additional studies must be carried out to spread a culture of respect for human dignity, with autonomous and informed participation in research.

Keywords: Knowledge. Ethics. Research. Patient Participation. Informed Consent. Personal Autonomy.

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Revista ARACÊ
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INTRODUCTION

Research is very important for the development of science, improving clinical practice, as well as health care. There has been great progress in the last 50 years with the development of new drugs, devices, equipment and techniques, however research aimed at improving health and eradicating diseases in human beings is still carried out and necessary as there are still gaps in diagnosis, treatment of existing health problems and emergence of new diseases, as occurred with the COVID-19 pandemic [1,2].

Research involving human beings is part of the evolution of science, but it is necessary to discuss how and why it is done. Questions in this sense have been carried out for a long time, mainly in relation to the autonomy of the research participant. [1,3].

During World War II (1939-1945) there were horrendous experiments carried out that provided a great leap in knowledge, but in the name of eugenics they ignored the autonomy, consent and well-being of the individuals who were guinea pigs in these researches.[3]

In 1945 the UNO (United Nations Organization) issued a letter in defense of peace and that human rights were promoted and defended [4], occasion when the Nuremberg Tribunal was created, in 1946, which tried 23 people involved in the purification project of Hitler's Aryan race [5–7].

In August 1947, an international document that became known as the Nuremberg Code was published, a historic landmark of ethics in research, where the need to respect the voluntariness and dignity of the participant is crystal clear. This code consists in the superimposition of the principlist ethics of Hippocratic roots (5th century BC); beneficence, non-maleficence and autonomy; with the protection of human rights. This document has ten points of guidelines for conducting human experiments. [6].

After that, the International Code of Medical Ethics (1949), the Declaration of Helsinki (1964) and the International Ethics Guide for Biomedical Research Involving Human Subjects (1982), whose last update took place in 2016, were successively created. [3,8].

The Free and Informed Consent Term (FICT) emerged in the wake of World War II, due to the cruelties that occurred in that period [9].

In Brazil, the FICT was introduced with the elaboration of the National Health Council (NHC) Resolution of June 13th, 1996, number 196/96[10]. This Resolution was created by an Executive Working Group (EWG), composed of representatives from multiple social and professional areas, involving physicians, theologians, lawyers, biologists, biomedical

Revista ARACÊ
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engineers, businessmen and user representatives, which prepared a new resolution (NHC n. 196/96) establishing the norms for research involving human beings [6].

The consent of a research participant is documented by means of a written informed consent form, signed and dated, [11,12] for this reason it cannot be characterized only as a paper where the researcher expresses in writing an invitation that an individual accepts to participate in a particular study, without understanding the reasons for doing so [13].

It is a process by which the research participant and/or his/her legal representative voluntarily confirm(s) his/her willingness to participate in research, after having been informed in detail of all aspects involving the study in which he/she will participate and having been opportunity to clarify all their doubts. Several research requirements must be explained in a transparent manner: justification, objectives, methods and procedures, expected benefits, potential risks and the inconvenience it may cause. Likewise, the follow-up mode must be recorded; the guarantee of full freedom to the research participant, to refuse to participate or withdraw their consent, at any stage of the research, without any penalty; guarantee of secrecy and privacy, compensation and indemnification, and also; that a copy will be delivered to the research participant.

All research involving human beings in the national territory must be approved by the CEP (Research Ethics Committee)/CONEP (National Research Ethics Commission) system [11].

In Brazil, currently, NHC Resolution 466/12 guides research in human beings, replacing Resolution 196/96. It is explicit that all research must have an informed consent in respect of human dignity, establishing its content and how it should be applied. Briefly, the first stage deals with the invitation and clarification to the guest about their participation in the research. This invitation must be made at the appropriate time, condition and place; using clear and accessible language; providing enough time for the guest to read the FICT, reflect and make a decision whether or not to participate in the research, being able to withdraw the authorization at any time, without prejudice to you.[11]

Functional Health Literacy (FHL) has been much discussed in the health area, related to health promotion [14], it is defined as the ability to obtain, process and understand basic information and services in order to make appropriate decisions regarding own health and medical care [15,16].

The term “health literacy” was first used in 1974 by Simonds [14], and in 1999 it was re-elaborated by the American Medical Association (AMA) as “Functional Health Literacy”

Revista ARACÊ
ISSN: 2358-2472

(FHL), recognizing it as a set of skills that encompass “reading, understanding and acting on health information”.[14]

It is believed that a person with satisfactory FHL has a better health condition, has a greater ability to understand preventive measures and a better understanding of the instructions to correctly take the medication.[14]

The World Health Organization (WHO) defines FHL as the cognitive and social skills that determine the motivation and ability of individuals to access, understand and use information as a way of promoting and maintaining health, which does not mean only and simply knowing how to read pamphlets related to health problems and schedule appointments. The Commission on Social Determinants of Health identified FHL as one of the social determinants of health, establishing a relationship between it and the population's quality of life, considering it as fundamental to self-care, health promotion and improvement. The lower the FHL, the worse the rates of hospitalization, delays in diagnosis, less knowledge of their own health status and greater risk of mortality. [14,17,18].

In Brazil, 27% of the population between 15 and 64 years old are considered functionally illiterate, which means that even though they know how to read and write, they do not have the reading, writing and calculation skills necessary for their personal and professional development [19], this problem is worsens when these people use the health service [14].

Thus, as a technical nurse responsible for the Santa Casa de Votuporanga Clinical Research Unit at the beginning of this research, accustomed to applying informed consent to research participants, and observing the difficulties shown by them, studying FHL in the application and understanding of the informed consent became of great interest for research.

The objective of the present study was to verify and analyze the Functional Health Literacy Test (FHL) in 40 clinical research participants in view of the understanding of the Free and Informed Consent Term (FICT).

Revista ARACÊ
ISSN: 2358-2472

METHOD

STUDY DESIGN

Observational, cross-sectional, descriptive research with a quantitative approach.

PLACE AND PERIOD OF STUDY

Data collection was carried out from March to September 2021, at Santa Casa de Votuporanga Clinical Research Unit, a philanthropic institution that provides care to patients of the Unified Health System (SUS) and is in Votuporanga (SP), Brazil.

In 2019, the Clinical Research Unit had 11 interventional and 6 observational clinical studies, totaling 157 research participants related to the cardiovascular system, nephrology, endocrinology (type 2 diabetes mellitus), dyslipidemia, among others.

RESEARCH PARTICIPANTS

Sixty individuals were invited, of whom 40 met the inclusion criteria, agreed and answered the questionnaires; 11 agreed, but were not able to answer the questionnaires alone, and for this reason, they were not included; and 09 did not want to participate. All these individuals had been patients at the Santa Casa de Votuporanga Clinical Research Unit for at least 30 days.

The inclusion criteria were age ≥ 18 years, without restriction of gender, race/ethnicity, religion or social status and who agreed to participate in this research by signing the informed consent form. Illiterate, semi-illiterate, hearing-impaired or visually impaired patients who had some functional disorder that prevented them from participating, as well as those who did not agree to sign the informed consent form or withdrew it at any time, were not included.

The sample size was calculated considering the finite population of study participants (N=157). The method used for data analysis (Critical-X2), effect size of 30% and probability of type 1 error of 0.05 were considered. Data analysis was performed using linear regression (Z-score).

DATA COLLECTION INSTRUMENTS

Aiming at assessing the understanding of the informed consent, a questionnaire developed by the researchers was used, containing the sociodemographic characterization of the participants, gender, age (in complete years), education, family income (in minimum

Revista ARACÊ
ISSN: 2358-2472

wages), and questions related to the informed consent and the study it was involved in (Appendix B). This questionnaire is based on what is recommended by the legislation in force in the national territory (Resolution 466/12) on the FICT and its respective content.

The B-THOFLA (Brief Test of Functional Health Literary in Adults) questionnaire was used to assess the FHL, validated for Portuguese.[17] This questionnaire assesses two literacy components: numerical or quantitative literacy and literacy based on comprehension. In all, there are 3 applied questionnaires that must be completed in a timely manner. Blank answers should be considered incorrect in the final score.

This instrument consists of 36 items of textual comprehension, which add up to 72 points and 12 numerical items that add up to 28 points, totaling 100 points. For each question, 1 point is assigned for the correct one and 0 points for the incorrect one. The interpretation is divided into three categories according to the score obtained, 0-59 (inadequate literacy), 60-74 (limited literacy) and 75-100 (adequate literacy) [(17)].

ETHICAL PROCEDURES

The project was initiated after approval by the Santa Casa de Votuporanga Clinical Research Unit, including the Research Ethics Committee of the Centro Universitário de Votuporanga (UNIFEV), where the informed consent was also assessed (Appendix C). CAAE number 32787320.9.0000.0078.

STATISTICAL ANALYSIS

All information about the research participants was coded and stored anonymously in an Excel® database. Statistical tests were performed using Stata® software, version 15.1. Associations with p value < 0.05 were considered statistically significant.

The sociodemographic profile and the in-depth questionnaire on the FICT were presented according to absolute and relative values, when categorical variables, and through the mean and standard deviation or median and interquartile range for continuous variables.

The presentation of the general results of the B-THOFLA was made by module: presenting the number of answers (total of questions in each module times the number of participants), average time to complete the module, percentage of correct answers, errors and incompleteness of the questions.

Revista ARACÊ
ISSN: 2358-2472

The final score is calculated as follows: a rule of three is applied to the results of the first module, which consists of 17 questions, so that the final score varies between 0-50 points. The three comprehension modules add up to 50 points. Thus, we have the final indicator with variability from 0 to 100, and the higher the score, the higher the health literacy condition.

Due to the sample size, two ways of analyzing the results are proposed: the first by evaluating the final score, as a continuous variable through a linear regression model. In this way, we will identify which factors affect the average variation in the FHL score.

The second methodology applied corresponds to the assessment model predicted by the instrument, in which scores between 0 and 59 are indicative of inadequate literacy, between 60 and 74 points, limited literacy and scores above 74 points are considered for adequate literacy. We describe the results by category using mean and standard deviation, as well as analysis of factors associated with adequate literacy using the chi-square test.

RESULTS

The study sample consisted of 40 individuals, equally distributed according to gender and with a mean age of 65.5 years. The largest proportion of the sample self-declared white (80%), and 55% of the participants had incomplete elementary school education, 9 (22.5%) people indicated having completed higher education or postgraduate studies. The average income reported was 3.5 minimum wages per person.

The description of information on the informed consent signed for participation in a study at the Hospital was divided between tables 1 and 2 to simplify the reading and description of the most relevant results. It is noteworthy that all participants were part of studies developed at the referral hospital and were in the research for more than thirty days and 06 patients participated in other research previously.

Table 1 - Information on the informed consent form and its doubts from the patient's perspective. Votuporanga, SP, Brazil, 2021

	n	%
Knows what FICT is?		
Yes	24	60
No	10	25
Not known	6	15
Took the FICT home?		
Yes	25	62.5
No	9	22.5

Revista ARACÊ
ISSN: 2358-2472

Not known	6	15
Signed an informed consent before the beginning of the research?		
Yes	35	87.5
No	1	2.5
Not known	4	10
Signed the term without reading it?		
Yes	19	47.5
No	18	45
Not known	3	7.5
Did the patient read the informed consent?		
Yes	1	2.5
No	10	25
Not known	3	7.5
Yes, complete	12	30
Yes, part of it	14	35
Who accompanied the patient in the reading?		
Doctor	3	7.5
Research coordinator	3	7.5
Family	6	15
Nobody	28	70
Who on the team explained the FICT?		
Research coordinator	15	38
Doctor	22	55
Not known	3	7.5
Had questions during the application of the form?		
Yes	4	10
No	35	87.5
Not known	1	2.5
Have doubts been explained?		
Yes	38	95
No	2	5
Found it difficult to understand the term?		
Yes	2	5
No	37	92.5
Not known	1	2.5
Knows what a placebo is?		
Yes	16	40
No	24	60

Some questions were asked to understand the patients' understanding of the study they were participating in. These questions are described in table 2.

Revista ARACÊ
ISSN: 2358-2472

Table 2 - Information and perceptions about knowledge in relation to the baseline study and the relationship between participating in the study, losses and gains from the patient's perspective. Votuporanga, SP, Brazil, 2021

	n	%
Does the study have a placebo?		
Yes	8	20
No	20	50
Not known	12	30
Do you know the duration of the study?		
Yes	8	20
No	31	77.5
Not known	1	2.5
What disease is the study about?		
Heart diseases	19	47.5
Hypertension	10	25
Diabetes	7	17.5
Renal insufficiency	3	7.5
Not known	1	2.5
Does the study have medication?		
Yes	25	62.5
No	13	32.5
Not known	2	5
Knowledge about the risks of the study?		
Yes	7	17.5
No	30	75
Not known	3	7.5
Knowledge about the benefits of the study?		
Yes	12	30
No	24	60
Not known	4	10
Knowledge about the possibility of withdrawing from the study?		
Yes	34	85
No	4	10
Not known	2	5
Do you know if dropping out of the study implies not stopping the treatment?		
Yes	34	85
No	5	12.5
Not known	1	2.5
Does the patient understand that participating in the research generates costs?		
Yes	1	2,5
No	39	97.5
Who was responsible for convincing the patient to participate in the research?		
Doctor	6	15
Researcher (physician)	1	2.5
The person himself	31	77.5
Family	2	5

Revista ARACÊ
ISSN: 2358-2472

Entering the analyzes focused on the FHL, we were able to assess the total responses in each component of the test. The average time to answer the first component was seven minutes. This time was longer for component 2, related to the comprehension assessment, which was 5 minutes, and the third component, 54 minutes. However, when we consider the three components of comprehension, the average time for completion gradually decreases. This indicator may be related to difficulties in time management and in understanding the instruments.

There is an inversely proportional relationship between the decrease in the average time to answer the component and the increase in the percentage of unanswered items. The numerical assessment had all fields filled in and the comprehension assessment 72.3% were not filled in.

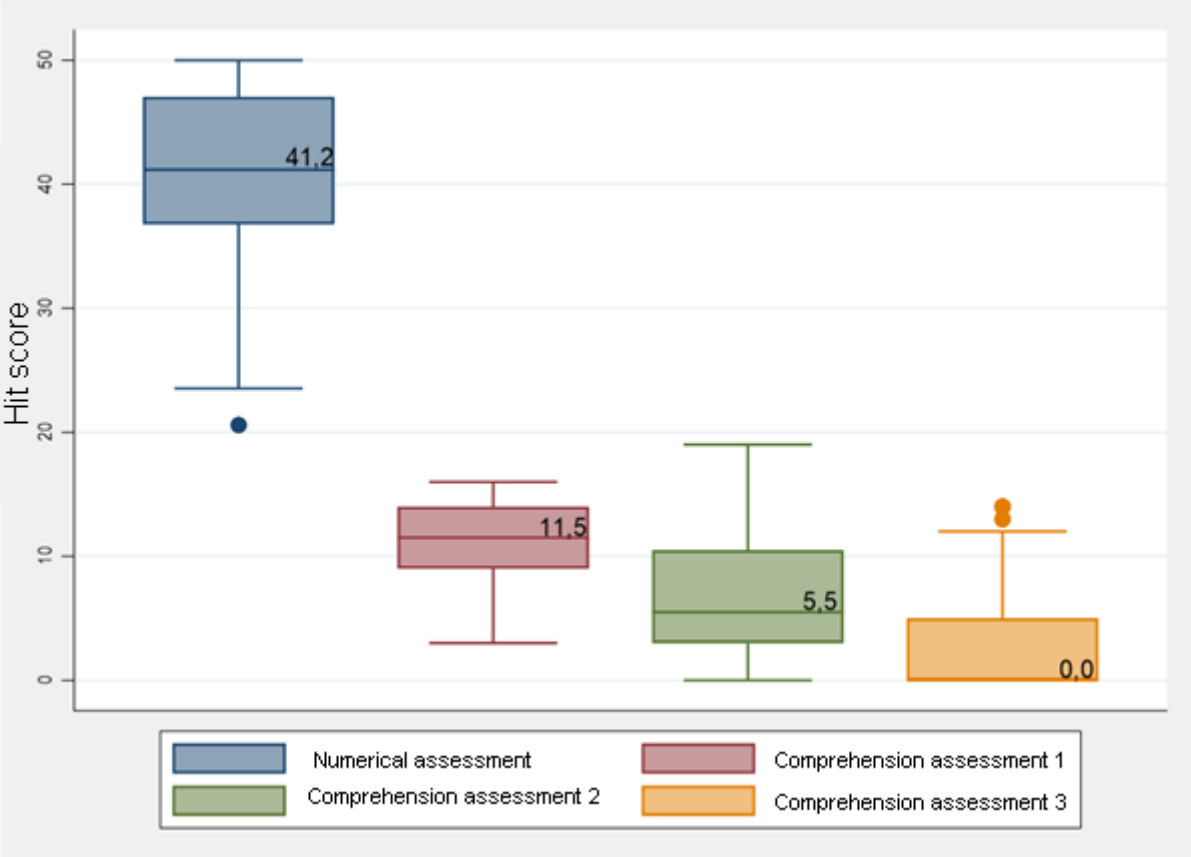
The distribution of scores for each component presents the median score as a reference. It is important to note that the score for each component varies, with the variability of component 1 ranging from 0 to 50 points, component two ranging from 0-16 and the last two components ranging from 0-20 and 0-24 points, respectively. In congruence with the information gathered about the filling time and the unfilled items are scored as “incorrect answers (score equal to 0)”, there is a decrease in the average score as the order of answers increases, with the score of correct answers for the numerical assessment 41.2; the comprehension rating 1 of 11.5; for comprehension 2 of 5.5 and for comprehension 3 of zero.

Considering that the analyzes of associated factors will be based on the total score, figure 1 presents the overall median score of the FHL test – 58.6 points for the sample in question, with variability between 33.5 and 99 points. The average score for the total indicator was 62.4 points.

The classification predicted by the instrument in question divides individuals into adequate, limited and inadequate literacy. For the study sample, 25% had adequate literacy and 52.5% had inadequate literacy (Figure 1).

Revista ARACÊ
ISSN: 2358-2472

Figure 1 - Boxplot of scores for each Functional Health Literacy Test component. Votuporanga, SP, Brazil, 2021



Using the continuous FHL test score as a reference, an unadjusted and adjusted linear regression model was designed to assess the possible factors associated with the mean variation of the score in question (TABLE 3). The results indicate that the older the individual, the lower the score obtained. Schooling, on the other hand, showed a directly proportional relationship, with an increase in schooling having an impact on the average increase in the total score. Income was also a factor associated with the mean variation of the FHL test score, but only in the unadjusted model. When included in the adjusted model, it lost statistical significance – possibly because schooling is a proxy indicator for income and vice versa, making it impossible to have both variables with statistical significance in the final model.

Gender was not associated with the mean variation of the FHL test score in the unadjusted model, but it started to show statistical significance in the multiple models. This result should be interpreted as follows: women have on average, a score 9.7 points higher than men in the study.

Revista ARACÊ
ISSN: 2358-2472

Among the factors described by patients about their knowledge of the baseline study and about the informed consent, only knowing what the informed consent would be and having participated in other studies had statistical relevance. Having knowledge about the informed consent resulted in an average increase of 13.18 points in the total score of the FHL test, while people who had already participated in previous studies had an average score 17.81 points higher than those who had not participated. This association was not maintained in the final model.

Table 3 - Factors that influence the Health Literacy Test Score. Votuporanga, SP, Brazil, 2021

	unadjusted coef*	**IC 95%**	**adjusted coef***	**IC 95%**
Gender				
Male	Ref		Ref	
Female	9.50	-2.00;21.00	**9,70**	**1.83;17.55**
Age	**-0.74**	**-1.30;-0.19**	**-0.45**	**-0.88;-0.02**
Education	**5.64**	**3.80;7.48**	**3.86**	**2.16;6.57**
Income	**3.90**	**2.09;5.71**	1.17	-1.01;3.34
Time that is entered in the research	-0.4	-9.60;8.80		
Knows what FICT is	**13.18**	**0.13;26.23**		
Finds it difficult to understand the consent form	-5.49	-27.27;16.29		
Have participated in another research	**17.81**	**3.26;32.36**		

R^2 of the adjusted model: 0.57
*Coef = Coefficient
Note: Results in bold show p value < 0.05

Regarding the adjusted model, we identified that gender, age and education were associated with the average variation of the total score of the FHL test, with women and more educated people having higher scores and increasing age was associated with a decrease in the average score.

The R^2 of the final model was 0.57, which indicates that 57% of the variability in the FHL Test Total Score was explained by age, gender and education, controlled by the income of the study participants (Table 3).

It is interesting to note that, through the analysis that considers the classification of the individual based on the total score of the FHL test, we observed the same pattern of associated factors. In this sense, we corroborate that a higher level of education, higher income, younger people are those who are more likely to be classified as having adequate literacy.

Revista ARACÊ
ISSN: 2358-2472

Other questions presented in table 4 showed no association with the outcome of interest.

Table 4 - Comparison between adequate literacy and limited or inadequate literacy in study participants and their associated factors. Votuporanga, SP, Brazil, 2021

	Adequate literacy	**Limited or inadequate literacy**	**p value**
Total	10 (25%)	30 (75%)	
Gender			
Male	4 (20%)	16 (80%)	0.716
Female	6 (30%)	14 (70%)	
Age (mean, SD)	**58.2 (3.12)**	**68.1 (1.62)**	**0.0057**
Education			
Up to high school	**3 (9.7%)**	**28 (90.3%)**	**<0.001**
Higher education and postgraduate	**7 (77.3%)**	**2 (22.2%)**	
Income	**5,8 (0.92)**	**2,8 (0.40)**	**0.0013**
Knows what FICT is			
Yes	9 (37.5%)	15 (62.5)	0.115
No	1(10%)	9 (90%)	
Not known	0 (0%)	6 (100%)	
FICT reading			
Yes	1 (100%)	0 (0%)	0.08
No	3 (30%)	7 (70%)	
Not known	0 (0%)	3 (100%)	
Yes, complete	5 (41.7%)	7 (58.3%)	
Yes, part of it	1 (7.1%)	13 (92.9%)	
In case of having read, the reading was done			
Not applicable	3 (33.3%)	6 (66.7%)	0.243
Alone	7 (33.3%)	14 (66.7%)	
Accompanied	0 (0%)	7 (100%)	
Not known	0 (0%)	3 (100%)	
Doubts during the application of the Consent Form?			
Yes	0 (0%)	4 (100%)	0.667
No	10 (28.6%)	25 (71.4%)	
Not known	0 (0%)	1 (100%)	
Difficult to understand the term			
Yes	10 (26.3%)	28 (73.7%)	1.00
No	0 (0%)	2 (100%)	
Not known	-	-	
Disease the study is about			
Heart diseases	4 (21.1%)	15 (78.9%)	0.727
Hypertension	4 (40%)	6 (60%)	
Diabetes	2 (28.6%)	2 (71.4%)	
Renal insufficiency	0 (0%)	3 (100%)	
Not known	0 (0%)	1 (100%)	

Revista ARACÊ
ISSN: 2358-2472

Participation in another research			
Yes	0 (0%)	7 (100%)	0.161
No	10 (30.3%)	23 (69.7%)	

DISCUSSION

Research with human beings has progressively increased in recent decades, encouraged by scientific and technological discoveries. However, although fundamental for progress, it cannot do without the ethical and philosophical principles of beneficence, non-maleficence, justice and autonomy, in respect of human dignity [20]. New principles also came into force in decision-making, such as the principle of protection, applicable to situations of need in which Third World populations find themselves, in terms of inequalities in public health and research in dependent countries [21,22].

Conducting research presupposes the signature of the consent form of the participants, individuals or groups that, by themselves and/or by their legal representatives, tacitly express their consent, in accordance with the relevant legislation. The Free and Informed Consent Process is understood to mean all the steps to be necessarily observed so that the person invited to participate in research can express themselves, autonomously, consciously, free and informed, but it is also and not least, an indispensable condition in the doctor-patient relationship [11].

However, long FICTs with texts that are difficult to understand, although they may eventually comply with the legislation, can constitute a mere bureaucratic procedure, so much so that the few studies carried out on the understanding of the FICT brought similar results to those found in this research.

The 40 participants in the present study were equally distributed between men and women, married (80%) and with a mean age of 65.5 years, configuring a predominance of elderly people. The level of education brings one of the main components of analysis of the study, which is the low education of the research participants, since 55% of them had only incomplete elementary education, which can also correspond to low income. These ingredients, particularly the educational level, may have resulted in the use of inaccessible language on the part of the FICT applicators and in the participants' lack of courage to admit that they did not understand the content and ask for clarification of their doubts. The results we found and recorded in table 4 corroborate this need.

The health professional responsible for applying the informed consent, whether the research physician or the study coordinator, is often a figure who, in the eyes of the patient

Revista ARACÊ
ISSN: 2358-2472

and/or their family members, expresses the image of power and knowledge, albeit unintentionally. It is not usual to be seen as an exchange relationship and can even be understood as psychic coercion [23,24]. Thus, discussing and/or objecting to their request for agreement to participate in research can be interpreted as an obstacle in the researcher-participant relationship. It should also be noted that the medical language and study protocols are technical and that, if not adapted to allow understanding, it can favor dystocic communication between the one who informs and the one who receives the information, considering the understanding and apprehension [25,26].

This impression was confirmed in a review study of the informed consent of 55 projects in the Health Sciences – Medicine knowledge area, registered in the Research Ethics Committee of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro, which were analyzed by the Ethics Committee and showed that the participants had difficulties in understanding the meanings of 76 medical terms and expressions; and only 12 of them could be replaced without affecting the content. The authors concluded that, in most cases, writing with scientific terms unknown to the general population is essential in items such as justification/objectives and procedures, and sometimes they constitute insurmountable obstacles to the understanding of research participants, but that there is considerable room for improvement [27].

Interesting point of view has Biondo-Simões et al. which recommend that research participants should be chosen from among those with the best level of education, with the habit of reading, with easy access to the internet and those with the best salary range [28]. In fact, in our study and in others, precisely, there is a majority of participants with schooling predominantly limited to incomplete primary education and low family income.

To understand the research, and to participate in it clearly, it is necessary for the participant to be autonomous, and thus, capable of receiving the information that is being given, encoding it, retaining it and producing meanings. In addition, it should be remembered that reading the FICT, as well as any text, is a brain activity that encompasses attention, memory, comprehension and cognitive linguistics. Possibly, restructuring the informed consent in order to make them more palatable, less careful with the quantity and more concerned with the quality of the information, considering the FHL, is the way to change this situation of vulnerability of research participants [29,30].

Thus, the importance of legislation, its compliance and inspection is clear because more vulnerable populations can be “indicted” as research participants. It seems impossible

Revista ARACÊ
ISSN: 2358-2472

that this happens nowadays, but to the astonishment of the national scientific community, the vulnerability of research participants and the lack of compliance with their inalienable rights, could be exposed in a study in Brazil, in 2003, where riverside people were subjected to the transmitting agent of malaria, in an American project entitled "Heterogeneity of malaria vectors in Amapá". The objective was to analyze the Plasmodium vectors in that state, and the research was approved by the FIOCRUZ and CONEP Ethics Committee, which suspended it when it came to light that the population was being coerced into feeding the barber mosquitoes with their own blood, in exchange for payment, which was omitted in the project submitted for approval [31].

Not unlike that, we are experiencing complaints, in the middle of the 21st century, of a study carried out in hospitals of a health insurance in São Paulo, which used early treatment of COVID-19, with drugs with no proven effectiveness, without the diagnosis being confirmed by RT-PCR exam or similar, without signing the informed consent and with data being manipulated by the investigators. There was probable concealment of diagnosis and cause of death in the death certificate, as well as tampering with medical records. The pre-print version of the article, released a few days after CONEP's approval of the protocol that should still be started, explicitly indicated that there was no conflict of interest [32]. The study was suspended and was registered on the Clinical Trials website, under number NCT 04348474, where it can still be consulted, entitled "Efficacy and Safety of Hydroxychloroquine and Azithromycin for treatment of Ambulatory Patients with Mild and COVID-19" [33]. There is an imbalance between the risks and benefits of using off-label medications, even in the midst of a pandemic caused by an unknown virus [34].

When analyzing the FHL, we chose to use a dichotomous classification (adequate literacy versus inadequate or limited literacy) due to the sample size of the study. Even so, the present study was able to demonstrate the importance of studying this theme, because the lower the educational level, the lower the literacy and the more difficulty in understanding the FICT, with p value <0.001, this shows that most research participants are vulnerable, if we take into account the definition of vulnerability in Res 466/12, which says that the "vulnerable subject is one who has his or her capacity for self-determination reduced or impeded" [11].

We observed that 72.3% of the research participants were unable to answer the last questionnaire within the proposed time, and in the total analysis, 52.5% had inadequate literacy, which apparently is the Brazilian reality. Still [14,35], especially when considering the

Revista ARACÊ
ISSN: 2358-2472

adjusted model, we identified that gender, age and education were significantly associated with the average variation of the total score of the FHL test, with women and more educated people having higher scores and increasing age was associated with a decrease in the mean score.

In this sense, an integrative review of studies that evaluated the level of FHL in the elderly population concluded that an insufficient FHL level is common, especially when there is low education associated. The authors even propose that public policies can help to solve the difficulties in the reading and writing relationship, to provide social insertion, citizenship and autonomy for people in the aging process. [36,37].

Other studies also associated schooling with FHL, as a variable of great importance [14,38]. The fewer years of formal education, the worse health literacy [39] and complete high school education were associated with better FHL scores, compared to individuals with a lower educational level [40]. Although FHL and schooling deal with different parameters, measured differently, increasing schooling can greatly collaborate to reduce the prevalence of inappropriate FHL.

Findings of FHL in a review of national and international literature found the same significant variables pointed out by our research: positive relationship with low education, older age, male gender and low income, which allows us to assume that our study is representative of reality. One of the reasons discussed by the authors is that studies related to FHL predominantly use adult and elderly individuals as participants, and none of them addressed the association between FHL and FICT, and there is a clear preference for the analysis of literacy in diseases, especially chronic ones, and this theme in Brazil is incipient [41].

A systematic review that included 27 studies, dealing with the understanding of the informed consent, showed that 48% were randomized and 52% were descriptive. The majority (78%) used tools developed by the authors and did not access the FHL or the readability of the term (89%). Some elements of the informed consent were more poorly understood like randomization, placebo, risks and therapy. The authors concluded that it is recommended that FHL always be verified by validated methods, such as the one we used, so that the FICT is in fact a protection instrument and not a dead letter. [42].

Another systematic review conducted by Allison Burks and Jessica Keim-Malpass [43] specifically on the application of the informed consent in 9 selected clinical studies where the FHL was accessed concluded that it is an extremely complex process that requires

Revista ARACÊ
ISSN: 2358-2472

understanding the potential risks and benefits and of treatment alternatives. The authors found that there is conflicting evidence in the literature and that, in the existing ones, most show that patients prefer the presentation of reduced and explanatory forms of the informed consent, which bring them more satisfaction, less fear and anxiety in this process, as most of them have language difficult to understand. It should be noted that none of the works selected in this systematic review was Brazilian.

As can be concluded, our study is highly relevant due to the scarcity of scientific data and, mainly, due to the importance that should be recognized to the autonomy of patients when included in clinical studies, as they are not always able to understand and judge the content of the informed consent and simply adhere without even questioning. It is high time to transform the FICT into something that is “much more than a signature on a piece of paper” [44].

STRONG POINTS

Our study, although unicentric, and therefore, its findings cannot be generalized, contributes to alerting about the care that researchers should have about the understanding of the information given to the participants of clinical trials in Brazil, which is still little known, but of great importance and extreme relevance.

Although there are some articles in this area, there is a lack of standardization in the scientific literature of validated tools to assess the understanding of the informed consent, which makes possible comparisons more difficult to be carried out [39].

To fill this knowledge gap, the present study sought to use a questionnaire fully based on Resolution 466/12 and compare it with the FHL using the B-THOFLA questionnaire, already validated for Brazilian Portuguese, which, as far as we are aware, it is an unprecedented proposal.

LIMITING FACTORS

Despite allowing all statistical tests, the sample was restricted to a single research center. The lack of a standard questionnaire on knowledge of the FICT made us build one, which can be used in other studies, and which has in its framework Resolution 466/12, in force as a pillar of research on human beings in Brazil.

Revista ARACÊ
ISSN: 2358-2472

CONCLUSIONS

It was possible to achieve the objectives outlined in this research, which corroborated the initial hypothesis that the FHL of research participants in the analyzed center is much lower than the ideal and that this is positively correlated with age (younger), gender (women) and education (higher educational level).

Certainly, more studies must be carried out to spread a culture of respect for norms so that human dignity is preserved, and patients participate in research autonomously and informed in the spirit of what is recommended by national legislation.

We believe that our study can contribute to the understanding of researchers, especially in Brazil, that health education actions aimed at research participants constitute tools of empowerment, decision-making autonomy and respect for research ethics.

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CONTRIBUTION

The authors of this manuscript actively participated in the project and agree with it.

CONFLICT OF INTEREST

The authors declare that no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was approved by the Research Ethics Committee of the Centro Universitário de Votuporanga/UNIFEV on 01Feb2021. CAAE: 32787320.9.0000.0078. Opinion number: 4.519.085.

PATIENT CONSENT FOR PUBLICATION

Informed consent was approved by the Research Ethics Committee of the Centro Universitário de Votuporanga/UNIFEV and applied to all research participants.

Revista ARACÊ
ISSN: 2358-2472

INFORMED CONSENT

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Revista ARACÊ
ISSN: 2358-2472

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