Comprehension and readability of the informed consent form in clinical research

Eurípedes Rodrigues Filho [1], *Mauro Machado do Prado* [2], *Cejane Oliveira Martins Prudente* [3]

Abstract

This article is an integrative literature review whose aims were to analyze the understanding and readability of informed consent forms applied to participants of researches involving humans, and to check the factors that influence their understanding and readability. Therefore, it intended to identify factors associated with the problem of obtaining a valid consent. The sample included eleven articles selected for this review, national and international, four of which were in Portuguese (36,36%), one in Spanish (9,10%) and six in English (54,54%). It was concluded that most of the studies analyzed confirms the hypothesis that the participants do not understand what they read in the informed consent form. Thus, the factors inferred as responsible for the difficulty in reading and understanding the informed consent forms were the educational level of the participants and the language used in the terms.

Key words: Informed consent. Reading-Comprehension.

Resumo

Compreensão e legibilidade do termo de consentimento livre e esclarecido em pesquisas clínicas

Este artigo é uma revisão integrativa da literatura cujo objetivo foi analisar a compreensão e a legibilidade de termos de consentimento livre e esclarecido de participantes de pesquisas que envolvem seres humanos, e verificar quais fatores influenciam sua compreensão e legibilidade. Por conseguinte, pretendeu-se observar os fatores associados ao problema da obtenção de consentimento válido. Integram a amostra desta revisão onze artigos selecionados, nacionais e internacionais, dos quais quatro em Português (36,36%), um em Espanhol (9,10 %) e seis em Inglês (54,54%). Concluiu-se que a maioria dos estudos analisados confirma a hipótese de que os participantes não compreendem o que leem no termo de consentimento livre e esclarecido. Logo, os fatores inferidos como responsáveis pela dificuldade de leitura e compreensão dos termos de consentimento livre e esclarecido foram o nível de escolaridade dos participantes e a linguagem utilizada nos termos.

Palavras-chave: Consentimento livre e esclarecido. Leitura-Compreensão.

Resumen

La comprensión y la legibilidad del consentimiento informado en investigaciones clínicas

Este artículo es una revisión integradora de la literatura cuyo objetivo fue analizar la comprensión y la legibilidad de los consentimientos informados de los participantes de las investigaciones con seres humanos; y comprobar cuáles son los factores que influyen en su comprensión y legibilidad. Por lo tanto, se buscó identificar los factores asociados con el problema de la obtención del consentimiento válido. Forman parte de la muestra de esta revisión once artículos seleccionados, nacionales e internacionales, de los cuales cuatro eran en portugués (36, 36%), uno en español (9,10%) y seis en inglés (54,54%). Se concluyó que la mayoría de los estudios analizados confirma la hipótesis de que los participantes no entienden lo que leen en el consentimiento informado. Así, los factores deducidos como responsables de la dificultad para la lectura y la comprensión de los consentimientos informados fueron el nivel educativo de los participantes y el lenguaje usado en los términos.

Palabras-clave: Consentimiento informado. Lectura-Comprensión.

1. Mestrando euripedesrodrigues@hotmail.com – Pontifícia Universidade Católica de Goiás/GO, Brasil. **2. Doutor** mauromachadodoprado@gmail.com – Universidade Federal de Goiás, Goiânia/GO, Brasil. **3. Doutora** cejanemp@hotmail.com – Pontifícia Universidade Católica de Goiás e Universidade Estadual de Goiás, Goiânia/GO, Brasil.

Correspondence

Eurípedes Rodrigues Filho – Rua 25-A, 470, Quadra 61 A, Lote 17, Aptº 601 Cond. Residencial Vienna, Setor Aeroporto CEP 74070-150. Goiânia/GO, Brasil.

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Origin and Hystory

It can be said, succinctly, that today the importance of the Term of Free and Informed Consent (TFIC) in the research with human beings around the world was due to the atrocities committed by scientists in concentration camps in Nazi Germany, and that the first document of ethical principles related to research was the *Nuremberg Code*, from 1947. This document clarifies, in its first paragraph that *the voluntary consent of the human being is absolutely essential*. This implies that the experimental subjects must be legally able to give consent, that is, must exercise the free power of choice, without any intervention of force element, fraud, lies, coercion, trickery or other ulterior form of constraint and should have enough knowledge about relevant aspects of the study to make their decision [1].

The following year, the *Universal Declaration of Human Rights* was drafted, from the General Assembly of the United Nations, which in its preamble reaffirmed the notion of human dignity, also configured as milestone for the promotion of justice, freedom and the equal rights among all people [2]. Posteriorly, the Declaration of Helsinki, of the World Medical Association, in 1964, establishing recommendations about research involving humans.

Regarding the TFIC, the Declaration of Helsinki states that: a) clinical research on a human being can not be undertaken without his free consent, after fully clarified - if legally incompetent, the consent must be obtained from his legal representative; b) the patient of clinical research should be in mental, physical, and legal state as to able to fully exercise his power of decision; c) the consent, as a standard, must be given by writing. However, the responsibility of clinical research always remains with the researcher and never falls on the subject, even after having obtained his consent [3].

This statement is constantly revised by the World Medical Association, being the latter held in 2013, in Fortaleza, Brazil [3]. A critical study states that *the Declaration of Helsinki, for the historical strength achieved, eventually becoming a global normative document, taken as moral and often placed itself above the laws of countries, from their unanimous acceptance worldwide reference* [4]. What is always feared with attempts to change this document, as in 2008 with the decision of Seoul, is that this heritage for humanity may lose the moral authority gained in over 40 years as a world reference in clinical trials for researchers, universities, laboratories, companies, journals and nations.

Considering several cases of manipulation (inclusion in research with no informed consent), in which sick vulnerable people were used as subjects of experimentation, some of which have become public in the United States of America (USA) in the 70s, the American Congress designed a commission in 1974 to prepare a complete study that would identify the ethical principles that should guide biomedical researches involving humans. After four long years of reflection and research, it emerged what was called the Belmont Report, with the establishment of the following basic ethical principles: beneficence (attention to risks and benefits); respect for people (the necessity of the TFIC); and justice (equity towards the research subjects). These principles have become classics within the study and practices of bioethics [5].

Regarding the TFIC (or IC), it is common ground to consider within the biomedical literature two types of consent: one used in health care and another in researches involving human beings [6]. This study will focus the second type of IC, whereas in the context of obtaining consent from the research participant, this is the most important document to the ethical evaluation of a research project that involves human beings, by a research ethics committee (REC). It is noteworthy that, for the RECs that analyzed studies involving human beings in our country, the guiding ethical principles for ethical decision making are listed in Resolution 466/12, from the National Board of Health (NHB) / Ministry of Health (MOH). It is emphasized that, being well established in this resolution, the recommendations discourses on a process of obtaining the consent of the research participant, as it seeks to guarantee their rights and duties, having the TFIC as a fundamental measure - in this study discussed under the aspects of comprehension and legibility [7].

Concept and components

As an essential condition in human research and in the relation researcher-participant of research, the TFIC is constituted as a voluntary decision. This decision must be made by a person with ability and autonomy, also having as validity criterion, the preexistence of information process. This same decision aims the acceptance or rejection of specific treatment or participation in research trial, so the participant should be aware of the nature, objectives, risks and consequences of their acceptance. It is the conceptualization presented by Saunders, Baum and Houghton, quoted by Clotet [8].

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The IC is not just a simple paper on which the researcher expresses by hand an invitation for someone to give their consent to participate in research. It is a complex document that unfolds itself in several elements, turning this proposal into a process of clarification and respect for human dignity. For research purposes, the IC has a logical structure, based on the elements of your concept.

The elements of the concept fall into two components: information and consent. The component aims to show all information concerning the stages of research, considering the risks and benefits, craving understanding of what is shown. In turn, the component of consent is intended to allow a decision and a voluntary agreement regarding the participation in the research [9]. Such decision and voluntary consent of the participant will be autonomous and will only apply if the information related to the research is complete and intelligible. The language should be clear and common to the routine of participants. This language, finally, must never influence the participant in his decision [10].

Regarding information that must be listed on the consent form, the Resolution CNS 466/12 establishes that the IC must contain, obligatorily, the following requirements: a) the justification, aims and all the procedures that will be used in research, with detailed information; b) explanation of the possible discomforts and risks of participation, besides the expected benefits, precautions to be employed to prevent and / or reduce adverse effects and conditions that can cause damage; c) clarification on how monitoring and assistance they are entitled, as well as posterior follow-ups to the closure and / or interruption of the research; d) ensure the participant complete freedom to refuse to participate or withdraw your consent at any time during the research without penalty; e) ensure the confidentiality and privacy of participants during all phases of the research; f) ensure that each participant will receive one copy of the TFIC; g) ensure the reimbursement of expenses of the participants, when appropriate; h) ensure compensation for any damage arising from the survey [11].

Comprehension and legibility

To facilitate the adequacy in vocabulary of the TFIC, Rossi, Goldim and Francisconi published in Portuguese, a glossary of terms related to health, in simple colloquial language [12]. Such glossary allows researchers to develop consent forms better adapted to the understanding, then facilitating communication with the participant. The understanding of TFIC is related to the ease / speed of reading and apprehension of the text meaning, factors that have close relationship with the form of writing and the vocabulary used.

Legibility refers to the size, type and color of the font formatting of words and construction of sentences, as well as spacing and paragraph alignment, and other elements of textual presentation [13]. The comprehension and legibility should be a key part of a TFIC. There is no autonomous decision making without adequate understanding of what is read. According Junges [14], the proper understanding implies in: *comprehending an action, being able to understand its nature and predict its consequences*. Therefore, the research participant should receive information about the study which will participate. It implies that learns about its nature and purpose, as well as the possible risks and benefits, so you can make an autonomous decision to participate or not in the research.

The survey for the preparation of this article did not find in Brazil scientific publication with the methodology used in this study, regarding the comprehension and legibility of the TFIC of researches involving humans. It is justifiable, therefore, to undertake an approach of the theme through integrative review, expecting the results to fill this gap. This article is aimed at: understanding and analyzing the legibility of terms of informed consent of participants in research involving human beings; and verify which factors influence in their comprehension and legibility.

Methods

It is integrative review, a method of literature review that allows to search, selection, critical evaluation and synthesis of scientific evidences. This method also allows the inclusion of experimental and non-experimental studies to fully understand the phenomenon analyzed, and identifies gaps in the literature and directs the development of future research [15]. The procedures of integrative review were conducted in six phases, described as follows:

1st phase: formulation of the guiding question

From the reflection on the theme of the comprehension and legibility of the TFIC involving human beings, the following question was made: "The research participants understand what they read in the term of free and informed consent"? From the horizon of this question proceeded the search for articles of research involving human beings that had as its theme the comprehension and legibility of informed consent.

2nd and 3rd phases: search and sampling in literature and data collection

There was a survey of publications that had as its primary focus the topic on the agenda, in the past ten years, in Portuguese, Spanish and English. The authors conducted a search of the Virtual Health Library (VHL). Descriptors in Health Sciences (DeCS) were used regarding the subject in focus, namely: "Termo de Consentimento Livre e Esclarecido", "Consentimiento informado", "Informed consent; "Compreensão", "Comprensión", "Comprehension" e; "Legibilidade", "Legibilidad", "Readability". The following databases were searched: Latin American and Caribbean Literature on Health Sciences (LILCHA); Scientific Electronic Library Online (SciELO); International Literature on Health Sciences (Medline); and United States National Library of Medicine (PubMED).

The survey was conducted from April to July 2013. From a universe of 227 articles, after applying the inclusion and exclusion criteria, 11 articles were selected for the sample. The inclusion criteria previously established for this study were: a) studies that analyzed the comprehension and the legibility of the informed consent relating to research involving human beings; b) articles in Portuguese, Spanish and English published in the period between 2003 and 2013.The exclusion criteria were: a) articles of literature review; b) studies that analyzed the TFIC related to health care; c) the articles that appear in two or more bases, and in this case, the reference is indicated in only one of them. Table 1 presents the databases consulted, the combination of descriptors in three languages mentioned above and the number of articles found and selected in the survey.

Table 1. Data base consulted, the combination of descriptors, and articles found and selected within the survey

Base de dados	Language	Descriptors	Articles found	Articles selected
SciELO	Portuguese	Consentimento livre e esclarecido, compreensão e legibilidade	44	1
Lilacs	Portuguese	Consentimento livre e esclarecido, compreensão e legibilidade	35	3
SciELO	Spanish	Consentimiento informado, comprensión, legibilidad	23	0
Lilacs	Spanish	Consentimiento informado, comprensión, legibilidad	20	0
PubMED	Spanish	Consentimiento informado, comprensión, legibilidad	15	1
PubMED	English	Informed consent, comprehension, readability	70	3
Medline	English	Informed consent, comprehension, readability	20	3
Total			**227**	**11**

4th phase: critical analysis of the studies included

After careful and thorough reading of abstracts, we selected those that could compose a sample of this integrative review. In this set, the complete articles that fully met the proposed criteria were read. The list of selected studies, containing the origin, the title, authors' names, the periodic synthesis and critical analysis of the results were organized in a framework.

5th and 6th: discussion of results and synthesis of the integrative review

In these phases, from the critical interpretation and synthesis of results, the identified data were compared in the analysis of the articles - which were later described.

Results and discussion

Table 2 presents a synthesis of the articles in the sample, reporting databases, titles, authors, journals and main results.

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Table 2. List of selected articles on the origin, title, authors, journal and main results

Origin	Title	Authors	Journal	Results
SciELO	How consenting without comprehending?	Miranda VC, AB Fêde ABS, Lera AT, Ueda A, Antonangelo DV, Brunetti K, Riechelmann R, Giglio AD	Rev Assoc Med Bras 2009; 55(3): 328-34	Research shows to be necessary to be about 18 years of study for the comprehension and reading TFIC, incompatible data if considering the reality of the studied population [16]
Lilacs	Researchers in gerontology and informed consent	Goldim JR, Glock RS	Revista Bioética 2005; 30 (3): 11-5	Five TFICs presented text structure considered difficult to understand and close to the limit of a very difficult structure. Only one TFIC appeared as reasonably difficult structure [17]
Lilacs	Comprehension of the TFIC	Biondo-Simões MLP, Martynetz J, Ueda FMK, Olandoski M	Rev Col Bras Cir 2007; 34(3): 183-8	Despite the TFIC being prepared to achieve score between 9 and 10, it was observed that it reached 7.5. The level of education influenced the ability of understanding, as well as the habit of reading and the access to internet [18]
Lilacs	Understanding of TFIC by patients participanting in drug researches in cardiology	Meneguin S, Zoboli ELCP, Domingues RZL, Nobre MR, César LAM	Arq Bras Cardiol 2010; 94(1): 4-9	50% did not understand the Informed Consent; and 32.9% did not read it, but signed, showing that the lower the education level, the lower the understanding [19]
PubMED	Estudio observacional y prospectivo del consentimiento informado de los pacientes en ensayos clínicos con medicamentos	Baines JPO, Grupo de Estudio Econsec	Med Clin (Barc). 2008;131(11):422-5	The average time between the delivery of TFICs by the researchers and their return by 85 participants (all adults) was 2.8 days, an insufficient time to read and understand, according to 7% [20]
Medline	Informed consent: document improvement does not increase patients' comprehension in biomedical research	Paris A, Brandt C, Cornu C, Maison P, Thalamas C, Cracowski JL Claire Thalamas, J-LC	British Journal of Clinical Pharmacology Br J Clin Pharmacol 2010;69(3): 231-7	It was not possible to demonstrate that the improvement of TFIC by the lexical-syntactic approach or by a working group, leads to a better understanding among participants [21]

Origin	Title	Authors	Journal	Results
PubMED	Repeated assessments of informed consent comprehension among HIV-infected participants of a three-year clinical trial in Botswana	Chaisson LH, Kass NE, Chengeta B, Mathebula U, Samandari T	PLoS ONE 2011; 6(10):1-10	Regarding the objectives of the study, the questionnaire was comprehended by 90% to 100% of participants, but only 44% to 77% understood what randomization, placebos, or risks are, considering that the majority of participants had educational level corresponding to university [22]
PubMED	Pilot study demonstrating effectiveness of targeted education to improve informed consent understanding in aids clinical trials	Sengupta S, Ronald LB, Strauss RP, Eron J, Gifford AL	NIH Public Aids Care. 2011; 23(11): 1.382-91	The results showed that the single application of contents related to TFIC in a language of secondary education may improve the real understanding one week after the intervention, although the retention of concepts may require periodic monitoring to ensure the comprehension throughout the course of a clinical trial [23]
Medline	Interactive informed consent: randomized comparison with paper consents	Rowbotham MC, Astin J, Cummings SR	PLosS ONE 2013 ; 8(3)	This study demonstrates that the combination of an introductory video, the TFIC printed on standard language, and an interactive questionnaire (online) based on tablet improves the understanding of the risk procedures in the research [24]
Medline	Analysis of the readability of patient information and consent forms used in research studies in anaesthesia in Australia and New Zealand	Taylor HE, Bramley DEP	Anaesth Intensive Care 2012; 40: 995-8	All TCLE analyzed, with legibility indexes for English language from Flesch and Flesch-Kincaid, respectively, exceeded the recommended level of comprehension by the National Ethics Committees of Australia and New Zealand [25]
PubMED	A randomized controlled study to assess patients' understanding of and consenting for clinical trials using two different consent form presentations	Abd-elsayed A, Sessler DI, Mendoza-cuartas M, Dalton JE, Said T, Meiner J, Upton G, Franklin C, Kurz	Edizione minerva anestesiologica 2012; 78 (5) 564-73	Application of two models of TFIC, standard and modified. The modified form did not improve the participants' comprehension, or willingness to consent in participating in clinical trials [26]

The discussion of results was divided into two groups: the first consisted of studies using Flesch Reading Ease (IFLF) Index and Flesch-Kincaid Readability (ILFK) as tools for understanding and verifying the readability of the IC. The second consisted in studies that used questionnaires constructed by the researchers themselves, for the same purpose.

The IFLF and ILFK are widely used in research involving IC to assess comprehension and legibility of the document. The IFLF was first proposed by Rudolf Flesch in 1948 and adapted by the American Navy by Kincaid (ILFK) in 1975, to check the degree of difficulty of reading the manuals prepared by the American government. The IFLF assesses the text's

degree of legibility on a percentage scale. The higher the value of IFLF, the greater the ease of reading and the lower the level of education required. The ILFK, in turn, is an index that estimates the years of education needed for a proper comprehension of the text. Values of the most effective ILFK are the ones requiring six to ten years of schooling [27].

Among the four studies of the first group, which used the IFLF and ILFK, it is a clinical study conducted in Brazil, at the Center for Studies of Hematology and Oncology, related to the Faculty of Medicine ABC, in São Paulo. This study concluded to be necessary about 18 years of study to the comprehension of the TFIC model presented by researchers, an incompatible data if compared to the reality of the population, in which more than 50% of people have less than eight years of study [16]. Besides this, another study, which consisted in verifying the adequacy of informed consent for researchers in biomedical gerontology, applied to ongoing researches in this area, also made use of the IFLF and ILFK. As a conclusion, they inform that five TFICs showed text structure considered "difficult", close to the threshold of the "very difficult". From this list, only one TFIC presented its structure classified as "fairly difficult" [17].

Flesch and Flesch-Kincaid Indexes were also used in another study that sought to measure the TFIC's degree of difficulty or the years of study required for their comprehension by individuals who participate of a research or treatment. For this purpose, a TFIC was elaborated to achieve a high level of comprehension and legibility with the population studied. However, the result was beneath expectations, since his comprehension was low. Nevertheless, the study shows an innovation not indicated in other studies using these indexes: it displays the reading habit and the internet access as facilitators of comprehension. While all previous studies cited before, which used the IFLF and ILFK, bring only the level of education as a decisive factor in comprehension and legibility of the TFIC, which puts with this level elements related to the behavior and habits of the participant, as the constancy in reading, being in print or on the internet [18].

Concluding the discussion of the first group, it presents a study of Anesthesiology in Australia and New Zealand. In this study, an analysis of legibility was performed to test the hypothesis that the language used in the information of TFIC to research participants would not meet the legibility standards or expectations of good clinical practice of research ethics committees of these countries. Fourty TFICs were analyzed with the application of IFLF and ILFK index.

The result found that the level of study required for the legibility of TFIC exceeds the level of primary and secondary study, and therefore the ability to understand by the general population in Australia and New Zealand. The study concluded that the complex language decreases legibility and brings negative impacts on the process of informed consent and the possible signing of the TFIC by the participant. Their results suggest that, during the provision of written information to research participants, that the researcher develop a TFIC with the utmost caution to ensure that the language used and its legibility is appropriate for the intended audience [25].

From the results of the four items listed above, it is concluded that education is fundamental for the research participants, regardless of where they live. All results from studies using these indices confirmed the relationship between low education and the difficulty in reading and comprehending the informed consent. Therefore, the main factor that influences the legibility and comprehension of TFIC would be the level of education, although the habit of reading, internet access and the appropriateness of the language used by the researcher in the development of the IC are factors that also contribute to ease reading and understanding of TFIC.

The questionnaire, as a tool for verification and survey data, is also in common use within Health Sciences. According to Parasuraman, cited by Chagas [28]: *A questionnaire is simply a set of questions designed to generate the data needed to achieve the project objectives*. That said, there are three types of questions that can be used in the construction of a questionnaire:

1) open questions that allow greater freedom of choice to the respondent, as it allows to answer in their own words, not limiting the argument to a list of choices given a priori;

2) multiple choice questions: consist in limiting the choice of a respondent from among the options presented, or even if more than one, a predetermined amount of options;

3) dichotomous questions: these consist in limitating to the respondent only two alternatives, which enclose between them an antagonism, as for example yes/no, right/wrong, true/false types.

The seven studies in the second group used all kinds of questionnaires mentioned above, as verification instruments of comprehension and

legibility of informed consent in research involving humans. The first study used a TFIC with 29 open questions in an structured questionnaire: *"Why did you agree to participate?"; "Did you read the TFIC before signing?"; "By signing it, were you sure that you understood it?".* The answers received statistical treatment to evaluate results. The results refer to the comprehension level of procedures related to the method applied in the research and to the risks arising from the voluntary participation, described in the TFIC.

The results show that 50% did not understand the TFIC and 32.9% did not read it, but signed. Still in this study, the TFIC was applied among participants who received placebo after randomization, identifying that 66.7% did not understand the meaning of this term. There was a strong correlation between the failure of understanding the meaning of "placebo" with the education level, showing that the lower the education level, the less comprehension. Therefore, it is concluded that, in the same sense of studies using Flesch and Flesch-Kincaid Index, education is a determining factor for comprehension and legibility of TFIC, as the choice of words by the researcher [19].

The second study of TFIC applied two questionnaires: one with eight multiple-choice questions related to the IC, and another, with also eight questions, but open, related to the clinical study. The results of this study received a simple quantitative treatment being evaluated in terms of percentage. It was concluded that the majority claimed to have fully understood the Informed Consent and only 2.4% admitted they did not understand the content of the IC form. It should be noted, however, that 36.5% did not answer this question. This study also sought to verify the conceptual perception of the participants in relation to the clinical study. The majority had a misperception about what is an experimental clinical trial and/or the particular nature of the studied pharmacological treatment, while about 10% did not know that their participation could not bring benefits and that could be subject to damage [20].

The third study of IC applied a questionnaire with 20 questions, the dichotomous type, with alternative (true or false) related to the comprehension of the TFIC. The responses of the participants had to evaluate statistical treatment of results. This study consisted of a survey in southern Africa, in which the same questionnaire was administered in English and in the native language (Setswana). The choice of language was at the discretion of the participants.

It was concluded that few researchers elucidate the patients about the nature and risks of the treatment on the IC, and an even smaller amount maintain the patient reported throughout the treatment process. To reach this result, the researchers administered questionnaires and TFICs to research participants before and during treatment [22]. Here, it is observed a differential in relation to other studies discussed, since the application of TFIC to participants is not only restricted only to the beginning of the research, but extends throughout the entire process, including at the end, for a period of approximately three years.

In the context of the above work, the fourth study of IC presents a research conducted in the United States that aimed on investigate the understanding of the participants not only before the clinical procedures start, but also throughout the process. To investigate this understanding, the authors applied a questionnaire with twenty-one open questions relating to all stages of obtaining the consent. In this study, the responses also had treatment for statistical evaluation of the results found.

Seeking not only investigate, but to improve the comprehension level of the research participant, the authors applied educational interventions that, through a pedagogical-didactic proposal, participants could elucidate aspects of the study which would participate, and thus facilitate their understanding. It is important to note that the last two cited studies converge not only to the use of questionnaires as a tool for verifying the understanding of the TFIC by participants, but also in the effective understanding of other aspects of the research by the population studied. It should also be noted that both studies developed their research with patients with HIV and there was a common desire to provide not only guidance on accession to the research, but also - and mainly - to inform about the disease itself and other aspects of the search process [23].

A fifth study of FIC, conducted in France, aimed to determine whether the modification of IC by a workgroup or the systematic improvement of its lexical-syntactic legibility could improve the understanding of written information given to participants in a biomedical research. It involved the application of a 28 questions questionnaire, divided into two parts: a) 16 questions to verify objective comprehension of the TFIC; b) 12 questions to verify the subjective understanding of the TFIC. To both types of questions, subjective and objective, scores of 100 points were applied, which, after statistical treatment of results showed no significant difference

among the three groups studied: a) participants who read the original TFIC; group b) participants who read the TFIC improved to facilitate lexical-syntactic reading; and group c) participants who read the TFIC improved by the working group. The conclusion of the researchers was that we could not demonstrate that the improvement of the TFIC by means of a lexical-syntactic approach or by a working group, leads to a better understanding of the population of participants, regardless of the method used [21].

The sixth study of IC, conducted in the USA, aimed to verify the understanding of informed consent and used as a reference two models, one standard and one modified. After the application of a questionnaire with seven open questions, the authors concluded that 75% of participants had facility to handle the standard format for TFIC, while 66% handled with more facility the modified format. About 90% of participants in each group correctly identified the largest intervention trial and the highest risk associated. Neither the personal characteristics of the participants or their ability to comprehend affected the rate of consent for the clinical trial. Therefore, comparing the results of applying two models of TFIC, standard and modified, there was the expected improvement of the comprehension of participants or their willingness to consent to participate in clinical trials [26].

The fifth and sixth studies of this group showed surprising results when applying different models of TFIC, in order to verify if there was improvement in legibility and consequently in comprehension of the content. The results of the fifth study indicate that it was not possible to demonstrate if the improvement of IC leads to a better understanding by the participants. The results of the sixth study indicate no expected improvement in participants' comprehension or willingness to consent to participate in clinical trials.

One last job, the seventh study of TFIC was also performed in the USA and aimed to compare the understanding of informed consent in clinical research, in two versions: the first, in an interactive way, with the use of tablets; the second, in a printed form. The questionnaire developed by the authors, consisting of 12 multiple-choice questions on the comprehension of informed consent was applied in two versions. After statistical analysis of the results, the authors' conclusion was that the use of tablets facilitates the understanding of the TFIC regarding the procedures and risks in clinical research [24].

In summary, all authors from the studies used the quantitative method with the statistical analysis of results. As for the instruments or verification tools of comprehension and legibility of TFIC, the studies were divided into two groups: on one hand, the group that used the IFLF and ILFK - the first four studies listed in the discussion; and another, the group that used the questionnaires prepared by the authors - the last seven studies of discussion. Regarding the results, all of the studies that based on the IFLF and ILFK index concluded that the adequation of the language of TFIC and the use of vocabulary in accordance with the level of education of participants in research involving human beings are essential to the compehension and legibility of the informed consent.

On the issue of education, Lobato, Caçador and Gazzinelli, in the research on the legibility of two ICs also used in clinical trial, aiming to correlate the degree of difficulty of the documents with the education level of the participants, also from the indices of Flesch Reading Ease test and the Readability Flesch-Kincaid, had values that relate to the conclusion that *the two TFICs used for participation in clinical trials were not suitable for the education of most of its remaining participants* [29]. Also highlighting, in this study, the relevance of the aspect of education.

Studies of the second group, that is, those who drew on questionnaires as instruments of verification of comprehension and legibility, showed as central concern the comprehension of TFIC, by the participant, not only for the participation in the research but throughout the course of the research. In turn, it is important to note that the fifth and sixth studies in the second group used different models of IC (standard and modified TFIC) to further evaluate, through the use of questionnaires, if there would be improvement or not in the comprehension by the research participants. The results were unexpected, because in one of them we could not demonstrate any improvement in the comprehension; in another, attest that there was no improvement of IC comprehension expected by researchers.

The seventh study of this group demonstrated differential over the others because it was not presented a modified TFIC, but the same IC, in print and in electronic form by using tablets. While the sixth and fifth studies found no difference in the result of the comprehension of the consent form presented is standard or modified, the seventh study concluded that the use of technology facilitates the understanding of IC. However, it is worth considering the use of tablets can not be, in turn, related to the habit of reading in the electronic media, which would the discussion to return to the assumption of previous results.

Thus, the issue in question has been studied and is being enhanced to question the scope of respect for the dignity and autonomy of the participant of research in order to achieve the proposition of sufficient understanding of the IC by the population, especially those in situations of social vulnerability.

Final considerations

Importantly, in relation to the results of the studies analyzed, which when applied to developed countries (six studies) diachronic results were obtained in relation to research conducted in developing countries (five studies). For example, it is cited the improvement of TFIC, regarded as indifferent procedure to the comprehension according to studies conducted in developed countries, being, however, an essential procedure for that same understanding when it comes to research participants from developing countries. It is worth noting; moreover, that in addition to the economic and sociocultural factors impacts in these differences also the difficulty level intrinsic of the language.

However, despite the disparity of results of the studies analyzed and factors that may have determined or conditioned such differences, it is important to emphasize that clarity of language and the appropriate vocabulary on level of comprehension and education of the person participating in the research are extremely fundamental characteristics in the process of TFIC, particularly in developing countries. The researcher must be careful to contextualize the meaning of words relating to the research, which are usually part of scientific vocabulary, to an everyday language, whose meaning should be more comprehensible to the scope of its participants.

Thus, the integrative review has enabled the construction of a synthesis of scientific knowledge on the subject and allowed to understand the complexities concerning the issues of comprehension and legibility of the TFIC, which, however - especially in developing countries - facilitated by the appropriateness of the language used, also involves questions of pedagogical-educational, economic and social order. This integrative review also enabled to realize the necessity of developing new studies and researches on IC for clinical researches. In a universe of 227 articles on IC found in the databases mentioned, only 11 were about the comprehension and legibility of IC applied in clinical research. Therefore, contrary, for example, to the great amount of studies related to clinical research IC applied in the area of health care, the amount of studies related to TFIC f clinical research is still very limited in the scientific community, concluding, therefore, the need for a greater mobilization of the scientific and academic community for this subject of interest relevant to society.

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Participation of authors

Eurípedes Rodrigues Filho: conception of the study, bibliographical revision, critical analysis, discussion of results and writting. Mauro Machado do Prado: co-orientation and critical revision. Cejane Oliveira Martins Prudente: orientation, and participation in the critical revision.

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