REVIEW ARTICLE

Strategies to favor comprehension of the consent form by clinical trial participants: an integrative review

Estratégias para favorecer a compreensão do termo de consentimento pelos participantes de ensaios clínicos: revisão integrativa

Estrategias para facilitar la comprensión del formulario de consentimiento por parte de los participantes en ensayos clínicos: una revisión integradora

Valquíria Fernandes Marques Vieira[1]
Sumaya Giarola Cecílio[2]
Lorenza Ferreira de Sousa[3]
Maria Flávia Gazzinelli Bethony[1]

[1] Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brasil.

[2] Faculdade Ciências Médicas de Minas Gerais (FCMMG), Belo Horizonte, Minas Gerais, Brasil.

[3] Instituto Guaicuy, Belo Horizonte, Minas Gerais, Brasil.

Correspondent author:
Valquíria Fernandes Marques Vieira
E-mail: fernandes.valquiria@gmail.com

How to cite this article: Vieira VFM, Cecílio SG, Sousa LF, Bethony MFG. Strategies to favor comprehension of the consent form by clinical trial participants: an integrative review. Rev. Eletr. Enferm. 2023;25:70441. https://doi.org/10.5216/ree.v25.70441 English, Portuguese.

Extracted from the Thesis "Understanding informed consent in clinical research: a concept proposal" (In Portuguese: "*Compreensão do consentimento informado em pesquisa clínica: uma proposta de conceito*") defended in 2022, in the Programa de Pós-Graduação em Enfermagem at the Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

Received: 03 October 2021
Accepted: 21 November 2022
Published online: 26 March 2023

ABSTRACT

Objective: to analyze the strategies used to favor the comprehension of clinical trial participants about the informed consent form, as well as the theoretical bases on which these are based. **Methods:** integrative literature review performed in 2019 and updated in 2021 in six electronic databases, plus a reverse search based on references of the included articles. **Results:** strategies of changing the content and the form of presentation of the consent form, as well as multimodal strategies were identified in the 21 selected articles. The identified strategies are mostly related to the traditional learning framework and resulted in a better understanding by individuals in the process of obtaining consent to participate in clinical trials, compared to the usual strategies. For the most part, the level of comprehension remained below 60.0%. **Conclusions:** the strategies resulted in an improvement in general understanding, although with persisting misunderstanding or limited understanding of fundamental concepts inherent to participation in clinical trials, reinforcing that the process of obtaining consent is a complex phenomenon that requires special attention from researchers, in the quest to ensure proper understanding of information, and an actually informed decision-making.

Descriptors: Comprehension; Informed Consent; Clinical Trial.

RESUMO

Objetivo: *analisar as estratégias utilizadas para favorecer a compreensão de participantes de pesquisas clínicas sobre o termo de consentimento livre e esclarecido, bem como, as bases teóricas em que se apoiam.* ***Métodos:*** *revisão integrativa da literatura realizada no ano de 2019 e atualizada em 2021 em seis bases de dados eletrônicas, adicionada de busca reversa a partir das referências dos artigos incluídos.* ***Resultados:*** *dos 21 artigos selecionados, foram identificadas estratégias de mudanças no conteúdo, da forma de apresentação do termo de consentimento, bem como estratégias multimodais. As estratégias identificadas relacionam-se, em sua maioria, ao referencial tradicional de aprendizagem e resultaram em melhor compreensão por parte dos indivíduos que estavam em processo de obtenção do consentimento para participar de ensaios clínicos, em comparação com as estratégias usuais, mas, para a maioria o patamar de compreensão manteve-se abaixo de 60,0%.* ***Conclusões:*** *as estratégias resultaram na melhora da compreensão geral, porém, com persistência da incompreensão ou compreensão limitada de conceitos fundamentais inerentes à participação em pesquisas clínicas, reforçando que o processo de obtenção do consentimento é um fenômeno complexo e que requer atenção especial dos pesquisadores, na busca de garantir a compreensão adequada das informações, garantindo, de fato, a tomada de decisão esclarecida.*

Descritores: *Compreensão; Consentimento Livre e Esclarecido; Ensaio Clínico.*

RESUMEN

Objetivo: *analizar las estrategias utilizadas para favorecer la comprensión de los participantes en la investigación clínica sobre el formulario de consentimiento informado, así como las bases teóricas en las que se fundamentan.* ***Métodos:*** *revisión bibliográfica integradora realizada en 2019 y actualizada en 2021 en seis bases de datos electrónicas, además de búsqueda inversa a partir de las referencias de los artículos incluidos.* ***Resultados:*** *de los 21 artículos seleccionados, se identificaron estrategias para modificar el contenido y la forma de presentación del formulario de consentimiento, así como estrategias multimodales. Las estrategias identificadas estaban relacionadas en su mayoría con el marco de aprendizaje tradicional y dieron lugar a una mejor comprensión por parte de las personas que estaban en proceso de obtener el consentimiento para participar en ensayos clínicos, en comparación con las estrategias habituales, pero para la mayoría de ellas el nivel de comprensión se mantuvo por debajo del 60%.* ***Conclusiones:*** *las estrategias resultaron en una mejora de la comprensión general, sin embargo, con la persistencia de incomprensión o comprensión limitada de conceptos fundamentales inherentes a la participación en la investigación clínica, reforzando que el proceso de obtención del consentimiento es un fenómeno complejo que requiere especial atención por parte de los investigadores, en la búsqueda de garantizar la adecuada comprensión de la información, asegurando, de hecho, la toma de una decisión informada.*

Descriptores: *Comprensión; Consentimiento Informado; Ensayo Clínico.*

INTRODUCTION

Clinical research involving human beings is expanding globally. According to the ClinicalTrials.gov registration database[1], there has been an exponential growth in the volume of clinical trials in recent decades, going from 2,119 registrations in 2000 to 361,141 in 2020, representing an approximate 170-fold increase[1].

In clinical trials, as well as in other designs, respect for the study volunteer's dignity and autonomy is a condition for preserving ethical aspects[2]. What makes this issue more complex is that in clinical trials, interventions with participants are performed by researchers. Consent is a key element for the ethical conduct of research and is based on the bioethical principle of autonomy, so that the act of consenting must be genuinely voluntary and based on adequate disclosure of information[3]. The concern with participants' comprehension is part of this process, because if the subject does not understand the action, it is not autonomous and has no validity[4,5].

Recent data reveal that in most cases, the traditional process of obtaining consent is not a sufficiently adequate method to share information and ensure understanding by the potential participant[6,7]. For this reason, researchers have developed several strategies to present the study information and promote its understanding by participants, using different approaches, from more visual, interactive formats or even digital technological resources[8-14].

Thus, it starts from the premise that in the process of obtaining consent, the use of strategies supported by educational references can favor a better understanding of clinical research information by the potential participant, in order to facilitate compliance with ethical precepts in research involving human beings.

However, despite the efforts of researchers to create and use strategies to improve the understanding of key elements of the consent process by clinical research participants, the problem of adequate understanding still persists[8,9]. The literature presents no consensus on the most effective way to inform participants during the consent process[7,8].

Systematic reviews[7,8] on interventions to improve the comprehension of information in the consent form by participants in clinical trials and individuals who will receive therapeutic actions have been conducted recent years. However, important limitations restrict the power of the findings, mainly in relation to the methodological quality of studies, making it impossible to conclude on which would be the best strategies. Comprehension has been the main evaluated outcome, measured through a written or oral test. Among the interventions evaluated in these reviews, the presence of a researcher to talk individually with study participants for a longer period of time showed potential to improve the understanding of informed consent[7,8].

The present study proposes to broaden the discussion beyond the effectiveness of strategies for disseminating information of clinical trials. Thus, it starts from the premise that a fundamental aspect to be analyzed in the process of obtaining consent, in addition to the strategy of communicating or disseminating information, is the theoretical basis underlying the strategies for promoting the comprehension of information.

The concern with turning attention to these bases is justified by the possibility, even with efforts of different researchers, of a predominance of strategies resulting in standardized and normalizing practices that consider the potential research participant as a mere receiver. If proven, such an assumption would place us in the ethical dilemma about clinical research and autonomy.

This study may contribute to propose guidelines and procedures to be used in the development of strategies to favor the understanding of information in consent

forms used in clinical trials. Additionally, it is expected that this investigation can generate subsidies to inspire researchers in the development of strategies that favor the understanding of information by participants of clinical studies, developed based on conceptions of knowledge, education and understanding adopted in consent processes.

Given the above, the objective of this review is to analyze the strategies used to favor the comprehension of clinical trial participants about the informed consent process, the theoretical bases on which they are based and the conclusions about their use.

METHODS

This is an integrative review developed in five steps: preparation of the guiding question; performance of a search in the literature; categorization of studies; interpretation of results and synthesis of the developed review[15,16].

The PICO strategy was used to develop the guiding question of the review[17] considering "P" (population) - the participants of clinical trials; "I" (intervention) - effective strategies to favor understanding, "C" (standard intervention) – process of application of the usual consent form; and the fourth element "O" - (outcome), improvement in the understanding of information disclosed in the consent process. The guiding questions of the study are: "What are the strategies used to favor the comprehension of the informed consent process by clinical trial participants and their respective theoretical bases?"; "What is the effect of these strategies on the understanding of the informed consent process by clinical trial participants?"; "What are the conclusions of the studies?".

The following databases were consulted: Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed); Cochrane Central Register of Controlled Trials (CENTRAL); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Web of Science (ISI); *SciVerse Scopus* and Virtual Health Library (VHL). Additionally, reverse searches of the reference lists of eligible studies were performed to identify additional relevant documents that could help answer the study questions.

For this purpose, the respective controlled terms of the Medical Subject Headings/Health Sciences Descriptors (MeSH/DeCS) vocabularies were used: Consent Forms; Informed Consent; Clinical Trial; Clinical Study; Comprehension and the following keywords: Consent Documents; Informed Consent Forms; Free and Informed Consent Forms; Conscious Authorization; Conscious Consent; Clarify Consent; Informed Consent; Comprehensibility; Reding Comprehension; Understanding; Legibility.

Terms referring to items (P) and (I) of the PICO acronym were not included in the search strategy, considering that when searching only randomized clinical trials, the study population would already be represented by participants in studies with this design. Although the initial search strategies were used with descriptors related to the intervention (I), this greatly limited the number of identified studies, so we decided not to use this element in the search strategy. All controlled and uncontrolled descriptors were investigated in English, Portuguese and Spanish.

The searches were performed from November to December 2019 and updated in September 2021. Different crossings were made with the previously mentioned controlled descriptors and keywords, as well as associations using the Boolean operators OR and AND (Table 1).

Inclusion criteria comprised experimental, randomized clinical trials in English, Portuguese, and Spanish in which positive results on the effectiveness of strategies to improve the comprehension of information in the consent document by eligible participants were identified.

The choice to include only studies that proved the effectiveness of strategies is justified by the very objective of this review: to analyze strategies that favor the comprehension of clinical trial participants about the informed consent form and its theoretical bases.

Exclusion criteria were review articles, duplicated in databases, electronically unavailable, simulated research or hypothetical protocols. There was no delimitation of the time frame. Only situations referring to clinical trials that would actually be implemented were considered. Studies conducted with simulated populations of fictitious studies were disregarded, given that a simulated population can overestimate the results by including only those who accepted to participate in a hypothetical intervention, or even underestimate the effects of strategies implemented to favor the understanding of the consent form, given the limited concern of participants with information from a fictitious study.

Two reviewers independently assessed the title and abstract of all potentially relevant studies to identify those that met the inclusion criteria. Any disagreement between the two reviewers was resolved with participation of a third author.

Studies that met the criteria were included in the EndNote® X5 (Clarivate Analytics, The United Kingdom) reference management software and articles were read in full.

Table 1 - Combinations of descriptors used in search strategies, September 2021

Combinations of DeCS
(("Consent Forms" OR "*Formularios de Consentimiento*" OR "*Termos de Consentimento*" OR "*Documentos de Consentimento*" OR "*Formulários de Consentimento Esclarecido*" OR "*Formulários de Consentimento Livre e Esclarecido*" OR "Informed Consent" OR "*Consentimiento Informado*" OR "*Consentimento Livre e Esclarecido*" OR "*Autorização Consciente*" OR "*Consentimento Consciente*" OR "*Consentimento Esclarecido*" OR "*Consentimento Informado*") AND ("Clinical Trial" OR "*Ensayo Clínico*" OR "*Ensaio Clínico*" OR "Clinical Study" OR "*Estudio Clínico*" OR "*Estudo Clínico*") AND (Comprehension OR *Comprensión* OR *compreensão* OR *compreensibilidade* OR "*Compreensão de Leitura*" OR *entendimento* OR *legibilidade*)) AND (db:("LILACS" OR "CUMED" OR "IBECS" OR "BDENF"))
Combinations of MeSH
("Consent Forms" OR "Informed Consent") AND ("Clinical Trial" OR "Clinical Study") AND (Comprehension)

Note: DeCs - Health Sciences Descriptors; MeSH - Medical Subject Heading; LILACS – Latin American and Caribbean Health Sciences Literature; CUMED - Centro Nacional de Información de Ciencias Médicas; IBECS - Índice Bibliográfico Español en Ciencias de la Salud; BDENF - Base de Dados Enfermagem; db – Database.

The main characteristics of included studies were extracted using a specific instrument created by the authors. The following variables were extracted: code; year of publication; country; population; sample detail; type of strategy adopted (contact time and theoretical framework); outcome measure; synthesis of results and recommendations.

In the area of Education, it is considered that the resource used is characterized as being governed by the pedagogical intention and conception of education assumed[9]. Therefore, there is always a theoretical principle behind the strategy that guides the entire educational process with a view to making a decision about consent, even if the option was not consciously made by the researcher. After a detailed reading of articles, the identified theoretical frameworks of education were classified as: Traditional Modern (Traditional, Dialogical, Behavioral or Psychosocial), or Post-Modern Thought[18]. When the theoretical bases were not described by the authors themselves, the researchers used the relations between the subject and the object of knowledge as a classification criterion.

For the presentation and discussion of results, each study included in the final sample was coded as follows: letter S (= Study) followed by Arabic numerals in order (1, 2, ..., 21). For Example, the first study was coded S1 and so on, until S21.

RESULTS

The final sample of the integrative review consisted of 21 articles. The summary of searches and the selection of articles was developed using the Preferred Reporting Items for Systematic Review and Meta-Analys (PRISMA) checklist[19] (Figure 1).

The systematic search in the main databases in the health area allowed identifying: Strategies that consist of changes in the written text of the consent form for better legibility and readability (S1, S2, S3, S4, S5), based on text and printed illustrations; and Multimodal strategies distinct from the conventionally used written text in consent forms.

There was a prevalence of multimodal strategies, which included: audiovisual materials (S7, S8, S9, S13, S16, S17); educational games (S12, S15); semiotic approaches (S6, S8, S10, S11, S14, S15, S18); and photo-novella (S11).

In some studies, multiple didactic resources were used in an integrated way, that is, integrating different resources in the same intervention, such as: informative conversation and pamphlet (S21), informative conversation and test/feedback (S10, S18), video, booklet and virtual assistance (S20), reading the informed consent aloud, test/feedback (S6, S8, S10, S11, S14, S15, S18).

Table 2 brings together the findings on the strategies employed to favor the comprehension of information from informed consent by clinical trial participants.

Table 3 presents the main results of studies analyzed according to the outcome measure, a synthesis of results and the authors' main recommendations for the use of strategies.

DISCUSSION

As observed in the 21 articles analyzed in this review, the use of strategies has proven effective in improving the understanding of informed consent in clinical research, which may confirm the premise that education can favor voluntary decisions. The study by Lobato et al.[31], which evaluated the knowledge about the Informed Consent information of adults in the Northeast of Minas Gerais, also refers to the need to associate educational interventions with potential participants befo-

Figure 1 - PRISMA flowchart: steps for selecting the articles

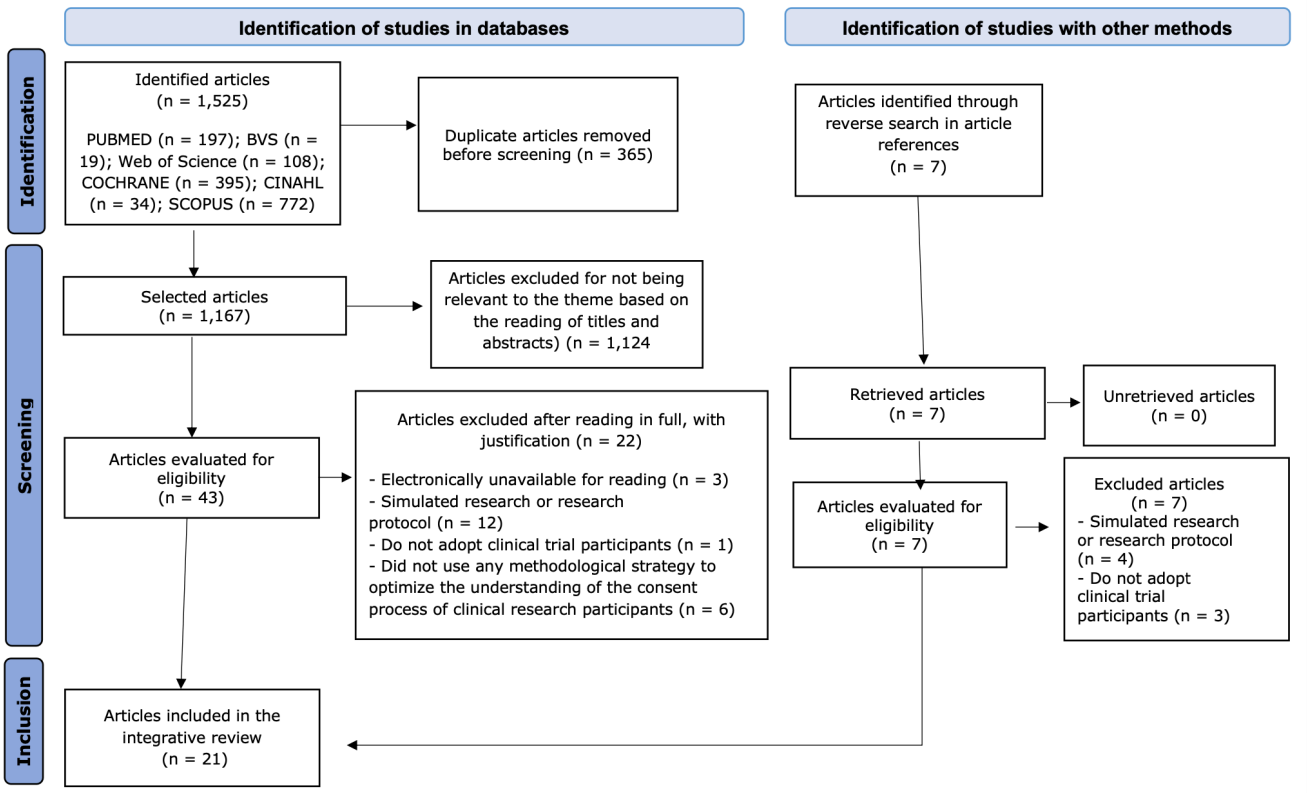

Table 2 - Characterization of studies included in the integrative review, September 2021

Continue...

Code / Year / Country	Population	Sample (n); IG (n); CG (n)	Type of strategy performed	Contact time (minutes)	Theoretical reference
Category 1: Strategies consisting of changes to the written consent text to improve legibility and readability					
S1[20] / 1994 / Australia	Adults with AIDS intolerant of zidovudine	113 IG (n = 61); CG (n = 52)	Short format informed consent	Not informed	Traditional
S2[21] / 2012/ New Zealand	Men and women admitted to hospitals	282 IG 1 (n = 94); IG 2 (n = 94); CG (n = 94)	G1- Booklet with simple language and fewer words + standard informed consent G2 - Booklet, with fewer words + informed consent short CG - Delivery of the traditional ICF	17	Traditional
S3[22] / 2016 / Thailand	Adults from a clinical pharmacokinetic study	550 IG (n = 275); CG (n = 275)	IG - Narrative informed consent, summary boxes, highlights, illustrations and clarification of doubts CG - Delivery of the traditional informed consent	20	Traditional
S4[23] / 2017 / Thailand	Pregnant women at risk of premature birth	232 IG (n = 120); CG (n = 112)	IG - Narrative informed consent, summary boxes, highlights, illustrations and clarification of doubts CG - Delivery of the traditional informed consent	30	Traditional
S5[24] / 2019 / Thailand	Parents of transfusion-dependent children with thalassemia	210 IG (n = 105); CG (n = 105)	IG - Narrative informed consent with summary boxes, highlights and illustrations CG - Delivery of the traditional informed consent	49	Traditional

Table 2 - Characterization of studies included in the integrative review, September 2021

Continuation...

Code / Year / Country	Population	Sample (n); IG (n); CG (n)	Type of strategy performed	Contact time (minutes)	Theoretical reference
Category 2: Multimodal strategies distinct from the conventionally used written text in consent forms					
S6[25] / 1996 / Holland	Men and women undergoing cancer treatment	180 IG (n = 90); CG (n = 90)	IG - Telephone approach, Test/feedback and clarification of doubts CG - Delivery of the traditional informed consent	30	Traditional
S7[26] / 2007 / Scotland	Adults with colorectal cancer	173 IG (n = 86); CG (n = 87)	IG - Video, CD-ROM or DVD CG - Delivery of the traditional informed consent	10	Traditional
S8[27] / 2007 / Canada	Adults with metastatic neoplasia	49 IG (n = 22); CG (n = 27)	IG - Documentary-style educational video with graphics, text and scenes to enhance dialogue, Test/Feedback CG - Delivery of the traditional informed consent	13	Traditional
S9[28] / 2009 / United States	Adults with stage I cancer	130 IG (n = 70); CG (n = 60)	IG - Video with scenes of actors signing up for a study CG - Delivery of the traditional informed consent	60	Traditional
S10[29] / 2011 / United States	HIV infected adults	21 IG (n = 12); CG (n = 9)	IG - Oral and written information session; Test/feedback and clarification of doubts CG - Delivery of the traditional informed consent	20	Traditional
S11[30] / 2012 / Korea	Healthy adult clinical trial participants	100 IG 1 (n = 50); CG (n = 50)	IG - Test/feedback or informed consent in photo-novella format CG - Delivery of the traditional informed consent	Not informed	Traditional
S12[31] / 2012 / Brazil	Adults residing in helminthiasis endemic areas	148 IG (n = 105); CG (n = 43)	IG - Board game with cards including objective questions and problem situations involving the contextualization of the disease and the implications of participating in the study CG - Delivery of the traditional informed consent	120	Dialogic
S13[32] / 2012 / Canada	Female farmers using a microbicide substance	36 IG (n = 18); CG (n = 18)	IG - Slides of a story based on participants' daily actions with colorful images and local language CG - Delivery of the traditional informed consent	50	Psychosocial Approach
S14[33] / 2014 / United States	Adults participating in an anti-drug study	104 IG (n = 52); CG (n = 52)	IG - Reading the informed consent aloud, Test/feedback, printed information CG - Delivery of the traditional informed consent	90	Traditional
S15[34] / 2015 / United States	Adults being treated for cancer	144 IG 1 (n = 45); IG 2 (n = 50); CG (n = 49)	IG 1 – enhanced informed consent IG 2 – enhanced informed consent, question and answer game for verbalizing consent, Test/feedback CG - Delivery of the traditional informed consent	60	Traditional

Table 2 - Characterization of studies included in the integrative review, September 2021

Conclusion.

Code / Year / Country	Population	Sample (n); IG (n); CG (n)	Type of strategy performed	Contact time (minutes)	Theoretical reference
S16[35] / 2015 / Gambia	Men and women being treated for malaria	311 IG (n = 155); CG (n = 156)	IG - Video adapted to linguistic diversity CG - Delivery of the traditional informed consent	51,4	Traditional
S17[36] / 2015/ United States	Parents of children who attended pediatric clinics	135 IG (n = 67); CG (n = 68)	IG -Graphic multimedia program on iPad and interactive exercises CG - Delivery of the traditional informed consent	Not informed	Dialogic
S18[37] / 2016 / United States	Adults admitted to dermatology, rheumatology/ immunology, pulmonology and family medicine clinics	200 IG 1 (n = 50); IG 2 (n = 50); IG 3 (n = 50); CG (n = 50)	IG 1 - paper consent, researcher-participant discussion and 13 guided interactive questions IG 2 - electronic consent, graphics and literal text narration with participants able to ask questions at any time IG 3 - multimedia consent procedure as above and 13 guided interactive questions CG - Delivery of the traditional informed consent with standard explanation by the researcher	15	Traditional
S19[38] / 2017 / Mexico	Parents of teenagers being treated for asthma	128 IG (n = 64); CG (n = 64)	IG - Discussion with parents separated from adolescents, more written information CG - Delivery of the traditional informed consent and discussion with parents and adolescents together	15	Dialogic
S20[39] / 2018 / United States	Latin women with breast cancer	77 IG (n = 38); CG (n = 39)	IG - interactive educational video, booklet and virtual service CG - Delivery of the traditional informed consent	30	Behavioral Approach
S21[40] / 2020 / Tanzania	Adult parents of children in a study with anthelmintic	254 IG 1 (n = 63); IG 2 (n = 62); IG 3 (n = 64); CG (n = 65)	IG 1- Pamphlet IG 2 – Verbal information session IG 3 – Verbal information session and pamphlet CG - Delivery of the traditional informed consent	15	Traditional

Note: Intervention Group (IG); Control Group (CG); Acquired Immunodeficiency Syndrome (AIDS); Digital Versatile Disc (DVD); Compact Disc Read-Only Memory (CD-ROM); Human Immunodeficiency Virus (HIV).

Table 3 - Synthesis of the selected studies according to procedures for assessment of the outcome of interest, synthesis of results and conclusions of studies on the tested strategies, September 2021

Continue...

Code	Procedure/measurement technique / assessment of outcomes of interest	Synthesis of results	Conclusions of studies
S1[20]	Eight true or false items on: the use of didanosine, efficacy, possible consequences for slowing the progression of HIV infection, treatment of HIV infection, comparison of efficacy and side effects with AZT, purpose of informed consent, appropriateness of the informed consent and the participant's understanding.	There was no statistical significance for the infor med consent format, but there was a weak interaction indicating that the IG increased mean comprehension scores (5.0 vs. 4.4, p = 0.079). After implementing the strategy, most participants (56.0%) got all the answers about the study information correct.	It is possible to quickly and simply identify subjects who did not understand all information presented. A complementary intervention strategy can be used specifically in this subgroup to provide additional information before they are enrolled in any particular study.

Table 3 - Synthesis of the selected studies according to procedures for assessment of the outcome of interest, synthesis of results and conclusions of studies on the tested strategies, September 2021

Continuation...

Code	Procedure/measurement technique / assessment of outcomes of interest	Synthesis of results	Conclusions of studies
S2[21]	Eight multiple-choice questions on: specific study issues, participant rights, and willingness.	Comprehension was better for participants who received the booklet and the short informed consent compared to the CG (62.0% vs. 49.0%, p = 0.0008).	A simple booklet is consistent to provide information about participants' rights, which is relevant to all research studies and to improve the understanding of those participating in clinical trials.
S3[22]	Twenty-four questions based on short cases that assessed understanding of general items, patient rights, scientific and ethical aspects.	Significant improvement in understanding in the IG compared to CG (83.3% vs. 76.0%, p < 0.001).	The strategy can be important to improve the quality of informed consent.
S4[23]	Twenty-five short case studies in which each case study consisted of a question followed by three answer options. Each participant could consult the provided consent form.	Improved understanding of the IG in relation to the CG (72.5% vs. 59.8%, p = 0.041). The IG achieved better results regarding the understanding of the five elements: foreseeable risks, compensation for injury, identification of any experimental procedures, confidentiality of records and number of participants required. There was greater effectiveness among participants with a medium or lower level of education and little effect on those with higher education.	The use of images, clarity and readability contribute to a better understanding of information.
S5[24]	Twenty-five questions based on short cases that assessed understanding on: general items, patient rights, scientific and ethical aspects.	Improved understanding of the IG compared to the CG (42.9% vs. 27.6%; p = 0.021). The IG obtained better results regarding the understanding of five elements: who can access the data, right to receive new information, identification of experimental procedures, treatment alternatives and number of participants required. The least understood element by parents in both groups was experimental treatment and randomization (31.4%).	Simplicity and concise format with greater processability (summary boxes, highlights and illustrations when appropriate) can improve participants' understanding. The intervention may be beneficial in research involving individuals with limited academic background.
S6[25]	Twelve open-ended questions on diagnosis, the nature and goals of the proposed treatment(s), the potential side effects of these treatments, the clinical situation and experimental context in which the treatment would be performed, and the characteristics of the clinical trial.	Improved understanding of IG compared to the CG (83.1% vs. 66.3%, p < 0.01). Intervention group achieved better results regarding the understanding of eight elements: risk, side effects, study context, objectives, randomization, treatment alternatives, voluntary nature of participation and right to withdraw from the study.	The intervention is a viable and effective means of increasing awareness and understanding of people with cancer about the fundamental aspects of informed consent. Convenience, privacy and duration of contact with the nurse were the characteristics that participants valued the most.
S7[26]	Twelve questions assessing participants' understanding of the study and their anxiety.	Improved understanding in the IG compared to the CG (90.0% vs. 78.0%, p < 0.007). There was a significant difference in the improvement of anxiety (p = 0.011).	The strategy proved to be a useful tool to improve the knowledge and anxiety of clinical research participants.

Table 3 - Synthesis of the selected studies according to procedures for assessment of the outcome of interest, synthesis of results and conclusions of studies on the tested strategies, September 2021

Continuation...

Code	Procedure/measurement technique / assessment of outcomes of interest	Synthesis of results	Conclusions of studies
S8[27]	Five questions about satisfaction with the method and six multiple-choice and true-false questions about objectives of clinical trials, safety, efficacy and side effects.	Improvement in the mean comprehension scores of the IG compared to the CG (108 vs. 106, p = 0.001). Comprehension scores increased more in the group that received audiovisual information. There was a significant difference in the number of participants who agreed that the video provided useful information (p < 0.001), they felt confident about understanding phase I clinical trials (p = 0.031), supported in their decision to participate in the study (p = 0.011) and would have more questions for their physicians (p = 0.017).	The intervention proved to be a useful and complementary tool to improve the participant's understanding of the consent process for randomized trials before decision-making.
S9[28]	Nineteen multiple-choice questions, plus some open-ended questions about: the purpose of the study, expected benefits and risks, and intended decision on enrollment.	Improved understanding of IG compared to CG (authors do not specify overall number of initial hits versus post-intervention hits), greater chance to hit phase 1 research objective, and 60.0% less chance to believe they would benefit in the long term or heal (p = 0.041). In IG (46.8%) believed they would benefit from the drug vs. 25.9% of the CG (p = 0.002).	Video clips can change beliefs regarding the purpose and benefit of a clinical trial.
S10[29]	Quality of Informed Consent (QIC) with 10 items that measured subjective understanding, and 21 items that measured objective understanding of purposes and description, risks, benefits, confidentiality of data, right to compensation in case of damage, voluntariness, and right to answer queries related to the study.	Improvement of mean comprehension scores of the IG compared to the CG (20 vs. 16, p = 0.002 – three months after implementation of the intervention). The IG improved understanding of items measuring purpose, risks, alternatives to participation, data confidentiality, research-associated injuries, voluntary consent, and participants' expectations.	Targeted education can improve understanding of informed consent one week after the intervention, but retention of concepts may require periodic monitoring throughout the course of a clinical trial.
S11[30]	Twenty questions assessed subjective understanding. Objective understanding was measured using: twenty questions (yes or no) and ten questions based on the Assessment Tool (MacCAT-CR) for Clinical Trials, which addressed the possibility of accidentally selecting responses in a questionnaire with structured choice-type questions.	Improved understanding of the IG compared to the CG (82.5% vs. 90.0%, p < 0.001). The photo-novella did not increase the levels of understanding in relation to the CG that received only the standard informed consent form.	The feedback questionnaire with any type of information sheet can improve understanding in informed consent.
S12[31]	Questionnaire on Quality Assessment of the Informed Consent with twelve open-ended questions about information addressed in the Informed Consent and eight that measured the influence on decision-making to participate in this clinical trial.	Significant improvement in IG comprehension compared to the CG (62.8% vs. 43.6%, p > 0.05). Participants of the IG had a higher percentage of correct answers about the adverse effects predicted in the protocol of this clinical investigation, the confidentiality of individual data, the benefits predicted in the clinical trial and its scientific objectives.	The strategy and the reading of the Informed Consent can favor a greater understanding of information and less influence on decision-making for participation in a clinical trial.

Table 3 - Synthesis of the selected studies according to procedures for assessment of the outcome of interest, synthesis of results and conclusions of studies on the tested strategies, September 2021

Continuation...

Code	Procedure/measurement technique / assessment of outcomes of interest	Synthesis of results	Conclusions of studies
S13[32]	The amount of questions/items contained in the questionnaire about randomization, double blind, placebo and research implications was not found.	Improved understanding of the IG compared to the CG (72.2% of participants got more than 75.0% right, while 72.2% of CG participants got 50.0-74.0% right, p = 0.075). The intervention appears to be effective in improving understanding of key concepts (randomization, double-blinding, placebo use).	The results suggest that the understanding of the consent form information can be improved if explained with local and personalized narratives.
S14[33]	Fifteen open-ended questions on understanding the protocol, protecting human beings, risks of participation, and benefits of participation.	Improved understanding in the IG compared to the CG (84.0% vs. 59.0%, p < 0.0001).	Administering a brief consent questionnaire and small financial incentives for correct answers can increase participants' motivation to remember information.
S15[34]	Consent Understanding Evaluation (CUE): approximately fifty open and closed-ended questions – twenty-five questions related to the purpose of the study, voluntariness, risks and design; eight on research and consent; eight on consent for the study.	There was no difference between the understanding of the IG compared to the CG (78.0% vs. 75.0%, p = 0.43). Participants who received Informed Consent with highlights, question and answer game for verbalizing consent, test/feedback scored 7.6 percentage points higher (p = 0.02) on open-ended questions about understanding than CG participants, although unadjusted comparisons did not reach statistical significance.	It is feasible to use markers and questions asking participants to verbalize the purpose, risks and voluntariness of the study and to discuss it with the research team.
S16[35]	Twenty-six questions (seven closed-ended, ten multiple choice and nine open-ended). Validated computerized audio questionnaire.	Significant improvement in the understanding of the IG compared to the CG in the short and long term - 7 and 28 days - (64.0% vs. 40.0%, p = 0.042).	The strategy can help to address the fundamental ethical challenge of obtaining informed consent in areas with low levels of literacy.
S17[36]	Seven questions about: clinical trial, randomization, placebo, concealment, double-blind, efficacy and informed consent.	Improvement in mean comprehension scores of the IG compared to CG (11.6 vs. 8.8; p < 0.001).	Interactive programs increase understanding by promoting active learning.
S18[37]	Twenty-seven true/false statements, covering the eight essential components of informed consent present in federal regulations regarding Human Research Protections.	Significant improvement in the understanding of the IG compared to the CG (97.9% vs. 96.3%). Intervention Group 1 (p = 0.007) and IG 3 (p = 0.04) improved participants' understanding of consent information.	Verbal and multimedia information session independently improved participants' comprehension. Interactivity and multimedia can be effective in promoting the participant's understanding and confidence in understanding a consent.
S19[38]	Knowledge and Appreciation Survey (KAS) with 30 questions (True-False) on understanding the procedures regarding the use and type of medication involved in the asthma study, research processes that included standard procedures for medication trials and those unique to the asthma study, participant rights and privileges, study risks/benefits.	Improved understanding of the IG compared to the CG (84.6% vs.74.1%, p = 0.011). Adolescents (>15 years old) and their parents had better results regarding the understanding of three elements: asthma medications, risks and benefits, and higher percentages of correct answers in questions related to the research process, rights/ benefits.	Younger adolescents should be given specific attention to explaining procedures and rights, which will provide an opportunity for meaningful inclusion in the assent process.

Table 3 - Synthesis of the selected studies according to procedures for assessment of the outcome of interest, synthesis of results and conclusions of studies on the tested strategies, September 2021

Conclusion.

Code	Procedure/measurement technique / assessment of outcomes of interest	Synthesis of results	Conclusions of studies
S20[39]	Thirteen questions about the decision to participate in a clinical trial; participants' perception of clinical trials (meaning of randomization) and consideration of clinical trials as treatment options for cancer.	Thirteen out of the eighteen IG participants scored high (greater than 75.0%) during the post-intervention evaluation period, and none of the eighteen in the CG scored high. The theory-based intervention was more effective in improving the understanding of clinical trial participants of the IG.	Interactive videos and virtual assistance tailored to the target audience are effective strategies to successfully address awareness and improve informed decision-making skills on participation. Using video can be a cost-effective way to reach minority populations.
S21[40]	Ten multiple-choice questions (each with four options) and seven true-false questions. The questionnaire was administered orally.	The IG that received an informative session obtained better scores in terms of understanding the knowledge about the disease and the study procedure. There was no statistically significant increase in participants' understanding through the pamphlet. The proportion of participants who correctly answered the 17 questions varied by question and group, ranging from 25 to 100%.	A pamphlet was not a good way to convey clinical trial information while an oral information session improved knowledge, but not all participants who received an information session correctly answered all questions.

Note: Intervention Group (IG); Control Group (CG); Azidotimidina (AZT); Human Immunodeficiency Virus (HIV); Versus (Vs.).

re signing the Informed Consent as a way to guarantee ethical precepts.

Regarding articles grouped in the category of strategies that consist of changes in the written consent text to improve legibility and readability, the reduction in the number of words, pages, and other visual alterations were mentioned[20-24]. As simple as such strategies may seem, they have contributed to improve participants' comprehension and to their reading of the document in its entirety. The simplification of language also helped to improve the understanding of participants with low education[23]. In relation to this matter, visual changes in the Informed Consent can simplify the content and make the information more explicit.

This is important when observing that many participants may not read the entire Informed Consent before signing it[41,42] and that overly long and technical consent documents may compromise the quality of Informed Consent[43].

In this sense, it is possible to associate the fundamentals of Functional Health Literacy (FHL) in the informed consent process[2]. Participants with a limited level of health literacy tend to retain up to 50.0% less information and do not feel ready to ask questions. Therefore, it is recommended that verbal and written communication are considered in the consent process. Or, as we have suggested in this review, to consider the association of an educational strategy in addition to reading the Informed Consent in the consent process. Thus, the Informed Consent and the strategy must use simple language, without scientific terms, with vocabulary mirrored in the participant and a clear slow speech, with information divided into small parts[2].

The approximation of consent information to the context experienced by the participant promotes the attention and openness necessary for the production of knowledge. When the consent information is anchored in the subjective experience of participants, they become more likely to give their own meaning to this information, a step considered essential for their comprehension[9].

Among the multimodal strategies identified in this review, audiovisual resources (audios and videos) have proven promising to favor the comprehension of potential participants. As audiovisual techniques are more sensorial, they facilitate a greater and faster understanding and interpretation of information[44]. In addition, audiovisual resources allow immediate verbal reinforcement of written information, which can facilitate the understanding and recall of information by clinical trial participants[26,27]. This fact may explain the high satisfaction regarding the participation decision of participants in S8[27], as well as the reduction of anxiety regarding the research of participants in S7[26].

The effectiveness of educational games observed in the studies of this review (board and question and answer)[31,34] can be explained by the fact that they facilitate the teaching and learning process, regardless of the context in which they are applied, presenting as effective strategies in favoring dialogue, joint construction of knowledge and the participant's own autonomy[45]. It is believed that games offer the subject the chance to produce and express their subjectivity, and require the mobilization of cognitive, relational and affective elements that together, facilitate the process of understanding the research and its implications[34,35].

The semiotic approaches observed were developed through strategies of telephone approach[25], virtual service[39], test and feedback (questions addressed to the participant with validation/correction of answers) [25,27,30,33,34], clarification of doubts[29], reading aloud the Informed Consent[33], informative conversation[37] and booklet[39]/pamphlet[40]. Although systematic and conventional modes of communication are used in the strategies, and they were multimodal (combination of different semiotic modes, such as spoken, written, gestures, sounds) in some situations, all were based on the transmission of information, as they remained in the expectation of ensuring the participant's understanding of specific and pre-directed items.

As much as semiotic approaches promote an expectation of being differentiated pedagogical strategies that value dialogue and the joint construction of knowledge, in this review, all distanced themselves from the dialogic method, since they were guided by the repetition of information about the purpose of the study, risks, benefits, placebo concepts, randomization and others.

In turn, the photo-novella, which is characterized as a sequence of photographs with text balloons similar to comics, differs from traditional pedagogical strategies in health education. The photo-novella uses an aesthetic resource that accesses the research participant from the subjective path[46]. However, the simple fact of using an artistic resource did not necessarily imply the researchers' commitment to the development of research participants' autonomy. Although the photo-novella has an artistic character, it was focused on the transmission of a structured thought.

It is observed that using strategies composed of multiple didactic resources, as brought by Bhupathi and Ravi[47], can increase the interaction with the participant, generate more discussions and with that, stimulate meaningful learning. However, even if the strategies using multiple didactic resources proposed greater interaction between participant and researcher (S6 to S21), they favored immediate verbal reinforcement of written information. In this case, the resource of repetition is evident. Although this is a widespread tool to study and understand any topic, it can favor automatic and intuitive responses.

Although the strategies identified in this review have enhanced participants' understanding of the Informed Consent information, two important points must be problematized. The first refers to the level of comprehension of participants; even though it increased from the use of strategies to favor consent, it still remained at the level of 50.0 to 60.0% of correct answers (S1, S2, S9, S5, S12). The second is related to the fact that although in some studies participants obtained more than 70.0% of correct answers on information from the consent processes of the studies they participated in, there were still key concepts that were not understood.

In this sense, a study (S5) demonstrated that despite the improvement in understanding, terms and concepts such as randomization and experimental treatment were less understood (31.4%). Another study (S18) showed that among participants who showed a high level of comprehension, 68.0% did not understand that other researchers could have access to their biological samples/health information. In addition, 26.0% mistakenly understood that their privacy and confidentiality would never be violated. In study S2, it was found that after a verbal information session, only half of parents of participants in a clinical trial understood the objectives and the right to withdraw their children from the study, and 62.0% of parents reported that nothing bad could happen after the treatment.

A possible explanation for the limitations identified in the comprehension of some key elements available in the Informed Consent may be related to the high trust in researchers, often considered as "holders of knowledge"[48].

The misunderstanding or incomplete understanding of the overly technical and specialized information involved in the consent process can impair participants' ability to recognize their rights and to make a deeper appreciation of the benefits and risks[49]. A Brazilian study of participants from 16 clinical trials showed that the adequate understanding of objectives, risks, benefits and the right to post-study care were practically unknown by participants[50].

Previous studies have shown that the consent process failed to express a truly autonomous decision-making by clinical trial participants[6,31,51,52]. Therefore, it is essential to explore new alternatives to communicate the Informed Consent information to participants in order to obtain an ethical and valid consent[10].

Another point of analysis regards the fact that in the studies found, there is not a standard to assess participants' understanding of the Informed Consent content, a condition that prevents the generalization and comparison of results of the different studies[6]. To a large extent, the level of understanding was measured through the score or proportion of correct answers given by participants to data collection instruments. The number of questions in a test ranged from four to fifty. The results were mostly expressed as percentages, being compared to the number of correct answers for each item at baseline and immediately post-intervention. Higher scores indicated greater comprehension or improvement in comprehension as a result of the strategy received by the intervention group compared to the control group.

In relation to this matter, perhaps what is being measured in the analyzed studies is participants' ability to memorize or recall information from the Informed Consent, to the detriment of a meaningful comprehension of the informed consent process of the study in which they are taking part. The authors make this assumption, as most studies used close-ended questions to assess participants' comprehension. In this format, the participant somehow already has a list of pre-selected options, which can corroborate an assessment of memorization.

It is believed that the use of close- and open-ended questions can favor researchers' real understanding of gaps in comprehension. Faced with the problems identified, is assumed the importance of researchers paying attention to the consent process as a way to develop health education and not just formalize something that is protocol[53]. By visualizing the consent process from the perspective of health education, we identify the different theoretical references used in the analyzed studies and access the meanings of education to favor the understanding of information[9].

On the epistemological bases that supported the strategies presented here, the Traditional Modern theoretical framework prevailed, characterized by sharing the same way of conceiving how it is understood - exposing the subject to the content of informed consent, recognized as a product ready to be consumed and reproduced by research participants[9].

Determined by the modern epistemological project, this sense of education is based on cognition, which in these strategies is understood as a model of representation constructed from a subject and an object of supposedly universal knowledge. In this perspective, the participant is denied any role in the construction of knowledge[9].

Few strategies were based on the dialogical framework (S12, S17, S19), in which information is modified in order to allow the construction of concepts by participants, supported by an interactionist matrix, according to which subject and object act on each other reciprocally. In this case, researchers do not impose their knowledge over that of participants. The information is modified in order to be anchored in subjectivity and articulated with the cultural context of the participant[9].

Only S13 relied on the psychosocial approach and considered the social representations, which allowed the approximation and the necessary estrangement with the unfamiliar universe for participants, allowing them to produce new meanings for the addressed phenomena from a perspective of subjective production[9].

In most studies, the fact of authors not explaining the theoretical framework on which strategies are based denotes a tendency to relegate the theoretical bases supporting such strategies. This can lead to the reiteration of the traditional way of promoting the understanding of information, even with the use of resources other than writing the consent document, and considered innovative[9].

The predominant knowledge transfer process in the articles analyzed here cannot be considered as the most appropriate to communicate study information and better ways need to be found to obtain a truly informed consent[40]. Therefore, a disruptive movement is needed with regard to the hegemonic way of developing consent. In addition, creatively, towards proposing strategies based on new theoretical approaches to improve participants' comprehension of the information they receive during the consent process.

In this sense, this work confirmed the assumption of the predominance of strategies that reflect in standardized and standardizing practices, and consider the potential research participant as a mere receiver of information. This generates an important reflection on the ethical challenge of obtaining valid consent. Despite the efforts of different researchers in the development of multi-strategies, the conceptions of knowledge, education and understanding are still in a field disconnected from the sense of autonomy.

In the present study, through the search strategies, only one study conducted in Brazil was retrieved[31], while all the others were from the international context. The country is recognized for its high potential for recruiting participants for clinical trials and ranks 24th in the world rank of clinical research[53]. Thus, the search strategies may not have been sufficient to locate the production of Brazilian researchers or, in fact, research on the subject is still incipient in this scenario.

There are Brazilian authors and research centers aware of the problem of understanding consent and dedicated to the development of related studies in this context. For example, Gazzinelli et al.[9] mention in one of their studies how they were impelled to develop interventions and inventive productions in clinical research based on different strategies. However, not all strategies developed by the group were quantitatively evaluated, which explains why only one study was included in this review[31].

Limitations of this review include not using an instrument to analyze the quality of articles. However, we emphasize that the main focus intended here was not exactly to analyze the effectiveness of interventions with a view to the future indication, but analyze inherent elements to interventions in which results with evidence of effectiveness were produced. A strong point of this review was the fact of using six databases in the search for articles.

CONCLUSION

There are a wide range of strategies used to improve clinical trial participants comprehension of the consent process. The use of didactic resources to facilitate the exposition of information was presented as the predominant strategy, followed by strategies based on changes in the format and content of the written text of the consent document.

Although participants obtained a better understanding of the study procedures by use of didactic resources cited above, in many studies, the level of comprehension remained below 60.0%, indicating their lack of understanding or limited understanding of certain fundamental concepts.

The Traditional Modern pedagogical theoretical base has been hegemonic. In this regard, the performance of empirical studies is recommended of development of strategies that propose to break with hegemonic pedagogical trends, sustained by the principle of modern scientific rationality.

The synthesis of the findings contributes to reflections in the field of Bioethics, above all, on how the way of conducting informed consent implies making an option for a certain conception of education, the basis for creating strategies that can encourage a greater or lesser protagonist role of participants.

FUNDING

This research did not receive financial support.

CONFLICT OF INTERESTS

None.

CONTRIBUTIONS ROLES - CRediT

VFMV: Conceptualization; Data Curation; Formal analysis; Investigation; Methodology; Project administration; Writing--original draft and Writing-review & editing.
SGC: Formal analysis; Methodology; Writing-original draft and Writing-review & editing.
LFS: Data Curation; Formal analysis and Investigation; Writing-original draft and Writing-review & editing
MFGB: Conceptualization; Formal analysis; Project administration and Writing-review & editing.

REFERENCES

1. ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000 [cited 2023 Mar 07]. Available from: https://clinicaltrials.gov

2. Cordeiro MD, Sampaio HAC. Aplicação dos fundamentos do letramento em saúde no consentimento informado. Rev. Bioét. 2019 July-Sept;27(3):410-8. https://doi.org/10.1590/1983-80422019273324

3. Cosac DCS. Autonomia, consentimento e vulnerabilidade do participante de pesquisa clínica. Rev. Bioét. 2017 Jan-Apr;25(1):19-29. https://doi.org/10.1590/1983-80422017251162

4. Jungues JR. Exigências éticas do consentimento informado [Internet]. Rev. Bioét. 2007 [cited 2023 Mar 07];15(1):77-82. Available from: https://revistabioetica.cfm.org.br/index.php/revista_bioetica/article/viewFile/32/35

5. Beauchamp TL, Childress JF. Princípios de ética biomédica. 4th ed. São Paulo (SP): Edições Loyola; 2001.

6. Ranjan R, Agarwal NB, Kapur P, Marwah A, Parveen R. Study of Awareness and Practice of Informed. Asia-Pac J Public Health. 2019 Nov 03;31(8):710-8. https://doi.org/10.1177/1010539519883135

7. Bader M, Zheng L, Rao D, Shiyanbola O, Myers L, Davis T, et al. Towards a more patient-centered clinical trial process: A systematic review of interventions incorporating health literacy best practices. Contemp Clin Trials. 2022 May;116:106733. https://doi.org/10.1016/j.cct.2022.106733

8. Gesualdo F, Daverio M, Palazzani, L, Dimitriou D, Diez-Domingo J, Fons-Martinez J, et al. Digital tools in the informed consent process: a systematic review. BMC Med Ethics. 2021 Feb 27;22:18. https://doi.org/10.1186/s12910-021-00585-8

9. Gazzinelli MF, Soares AN, Carneiro ACLL, Diemert D. Intercessões entre pesquisa clínica e educação: por uma promoção de conhecimento inventiva. 1st ed. Curitiba (PR): Editora CRV; 2018. https://doi.org/10.24824/978854442031.7

10. Rothwell E, Wong B, Rose NC, Anderson R, Fedor B, Stark LA, et al. A randomized controlled trial of an electronic informed consent process. J Empir Res Hum Res Ethics. 2014 Oct 02;9(5):1-7. https://doi.org/10.1177/1556264614552627

11. Quevedo A, Condo C, Valenzuela G, Molina L, Castillo E, Palacio A, et al. Informed consent comprehension among vulnerable populations in Ecuador: video-delivered vs. in-person standard method. Account Res. 2018 May 15;25(5):259-72. https://doi.org/10.1080/08989621.2018.1470931

12. Dickert NW, Eyal N, Goldkind SF, Grady C, Joffe S, Lo B, et al. Reframing Consent for Clinical Research: A Function-Based Approach. Am J Bioeth. 2017 Nov 17;17(12):3-11. https://doi.org/10.1080/15265161.2017.1388448

13. Paris A, Deygas B, Cornu C, Thalamas C, Maison P, Duale C, et al. Improved informed consent documents for biomedical research do not increase patients' understanding but reduce enrolment: a study in real settings. Br J Clin Pharmacol. 2015 July 03;80(5):1010-20. https://doi.org/10.1111/bcp.12716

14. Meneguin S, Ayres JA. Percepção do termo de consentimento informado pelos participantes dos ensaios clínicos [Internet]. Invest Educ Enferm. 2014 Jan-Apr;32(1):95-102. https://doi.org/10.17533/udea.iee.v32n1a11

15. Hopia H, Latvala E, Liimatainen L. Reviewing the methodology of an integrative review. Scand J Caring Sci. 2016 Apr 14;30(4):662-9. https://doi.org/10.1111/scs.12327

16. Mendes KDS, Silveira RCCP, Galvão CM. Revisão integrativa: método de pesquisa para a incorporação de evidências na saúde e na enfermagem. Texto contexto – enferm. 2008 Oct-Dez;17(4):758-64. https://doi.org/10.1590/S0104-07072008000400018

17. Santos CMC, Pimenta CAM, Nobre MRC. A estratégia PICO para a construção da pergunta de pesquisa e busca de evidências. Rev. Latino-Am. Enfermagem. 2007 June;15(3):508-11. https://doi.org/10.1590/S0104-11692007000300023

18. Libâneo JC. As Teorias Pedagógicas Modernas Revisitadas pelo Debate Contemporâneo na Educação. In: Libâneo JC, Santos A. A Educação na Era do Conhecimento em Rede e Transdisciplinaridade. 2nd ed. Campinas: Alínea; 2009. p. 1-37

19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021 Mar 29;372:n71. https://doi.org/10.1136/bmj.n71

20. Tindall B, Forde S, Ross MW, Goldstein D, Barker S, Cooper DA. Effects of two formats of informed consent on knowledge amongst persons with advanced HIV disease in a clinical trial of didanosine. Patient Educ Couns. 1994 Dec;24(3):261-6. https://doi.org/10.1016/0738-3991(94)90069-8

21. Benatar JR, Mortimer J, Stretton M, Stewart RA. A booklet on participants' rights to improve consent for clinical research: a randomized trial. PLoS One. 2012 Oct 19;7(10):e47023. https://doi.org/10.1371/journal.pone.0047023

22. Koonrungsesomboon N, Teekachunhatean S, Hanprasertpong N, Laothavorn J. Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study. Eur J Clin Pharmacol. 2016 Apr;72(4):413-21. https://doi.org/10.1007/s00228-015-2000-2

23. Koonrungsesomboon N, Tharavanij T, Phiphatpatthamaamphan K, Vilaichone RK, Manuwong S, Curry P, et al. Improved participants' understanding of research information in real settings using the SIDCER informed consent form: a randomized-controlled informed consent study nested with eight clinical trials. Eur J Clin Pharmacol. 2017 Feb;73(2):141-9. https://doi.org/10.1007/s00228-016-2159-1

24. Koonrungsesomboon N, Traivaree C, Tiyapsane C, Karbwang J. Improved parental understanding by an enhanced informed consent form: A randomized controlled study nested in a paediatric drug trial. BMJ Open. 2019 Nov 26;9(11):e029530. https://doi.org/10.1136/bmjopen-2019-029530

25. Aaronson NK, Visser-Pol E, Leenhouts GH, Muller MJ, Van der Schot AC, Van Dam FS, et al. Telephone-based nursing intervention improves the effectiveness of the informed consent process in cancer clinical trials. J Clin Oncol. 1996 Mar 01;14(3):984-96. https://doi.org/10.1200/JCO.1996.14.3.984

26. Hutchison C, Cowan C, McMahon T, Paul J. A randomised controlled study of an audiovisual patient information intervention on informed consent and recruitment to cancer clinical trials. Br J Cancer. 2007 Sept 11;97(6):705-11. https://doi.org/10.1038/sj.bjc.6603943

27. Strevel EL, Newman C, Pond GR, MacLean M, Siu LL. The impact of an educational DVD on cancer patients considering participation in a phase I clinical trial. Support Care Cancer. 2007;15(7):829-40. https://doi.org/10.1007/s00520-006-0199-2

28. Kass NE, Sugarman J, Medley AM, Fogarty LA, Taylor HA, Daugherty CK, et al. An intervention to improve cancer patients' understanding of early-phase clinical trials. IRB [Internet]. 2009 May-June [cited 2023 Mar 07];31(3):1-10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2872090/pdf/nihms196466.pdf

29. Sengupta S, Lo B, Strauss RP, Eron J, Gifford AL. Pilot study demonstrating effectiveness of targeted education to improve informed consent understanding in AIDS clinical

trials. AIDS Care. 2011 Nov;23(11):1382-91. https://doi.org./10.1080/09540121.2011.565031

30. Jeong IS, Hong JH, Jung SK, Cho J. The effect of feedback with photo-novella information sheets on subjects' understanding in informed consent for research. Ther Innov Regul Sci. 2012;46(6)661-8. https://doi.org/10.1177/0092861512456837

31. Lobato L, Souza VD, Caçador B, Soares AN, Wingester ELC, Gazzinelli MF. Efeitos de intervenção educativa na qualidade ética do consentimento livre e esclarecido. Rev. Bioét. 2012 [cited 2023 Mar 07];20(3):479-89. Available from: https://revistabioetica.cfm.org.br/index.php/revista_bioetica/article/view/769/821

32. Ndebele PM, Wassenaar D, Munalula E, Masiye F. Improving understanding of clinical trial procedures among low literacy populations: an intervention within a microbicide trial in Malawi. BMC Med Ethics. 2012 Nov 08;13:29. https://doi.org/10.1186/1472-6939-13-29

33. Festinger DS, Dugosh K, Marlowe DB, Clements NT. Achieving new levels of recall in consent to research by combining remedial and motivational techniques. J Med Ethics. 2014 Mar 18;40(4):264-8. https://doi.org/10.1136/medethics-2012-101124

34. Kass NE, Taylor HA, Ali J, Hallez K. A pilot study of simple interventions to improve informed consent in clinical research: Feasibility, approach, and results. Clin Trials. 2015 Feb;12(1):54-66. https://doi.org/10.1177/1740774514560831

35. Afolabi MO, McGrath N, D'Alessandro U, Kampmann B, Imoukhuede EB, Ravinetto RM, et al. A multimedia consent tool for research participants in the Gambia: a randomized controlled trial. Bull World Health Organ. 2015 Mar 23;93(5):320-8A. https://doi.org/10.2471/BLT.14.146159

36. Tait AR, Voepel-Lewis T, Levine R. Using digital multimedia to improve parents' and children's understanding of clinical trials. Arch Dis Child. 2015 May 18;100(6):589-93. https://doi.org/10.1136/archdischild-2014-308021

37. Simon CM, Klein DW, Schartz HA. Interactive multimedia consent for biobanking: a randomized trial. Genet Med. 2016 Jan;18(1):57-64. https://doi.org/10.1038/gim.2015.33

38. Annett RD, Brody JL, Scherer DG, Turner CW, Dalen J, Raissy H. A randomized study of a method for optimizing adolescent assent to biomedical research. AJOB Empir Bioeth. 2017;8(3):189-97. https://doi.org/10.1080/23294515.2016.1251507

39. Chalela P, Muñoz E, Gallion KJ, Kaklamani V, Ramirez AG. Empowering Latina breast cancer patients to make informed decisions about clinical trials: a pilot study. Transl Behav Med. 2018 June;8(3):439-49. https://doi.org/10.1093/tbm/ibx083

40. Palmeirim MS, Ross A, Obrist B, Mohammed UA, Ame SM, Ali SM, et al. Informed consent procedure in a double blind randomized anthelminthic trial on Pemba Island, Tanzania: do pamphlet and information session increase caregivers' knowledge?. BMC Med Ethics. 2020 Jan 06;21(1):1-9. https://doi.org/10.1186/s12910-019-0441-3

41. Associação da Indústria Farmacêutica de Pesquisa (Interfarma). A importância da pesquisa clínica para o Brasil [Internet]. São Paulo: Interfarma; 2021 [cited 2023 Mar 07]. Available from: https://www.interfarma.org.br/wp-content/uploads/2021/12/Interfarma_Estudo-Pesquisa-clinica-2021-1.pdf

42. Gomes ATL, Salvador PTCO, Goulart CF, Cecilio SG, Bethony MFG. Innovative Methodologies to Teach Patient Safety in Undergraduate Nursing: Scoping Review. Aquichan. 2020 Jan-Mar;20(1):e2018. https://doi.org/10.5294/aqui.2020.20.1.8

43. Carvalho ICN, Nascimento MOF, Pinto ACS, Melo ERF, Carvalho GRN, Santos MCT. Educational technology: Nursing and educational games in health education. RSD. 2021 June 15;18;10(7):e18710716471. https://doi.org/10.33448/rsd-v10i7.16471

44. Sanchez K, Eghaneyan BH, Killian MO, Calabassa LJ, Trivedi MH. Depression education fotonovela for engagement of Hispanic patients in treatment: a randomized clinical trial. BMC Psychiatry. 2021 Dec 23;21:635. https://doi.org/10.1186/s12888-021-03641-0

45. Bhupathi PA, Ravi GR. Comprehensive Format of Informed Consent in Research and Practice: A Tool to uphold the Ethical and Moral Standards. Int J Clin Pediatr Dent. 2017 Jan-Mar;10(1):73-81. https://doi.org/10.5005/jp-journals-10005-1411

46. Nascimento TG. Avaliação do processo de consentimento de pesquisa clínica [Tese na Internet]. [Ribeirão Preto]: Universidade de São Paulo; 2017 [cited 2023 Mar 07]. Available from: https://doi.org/10.11606/T.22.2018.tde-28112017-162459

47. Kadam RA. Informed consent process: A step further towards making it meaningful!. Perspect Clin Res. 2017 July-Sept [cited 2023 Mar 07];8(3):107-12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5543760

48. Rodrigues E Filho, Prado MM, Prudente COM. Compreensão e legibilidade do termo de consentimento livre e esclarecido em pesquisas clínicas. Rev. Bioét. 2014 Aug;22(2):325-36. https://doi.org/10.1590/1983-80422014222014

49. Almeida CH, Marques RC, Reis DC, Melo JMC, Diemert D, Gazzinelli MF. A pesquisa científica na saúde: uma análise sobre a participação de populações vulneráveis. Texto contexto - enferm. 2010 Mar;19(1):104-11. https://doi.org/10.1590/S0104-07072010000100012

50. Zagaja A. Quality of informed consent in clinical trials. J Pre Clin Res. 2020;14(1):22-4. https://doi.org/10.26444/jpccr/119621

51. Amorim KPC, Garrafa V, Melo AD, Costa AVB, Oliveira GCL, Lopes HG, et al. Participantes de ensaios clínicos em oncologia: perfil e aspectos envolvidos nas suas decisões. Trab. educ. saúde. 2018 Sept-Dec;16(3):1381-402. https://doi.org/10.1590/1981-7746-sol00139

52. Lobato L, Gazzinelli MF, Gazzinelli A, Soares AN. Conhecimento e voluntariedade para participação em pesquisas: um estudo descritivo com participantes de um ensaio clínico. Cad. Saúde Pública. 2014 June;30(6):1305-14. https://doi.org/10.1590/0102-311X00127813

53. Simonds VW, Garroutte EM, Buchwald D. Health Literacy and Informed Consent Materials: Designed for Documentation, Not Comprehension of Health Research. J Health Commun. 2017 July 31;22(8):682-91. https://doi.org/10.1080/10810730.2017.1341565