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Quality of Informed Consent in Phase III Clinical Trials in Portugal: The Participants' Perspective

Qualidade do Consentimento Informado em Ensaios Clínicos de Fase III em Portugal: A Perspetiva dos Participantes

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ABSTRACT

Introduction: Some studies show that participants do not always fully understand the informed consent form (ICF), which is one of the reasons for drop-outs. This study aimed to adapt the Quality of Informed Consent (QuIC) questionnaire into a valid instrument to be applied to the Portuguese population and to measure its reliability and validity in the Portuguese population, by applying it to a sample of participants in controlled trials.

Methods: The QuIC questionnaire was developed to assess the quality of informed consent in clinical trials and consists of two parts, addressing both the objective (part A) and the subjective (part B) understanding. After being translated and validated into Portuguese, it was implemented in 100 cardiac participants of phase III clinical trials in a University Hospital Center.

Results: The QuIC-PT questionnaire showed excellent stability over time and good validity. All patients evaluated their participation and their health positively and recognized the main purpose of the clinical trial. Almost all participants understood their role in helping future patients and the purpose of the trial and realized that, by signing the ICF, they were participating in a clinical trial. However, none of them knew that their experimental treatment was not proven to be the best alternative for their condition.

Conclusion: The QuIC-PT questionnaire seems to be a valid and useful instrument to evaluate the participants' understanding of the ICF. In this study, we found that some concepts, like 'study protocol' or 'randomization', were not well understood by participants when signing the ICF, especially by participants with lower education levels. They also believed that the experimental intervention would solve their health condition. Greater awareness about the importance of the informed consent process and ICF is necessary so that participants can fully understand the protocol, especially the risks involved, and their rights as participants.

Keywords: Informed Consent; Clinical Trials, Phase III as Topic; Comprehension; Patient Reported Outcome Measures

RESUMO

Introdução: Alguns estudos revelam que os participantes nem sempre compreendem completamente o formulário do consentimento informado (FCI), sendo uma das razões que levam à desistência. Este estudo teve como objetivo adaptar o questionário *Quality of Informed Consent* (QuIC) num instrumento válido para ser aplicado à população portuguesa e medir a sua fiabilidade e validade, aplicando-o a uma amostra de participantes em ensaios clínicos.

Métodos: O questionário QuIC foi desenvolvido para avaliar a qualidade do consentimento informado em ensaios clínicos e é constituído por duas partes, avaliando a compreensão objetiva (parte A) e a subjetiva (parte B). Depois de traduzido e validado para português, foi aplicado em 100 participantes cardíacos de ensaios clínicos de fase III num Centro Hospitalar Universitário.

Resultados: O questionário QuIC-PT mostrou uma excelente estabilidade ao longo do tempo e boa validade. Todos os doentes avaliaram positivamente a sua participação e a sua saúde, e reconheceram o principal objetivo do ensaio clínico. Quase todos os participantes compreenderam o seu papel em ajudar futuros doentes, perceberam que ao assinar o consentimento informado estariam a participar num ensaio clínico, e compreenderam o seu principal objetivo. Contudo, nenhum deles sabia que o tratamento experimental não estava comprovado como a melhor alternativa para a sua doença.

Conclusão: O questionário QuIC-PT provou ser um instrumento válido e útil para avaliar a compreensão dos participantes do FCI. Neste estudo, verificou-se que alguns conceitos, como 'protocolo do estudo' ou 'aleatorização' não foram bem compreendidos pelos participantes quando assinaram o FCI, especialmente pelos de baixa escolaridade. Os participantes também consideraram que a intervenção experimental resolveria sua condição de saúde. É necessária uma maior consciencialização sobre a importância da leitura do FCI, para que os participantes possam compreender plenamente o protocolo, especialmente os riscos envolvidos, e seus direitos como participantes.

Palavras-chave: Compreensão; Consentimento Informado; Ensaios Clínicos, Fase III; Resultados Relatados pelo Doente

INTRODUCTION

In Portugal, the National Ethics Committee for Clinical Research received, in 2022, 181 clinical trial (CT) submissions, 98.8% with a favorable decision. The main therapeutic area of the CT submissions was oncology (26), followed by bioequivalence and bioavailability studies (21), infectious diseases (10), neurobiology (6), and hematology (6).[1] On that date, a centralized submission was initiated.

After the Second World War, concerns about the procedures and norms of human research grew substantially. The Nuremberg Code was then developed in 1947, defining ethical principles to be followed by healthcare professionals in clinical research. This document alluded to the concept of free and informed consent, to be given by the participant before the beginning of the research.[2,3] Other documents with similar aims were also developed, including the Declaration of Helsinki (1964), the Belmont Report (1979), and the Guideline for Good Clinical Practice (1996).

In 1994, a law was introduced in Portugal, establishing

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rules for the conduct of CT, namely the respect for the physical and moral integrity of the participants. Later, in 2014, a Clinical Research Law was created to regulate all CT conducted on humans in Portugal, requiring high ethical standards, dignity, and safety of participants, as well as highlighting the importance of IC (informed consent) (Decree-law no. 73/2015, July 27th).[4] Following this legislation, and beyond any scientific interest, all CT must respect and preserve the dignity and rights of the participants.

Within this context, IC is defined as "a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate".[5] Before any data collection or protocol-defined procedure, all information regarding the CT should be given and explained to the participant, such as the procedures involved and potential benefits and risks. The investigator, or a person appointed by him/her, plays an important role in the IC process, and should be available to answer the participant's questions and clarify his/her doubts. In addition, the investigator should ensure that participants may freely decide to participate. The written signature of the informed consent form (ICF) by the participant indicates his/her commitment, understanding, and voluntary decision to engage in the clinical research.[6]

Some studies indicate that the ICF in CT are perceived as complex. There is evidence that participants, particularly those with a lower level of education, may not understand the randomization process[7,8] or frequently used research terms like 'blinding' and 'placebo'.[9,10] The fact that the information may not be fully understood may influence the participants' decisions or their behavior during the research.[11]

A systematic review done by Montalvo *et al* states that the participants' health literacy, reading, and comprehension skills should be assessed before the assignment of the IC, using validated tools.[10] However, there is no standardized method to measure the participant's level of understanding of the ICF before s/he decides to accept or reject to participate in the research.[12] Nevertheless, some questionnaires have been created such as the Hoyos' questionnaire,[13] the Process and Quality of IC,[14] and the Quality of IC (QuIC).[15] The QuIC, developed by Joffe *et al* in 2001, is a pioneering assessment tool of subjects' objective and subjective understanding of CT.[13-16] It is a self-administered questionnaire to be implemented between three to 14 days after the patient signs the ICF for the CT.

This study aimed to adapt the QuIC questionnaire into a valid instrument to be applied to the Portuguese population, and to measure its reliability and validity by applying it to a sample of participants enrolled in CT at a Portuguese hospital center.

METHODS

Cultural and linguistic adaptation

The QuIC cultural and linguistic adaptation was based on the sequential approach, following the International Society for Pharmacoeconomics and Outcomes Research criteria.[17] The adaptation of the QuIC for the Portuguese population was authorized by the original author, Steven Joffe from the Boston Children's Hospital, in the United States of America. The translation of the QuIC from English to European Portuguese was performed by two professional Portuguese bilingual translators. The two versions were compared, and a reconciled version was obtained and sent to an English bilingual translator for backtranslation, allowing its comparison with the original version of the questionnaire. After this process, two CT specialists made a clinical review of the Portuguese version of the questionnaire. We also conducted a cognitive debriefing session with ten CT participants to evaluate the level of understanding and acceptability of the Portuguese version of the QuIC (QuIC-PT).

Study design and participants

We implemented the QuIC-PT in participants of CT conducted at a University Hospital Centre in Portugal. This observational study started after the favorable decision of the Ethics Committee of the University Hospital Centre (095-CES-2019) and the Ethics Committee of the Faculty of Medicine (025-CE-2019).

Eligible participants in our validation study were (i) participating in a phase III CT for drug development, (ii) aged 18 years or older, (iii) without cognitive impairment that would not allow them to complete the questionnaire, (iv) able to understand and speak Portuguese, and (v) who provided their IC to our study. Participants were selected at enrolment for one of nine CT in cardiology taking place at the hospital.

Data collection

Participants were asked to complete the QuIC-PT form in a separate room without any external help, except for the participants who could not read. For these, the questions and response options were read out loud so as to not interfere with the participant's choices. We collected sociodemographic characteristics of the participants like sex, age, employment and marital status, and educational level. Each participant was asked to give, from 0 to 10, his/her opinion about (i) his/her participation in the CT and (ii) the perception of his/her health status. We also collected data about the CT where they were enrolled, such as study type and phase, the administration type (intravenous, oral, subcutaneous), and the place of recruitment (in a medical appointment, during hospitalization or after hospitalization). All data

was collected without the identification of the participants.

The quality of IC measurement instrument

The QuIC questionnaire comprises a total of 35 items to assess the objective understanding (part A, 21 items), and subjective understanding (part B, 14 items) of the ICF. According to its author, it requires about seven minutes to be completed.[15] The possible answers in part A are "disagree", "unsure" and "agree". A wrong answer is always scored with 0 points, a correct one receives the maximum scores of 33, 50 or 100, depending on the importance of the item in comparison to others, and an "unsure" answer receives a score equal to half of the maximum value. The total score of this part A is achieved by adding all points of each item and dividing them by the number of answered items. On the other hand, the possible answers in part B range from 1 ("I didn't understand this at all") to 5 ("I understood this very well") and are scored by calculating the average of the 14 items and scaling it to a 0 to 100 interval.[15] Items with a mean score of 75% or above mean that the participants understood the sentence and its meaning.

In the original study, the content validity was verified by an expert panel and the test-retest reliability was considered good, with an intraclass correlation coefficient (ICC) of 0.66 for part A and 0.77 for part B.[15]

In this study, we dropped three questions from the original part A (A6, A7 and A8) because they were oriented towards phase I and II CT. As our sample only included participants in phase III CT, the QuIC-PT has a total of 32 items. We calculated the mean score for each item of QuIC and computed the number of correct answers in part A.

Reliability

To test the reliability of the QuIC-PT, we assessed its stability over time. We randomly asked 30 participants to fill out the QuIC-PT twice, depending on their availability to go to the hospital, and we used the ICC to test. An ICC score lower than 0.50 means a weak correlation, between 0.50 and 0.75 a moderate correlation, between 0.75 and 0.90 a good correlation, and a score higher than 0.90 an excellent correlation.[18]

Validity

To test the validity of the QuIC-PT, we assessed the content, construct and criterion validity.[19] Content validity was assessed through the clinical review performed by two CT experts and through a cognitive debriefing session with ten participants in CT to guarantee the relevance of the QuIC-PT items.

Construct validity was assessed by hypothesis testing the number of correct answers in known groups or subsamples.[19] Therefore, we analyzed the number of correct answers and sociodemographic characteristics. Student's *t*-test and ANOVA were used for each variable and multiple linear regression for more than one independent variable.

Criterion validity was tested by comparing the number of correct answers with the self-assessment of the patient's participation in the CT.

At last, we also compared the number of correct answers with the characteristics of CT.

RESULTS

Cultural and linguistic adaptation

In the original study of the QuIC, the authors applied this instrument to patients participating in cancer CT. Similar to other studies which used QuIC in other conditions or diseases than cancer CT,[20,21] the cultural and linguistic adaptation required the change of the expression "cancer patients" (in A2 and A14) to "patients", "cancer clinical trial" (introduction of part A and A2) to "clinical trial" and "my type of cancer" (A4, A5, A8, A9 and A12) to "my disease". These changes turned the Portuguese version of the QuIC more generalizable and applicable to other diseases. Tables 1 and 2 in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20570/15475) describe the original version of QuIC and the Portuguese version.

After the clinical review and the cognitive debriefing with patients, no ambiguity or difficulties in the questionnaire acceptance were observed, demonstrating the content validity of this measurement instrument.

Sample characteristics

By following COSMIN guidelines,[19] we obtained a sample of 100 participants enrolled in cardiology CT. Its sociodemographic characteristics are presented in Table 1.

Eighty-five percent of the participants were male, and the mean age was 67.3 years. Most were retired (70%) and married or cohabiting (74%). About half of the participants had completed four years of education or less. When assessing their health status in a 0 - 10 scale, 79% of the participants chose the levels between 7 and 10, and none of them selected levels 1 and 2.

Regarding the CT characteristics (Table 2), 55% of the participants were from open-label CT, against 45% participating in randomized controlled trials. In most CT, investigational treatment required subcutaneous administration, and 76% of the participants were recruited during a medical appointment. Most participants (91%) classified their satisfaction with CT participation as "good" or "very good".

Participants' objective understanding (part A)

Most of the part A items showed high mean score (Table 3). Item A2 had 100% of correct answers, the questions

Table 1 – Sociodemographic and health perception characteristics of the sample (n = 100)

Variable	Value	n
Sex	Male	85
	Female	15
Age (years)	< 65	33
	≥ 65	67
	Min - max	40 - 84
	Mean ± standard deviation	67.3 ± 9.2
Marital status	Single	5
	Married / cohabiting	74
	Widowed	10
	Separated / divorced	11
Employment status	Employed	19
	Unemployed	5
	Retired	70
	Disabled	3
	Does housework	1
	Inactive	2
Years of education	None	1
	≤ 4	49
	5 - 6	22
	7 - 9	9
	10 - 12	12
	> 12	7
Self-assessment health	Poor / very poor (0-3)	1
	Average (4-6)	20
	Good / very good (7-10)	79
	Min - max	3 - 10
	Mean ± standard deviation	7.5 ± 1.6

Table 2 – Characteristics of CT

Variable	Value	n
Type of study	Open-label	55
	Randomized controlled trial	45
Administration path	Intravenous	10
	Oral	35
	Subcutaneous	55
Place of recruitment	During consultation	76
	On inpatient admission	12
	After inpatient admission	12
Assessment of the participation in the CT	Very good (1)	30
	Good (2)	61
	Reasonable (3)	9
	Bad (4)	0
	Very bad (5)	0
	Min - max	1 - 3
	Mean ± standard deviation	1.8 ± 0.6

CT: clinical trial

A1, A11 and A17 had, at least, 90% of correct answers, and A3, A5, A9, A12, A13, A14, A16 and A18 presented a percentage between 50% and 79%. Also, 42% of participants answered item A8 correctly, and four items (A4, A7, A10 and A15) obtained between 20% and 22% of correct answers. Lastly, all the participants did not answer item A6 correctly.

Participants' subjective understanding (part B)

Table 4 presents the mean score of part B of the QuIC-PT, in which the respondents assess their knowledge about their CT, from 1 to 5. The final score ranged from 0 to 100.

Items with a mean score of 75% or above mean that the participants understood the sentence and its meaning. We detected that eight out of the 14 items were understood or very well understood by the participants (B1, B4, B5, B7, B8, B10, B12 and B13). Item B11 was the least understood item, with more than half of the participants answering that they "did not understand" it, or "did not understand at all".

Reliability and validity

All ICC scores were equal to 1.000, except for items B2 (0.997), B4 and B14 (0.998) and B10 (0.994), all of them higher than 0.90. Therefore, the QuIC-PT questionnaire showed good stability over time.

Regarding construct validity (Table 5), among the socio-demographic variables, only age, employment status and education determined the number of correct answers. Younger patients (less than 65 years old) and those employed or with more than elementary education tend to provide higher numbers of correct answers. However, following multiple linear regression, only education level was significantly associated with the number of correct answers (β = 0.417; $p < 0.001$). On the other hand, we did not find any association between CT characteristics and the number of correct answers.

Finally, for the criterion validity, the number of correct answers was not associated with patient assessment of CT participation.

DISCUSSION

We found that the QuIC-PT questionnaire is a feasible tool to measure the knowledge and quality of the IC in the Portuguese population and that, even though the QuIC questionnaire was originally developed for CT in oncology, it was possible to adapt this questionnaire to other diseases.[20,21]

The QuIC questionnaire was one of the first measuring instruments aiming to measure participants' objective and subjective understanding of CT. This means that this questionnaire measures not only if the participants are well-informed, but also if they feel well-informed.[14] The QuIC-PT questionnaire can also provide insight about which CT information should be clarified in the written ICF and further by the investigator when collecting the IC.

The results from items concerning the recognition of participating in a CT (items A1 and B1), helping future participants (A11 and B8), knowing who to contact to clarify

Table 3 – Mean score and percentage of correct answers of the Part A of the QuIC-PT

Questions	Disagree	Unsure	Agree	Mean
A1. When I signed the consent form for my current therapy, I knew that I was agreeing to participate in a CT.	1%	1%	**98%**	98.5[1]
A2. The main reason CTs are done is to improve the treatment of future patients.	0%	0%	**100%**	50.0[2]
A3. I have been informed how long my participation in this CT is likely to last.	18	6%	**76%**	79.0[1]
A4. All the treatments and procedures in my CT are standard for my disease.	24%	54%	**22%**	49.0[1]
A5. In my CT, one of researchers' major purposes is to compare the effect (good and bad) of two or more different ways of treating patients with my disease, in order to see which is better.	9%	15%	**76%**	41.8[2]
A6. The treatment being researched in my CT has been proven to be the best treatment for my disease.	**0%**	35%	65%	8.8[2]
A7. In my CT, each group of patients receive a higher dose of the treatment than the group before, until some patients have serious side effects.	**20%**	72%	8%	18.8[3]
A8. After I agreed to participate in my clinical, my treatment was chosen randomly (by chance) from two or more possibilities.	25%	33%	**42%**	19.5[3]
A9. Compared with standard treatments for my disease, my CT does not carry any additional risks or discomforts.	**59%**	18%	23%	68.0[1]
A10. There may not be direct medical benefit to me from my participation in this CT.	72%	14%	**14%**	10.5[2]
A11. By participating in this CT, I am helping the researchers learn information that may benefit future patients.	0%	3%	**97%**	98.5[1]
A12. While you are in this CT, its rules determine how my doctor can change my treatment.	12%	35%	**53%**	23.4[3]
A13. Because I am participating in a CT, it is possible that the study sponsor, various government agencies, or others who are not directly involved in my care could review my medical records.	14%	17%	**69%**	77.5[1]
A14. My doctors did not offer me any alternatives besides treatment in this CT.	**63%**	9%	28%	67.5[1]
A15. The consent form I signed describes who will pay for treatment if I am injured or become ill as a result of participation in this CT.	23%	55%	**22%**	49.5[1]
A16. The consent form I signed lists the name of the person (or persons) whom I should contact if I have any questions or concerns about the CT.	8%	13%	**79%**	85.5[1]
A17. If I had not wanted to participate in this CT, I could have declined to sign the consent form.	4%	6%	**90%**	46.5[2]
A18. I will have to remain in the CT even if I decide someday that I want to withdraw.	**54%**	14%	32%	30.5[2]

CT: Clinical trial.
[1]: Score between 0 and 100.
[2]: Score between 0 and 50
[3]: Score between 0 and 33.
Numbers in **bold** mean correct answers

doubts about the research (A16 and B12), the acceptance or refusal to sign the IC is voluntary (A17 and B13) and the rights of sharing clinical and personal data (A13 and B10), demonstrate that these are the most understood domains, in which the knowledge and understanding are in concordance. Similarly to other studies,[20,21] almost all participants (90% or more) of our sample were aware that signing the ICF represented their agreement to take part in the CT (items A1 and A17) and recognized that the CT may add information and improve treatment of future patients (A2, A11). Most participants (65%) reported having understood the CT "well" or "very well" when signing the ICF, but several ICF aspects were not fully understood.

According to a systematic review by Montalvo and Larson (2014), the participants showed a lack of basic understanding of research terms such as 'randomization', 'placebo', 'risks', and 'therapeutic misconception'.[10] In our study, less than a third of participants answered questions related to treatment correctly, including that CT evaluate treatments that are not standard of care (A4) nor proved to be the best

Table 4 – Mean score of the Part B of the QuIC-PT

Questions	I did not understand this at all				I understood this very well	Mean score
B1. That fact that your treatment involves research.	2%	2%	2%	9%	85%	93.3
B2. What the researchers are trying to find out in the CT.	13%	7%	19%	25%	36%	66.0
B3. How long you will be in the CT.	19%	4%	6%	8%	63%	73.0
B4. The treatments and procedures you will undergo.	9%	1%	10%	22%	58%	79.8
B5. Which of these treatments and procedures are experimental?	6%	2%	5%	9%	78%	87.8
B6. The possible risks and discomforts of participating in the CT.	26%	4%	12%	20%	38%	60.0
B7. The possible benefits to you of participating in the CT.	4%	1%	7%	20%	68%	86.8
B8. How your participation in this CT may benefit future patients.	1%	1%	2%	9%	87%	95.0
B9. The alternatives to participation in the CT.	29%	11%	10%	10%	40%	55.3
B10. The effect of the CT on the confidentiality of your medical records.	7%	1%	5%	18%	69%	85.3
B11. Who will pay for treatment if you are injured or become ill because of participation in this CT.	57%	6%	11%	10%	16%	30.5
B12. Whom you should contact if you have questions or concerns about the CT.	5%	1%	2%	4%	88%	92.3
B13. The fact that participation in the CT is voluntary.	0%	0%	1%	1%	98%	99.3
B14. Overall, how well did you understand your clinical when you signed the consent form?	3%	9%	23%	32%	33%	70.8

CT: Clinical trial

treatment options (A6), despite mentioning that they understood the treatment very well (B4 and B5). These results are quite concerning since the participants believed that the treatment provided was already approved, which was the purpose of that CT. Additionally, more than half of the participants did not understand the concept of randomization and that they might not receive the experimental treatment (A8). This may translate into false expectations of the participants, which is consistent with the vast majority of patients expecting a "direct medical benefit" due to CT participation (A10 and B7).

Despite almost all participants having recognized the voluntary nature of participating in the CT, not all seemed to be aware of its implications or their rights as participants. Certain aspects, such as the study's length (A3), its lack of assessment of safe treatment doses (A7) and its lack of information on cost-bearers in case of injury (A15 and B11), were also not fully clear. In addition, item B6 showed that respondents were not familiar with possible risks of participating in the CT, despite having agreed to participate. Moreover, some participants mentioned that participating in the study was their only treatment option (A14, B9), and almost 50% believed that they were not able to withdraw (A18). Atal and Dune found similar results, which highlights a poor understanding of the experimental nature of the treatment, the possible risks and compensation proceedings.[20]

The individuals' lack of understanding of relevant topics, such as their rights as participants and the option to withdraw during the CT, is concerning. In general, we observed lower mean scores in part A of the questionnaire than in part B, indicating that the participants were not as well informed as they felt. It is not the signed document that indicates the participant's correct understanding of all the information, and although the researcher has a duty to guarantee this, our results do not fully confirm it.

These results highlight the need for some adaptations, not only to the ICF, but also when answering participants' questions. The ICF should contain simple language and focus on relevant information, while the person responsible for clarifying the participant should repeat the information in a few simple words, give the participant the opportunity to ask questions and clarify doubts and, above all, ensure that the participant knows the main points of the IC.[3,22] Some studies in the literature showed that interactive computer presentations, videos, vignettes and visual aids, as well as simplified paper documents with shorter and concise phrasing are some examples of interventions that may result in a significant improvement of participants' understanding of the IC.[23,24] Therefore, as the CT evolves, it is possible to have new data related to the experimental treatment/intervention (such as new adverse effects, safety, changes in methodologies, procedures and outcomes), and it should be provided to the participants. Therefore, the participants 're-consent' must be obtained, and the research team must

Table 5 – Determinants of the correct answers

Variable	Value	n	Mean	Standard deviation	|t|	Sig
Sex	Male Female	85 15	10.5 9.6	1.9 1.7	1.638	0.105
Age (years)	< 65 ≥ 65	34 66	11.2 9.9	1.7 1.9	3.550	< 0.001
Marital status	Married Not married	74 26	10.2 10.8	1.9 1.8	1.335	0.185
Employment status	Employed / housework Not employed / retired	20 76	11.4 10.0	1.8 1.9	2.941	0.004
Education	Basic (≤ 4 years) > Basic	50 50	9.4 11.3	1.7 1.6	5.781	< 0.001
Self-assessment health	Good / very good (7 - 10) Lower (≤ 6)	79 21	10.3 10.6	0.2 0.4	0.622	0.536
Type of study	Open-label Randomized controlled trial	55 45	10.4 10.2	1.8 2.0	0.660	0.511
Administration path	Intravenous / oral Subcutaneous	45 55	10.0 10.6	1.9 1.9	1.654	0.101
Place of recruitment	During consultation Other	76 24	10.5 9.8	1.8 2.1	1.624	0.108
Assessment of the participation in CT	Very good Good / reasonable	30 70	10.8 10.1	2.0 1.9	1.704	0.092

CT: Clinical trial

make sure that s/he has understood the new information.[22]

This study suggests that the participants' understanding of the IC should be assessed. Subsequently, this additional information brings about the responsibility to act.[25] The research team is responsible for identifying, clarifying, and discussing any confusing topics with the participant, making sure that s/he feels and actually is well-informed. The distinction between those who fully understand the ICF and those who do not should be part of the study and a checkpoint for joining the CT.

One of the strengths of this study was showing that it was possible to adapt the original QuIC to other diseases than cancer. The participants were attending cardiology CT (in the areas of dyslipidemia, acute coronary syndrome, heart failure and angina pectoris). In addition, most of the participants were men (85%), and 67% of them were aged 65 or older. As such, we also found that the sample used is representative of the Portuguese reality, since this type of diseases are more prevalent in older men.[26] Since the adapted QuIC has the potential to be used for other diseases, it allows for the comparison of consent processes within healthcare institutions.

However, the Portuguese version may have some limitations, the first being that it was designed for phase III clinical trials, and we are not sure whether that could be appropriate to other designs. We are also aware that this questionnaire does not address all the relevant issues of an ICF, such as the complexity of procedures/treatments, the awareness that they have to transmit all relevant aspects to the investigators (the medication they take, symptoms they have, emergency room visits), or the importance of compliance, and that ICF differ between CT and sponsor companies. Despite this, our results suggest several aspects to be improved in the IC process. The participants' education level, reading, and comprehension skills should be considered during the IC process, as well as the presence of the three essential elements (voluntarism, informed consent, and decision-making capacity),[22] to ensure that the participant's written consent is truly informed and free. In fact, we observed that educational level was independently associated with lower scores, reflecting the need to adjust information for these groups. Interestingly, we found no association with patient satisfaction regarding their CT participation, perhaps because 91% of patients rated it as 'very good' or 'good'.

Further studies with a larger sample, with other diseases, and with participants from different CT phases are needed to compare results and improve the questionnaire so that it can become a widely usable instrument to measure the quality of the ICF of a CT. The development of strategies and/or interventions to improve participants' understanding of ICF in CT, as well as the evaluation of their effectiveness, can be extremely valuable for the people involved.

CONCLUSION

The QuIC-PT seems to be a valid and useful instrument to evaluate the participants' understanding of the ICF,

allowing the improvement of the ICF and the best explanation possible adjusted to the individual's needs. Relevant concepts, like study procedures, randomization, and safety risks, were not well understood by participants when they signed the ICF. Furthermore, the participants' belief that the experimental intervention would solve their health condition is the main reason why they agreed to participate in the research, which may be misleading.

AUTHOR CONTRIBUTIONS

PLF: Conceptualization, methodology, formal analysis, data curation, writing - original draft, writing - review & editing, project administration, supervision.

AB: Conceptualization, formal analysis, investigation, writing - original draft, writing - review & editing.

IR: Validation, writing - review & editing.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

DATA AVAILABILITY

Data will be made available on request.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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