DOI: 10.1111/dewb.12199

ORIGINAL ARTICLE

WILEY developing world bioethics

Consent for participating in clinical trials - Is it really informed?

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Abstract

The article explores the challenges of ensuring voluntary and informed consent which is obtained from potential research subjects in the north-eastern part of Romania. This study is one of the first empirical papers of this nature in Romania. The study used a quantitative survey design using the adapted Quality of Informed Consent (QuIC) questionnaire. The target population consisted of 100 adult persons who voluntarily enrolled in clinical trials. The informed consent form must contain details regarding the potential risks and benefits, the aim of the clinical trial, study design, confidentiality, insurance and contact details in case of additional questions. Our study confirmed that although all required information was included in the ICF, few clinical trial participants truly understood it. We also found that the most important predictive factor for a good subjective and objective understanding of the clinical trial was the level of education. Our study suggests that researchers should consider putting more effort in order to help clinical trials participants achieve a better understanding of the informed consent. In this way they will ensure that participants' decision-making is meaningful and that their interests are protected.

KEYWORDS
informed consent, clinical trials, understanding, participants

1 | INTRODUCTION

Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation. Informed consent is a prerequisite for enrolling human subjects in biomedical research.[1]

The concept of "Informed consent" was enshrined in the Nuremberg Code (1947)[2], was reaffirmed in the 1964 Declaration of Helsinki and currently is one of the guiding principles for conduct in medical research.[3] Informed consent in clinical research has two specific goals: to respect and promote a participant's autonomy and to protect participants from harm.[4]

A method to assess the quality of the informed consent in clinical research is by determining participants' understanding of the information provided in the process of informed consent.[5] Understanding

[1]CIOMS. (2002). International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guideline 4. Geneva.

[2]Grodin MA, Annas GJ. Legacies of Nuremberg. Medical ethics and human rights. *JAMA*. 1996; 276(20):1682–3.

[3]Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA*. 2000; 283(20):2701–11.

[4]Will JF. A brief historical and theoretical perspective on patient autonomy and medical decision making: Part II: The autonomy model. *Chest*. 2011; 139(6):1491–7.

[5]Will JF. A brief historical and theoretical perspective on patient autonomy and medical decision making: Part II: The autonomy model. *Chest*. 2011; 139(6):1491–7.

plays a significant role in research because it directly affects how ethical principles are applied in practice.[6]

Research consent typically emphasizes disclosure on the presumption that more information aids potential participants in decision-making.[7] However, some authors[8,9,10] concluded that the investigation participants might frequently not understand the information provided by the researchers. Therefore in the last years, stakeholders tried to improve the informed consent process, by using multimedia tools and technologies or using quizzes that give immediate feedback.[11,12]

In Romania, the concept of informed consent in research is quite new, and it has not been grounded in the scientific society, less in the civic society.[13] The literature review did not reveal studies conducted in Romania that investigates the participants' understanding of the information provided by the researchers before enrolling them in biomedical research. Starting from this literature gap, we intend to study the understanding of the information provided by the researchers to the participants and the factors that may influence it.

2 | MATERIAL AND METHODS

This article explores the ethical challenges of ensuring voluntary and informed consent which is obtained from potential research subjects in the north-eastern part of Romania. The objectives of the study research were: to analyze participant's objective understanding of the information provided by the investigator before the start of the research procedures (e.g. do the participants understand the nature of the clinical trial?); to analyze participant's subjective understanding of the information provided by the investigator prior to enrollment in the research study (e.g. do the participants think that they are well informed?); and to identify factors that could influence participant's objective and subjective understanding.

This study used a quantitative survey design. Data was collected using a questionnaire in Romanian, the language spoken by the study participants. Twenty-nine (29) questions were asked of all participants, with an additional five questions asked of participants in phase II and III clinical trials. The questionnaire consists of two parts, with Part I assessing objective understanding and Part II assessing subjective understanding. The questionnaire was adapted from the Quality of Informed Consent (QuIC) scale first developed by Joffe et al.[14] and used with Prof. Joffe's express permission.

In addition to the QuIC questions, socio-demographic data (age, gender, backgrounds, education, how many studies did the subject previously participate in) were also collected. The questionnaires were provided by the researcher during a face-to-face discussion with the study participants. Data were collected from two Research Centers from Iasi, Romania, between January and July 2016, and between November 2016 and February 2017.

The target population consisted of 100 adult persons who voluntarily enrolled in clinical trials. The participants were split into two groups, one with 50 healthy volunteers recruited from a research center that conducts only phase I clinical trials and another with 50 cancer patients recruited from a research center that conducts phase II and III clinical trials. The researcher recruited participants after they signed the informed consent for their clinical trials.

Risks of participation in this study were small and consisted of a low level of discomfort that could appear because of the nature of the questions. To prevent this risk the researcher conducted the discussion in a non-critical manner, the participants weren't rushed, and they received answers when they had questions, or they didn't understand something. The questionnaire was anonymous. The researchers that ran the clinical trials didn't have access to the positive or negative responses to the questionnaire, and the participation in the clinical trials wasn't affected.

There were no direct benefits for the participants in this study. The study was approved by relevant Research Ethics Committees, and informed consent was sought from all respondents.

Statistical analysis was performed with SPSS v20 software. We performed descriptive statistics and assessed potential correlations with the Pearson correlation coefficient. Statistical significance was set at 0.05.

3 | RESULTS

A total of 100 participants answered the questionnaire. Of these individuals, 50 were healthy volunteers participating in phase I clinical trials and 50 were cancer patients participating in phase II and III clinical trials.

The phase I participants were aged between 18 and 25 (66%), were male (72%) and came from an urban area (100%). None of the responders was a first-time participant in clinical studies (52% had participated several times before) and most had at least 12 years of education (76% had finished high school). The participants from the Regional Institute of Oncology were older (50% were aged between 46 and 60 years), came from both rural and urban areas

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(42% and 58%, respectively), and were less educated (46% had finished high school) than those from the phase I studies. None of the respondents from phase II and III studies had previously participated in clinical studies. The results are presented in Table 1 and Table 2.

3.1 | Objective understanding

Regarding the purpose of research, all participants from the phase I studies agreed that clinical studies are designed to improve treatment for future patients (100% agreed) and that phase I clinical studies aim to determine the safety of a new drug (100% agreed). Also, all of the respondents understood that their participation helps researchers gather information that might benefit future patients. However, participants answered "not sure" to some of the questions. When asked if the purpose of their clinical study was to find the largest dose of a new drug that can be administered without any significant side effects, 48% of the patients answered "not sure". Similarly, when asked if the purpose of the researchers was to identify all effects of a new drug (both good and bad), 28% were unsure about the truthfulness of the statement. We found an inverse correlation between the level of education and the likelihood of answering "not sure" to one of the two aforementioned questions (r = 0.44 and r = 0.54, significant at the 0.01 level).

Not all of the participants for phase II and III studies agreed that clinical studies are designed to improve treatment for future patients (30% disagreed or were unsure). Also, 20% were unsure if the purpose of the clinical study was to compare the effects of two or more cancer treatments or not and 26% chose "not sure" when asked to agree or disagree with the statement that "one of the major aims of researchers is to test the safety of a new treatment or drug". Similar percentages were recorded for most of the questions evaluating the participant's objective assessment – 20-26% of the responders were unsure if the given statement was true or false. Those that were unsure or disagreed with one statement most likely were unsure or disagreed with all the statement regarding the purpose of research; this also correlated with their level of education (r was between 0.4 and 0.69, significant at the 0.01 level). However, almost all patients (88%) agreed that the results of the current clinical study will help future cancer patients.

The participant's understanding of the study design was assessed by three questions. While most of the responders (96%) understood the principle of random assignment to treatment arm, over half (56%) were unsure if the dose of the drug progressively increases from one group to another until serious side effects are noted. Factors that correlated significantly with answering "not sure" to this question were the level of education and the lack of understanding that the purpose of phase I studies is to find the largest dose that can be administered safely (r = 0.63 significant at the 0.01 level and r = 0.27 significant at the 0.05 level).

The participants in phase II and III clinical studies unanimously agreed that the treatment being researched in the study is known to be the best for their disease (100% agreed). Regarding the idea that each trial arm receives a progressively increased dose, 20% of the responders were unsure and 4% disagreed. Similar results were noted when the understanding of randomization was assessed (26% were not sure). These results significantly correlated with the level of education (r=0.40, significant at the 0.01 level) and with the existence of previous questions that were also answered with "not sure".

Regarding the participant's understanding of the risks and benefits, all participants from phase I studies agreed that there is the possibility that they will not have any direct medical benefits from the clinical study.The understanding of risks and benefits in participants for phase II and III studies was somewhat different – 58% of the patients believed that the clinical trial holds no additional risk or discomfort when compared with standard care and 24% disagreed with the idea that clinical trial participation might not have any direct medical benefits. These answers correlated with the level of education (r = 0.28 and r = 0.33, significant at the 0.05 level).

Other issues, such as confidentiality, possibility to withdraw from the clinical study and the voluntary feature of participating in a clinical study were clearly explained to the respondents before the beginning of the phase I trial, since 100% of the individuals that answered the questionnaire understood these ideas. Also, all of the respondents agreed that they were informed about who was going to pay for medical care in the event of side effects or injury secondary to study participation. All participants (from phase I, II and III clinical studies) agreed that they knew who to contact in case they had additional questions or if they did not understand something from the informed consent form. In the phase II/III clinical trials responders, most (84%) were unsure regarding the possibility of a third party gaining access to their medical information and did not know who is supposed to ensure their medical care in case of side effects caused by the new drug (76%). Additionally, most were unsure regarding their possibility to withdraw from the clinical trial at any time (68%), a finding that correlated with the sex of the respondent (r = 0.38, significant at the 0.05 level) and with not being sure who will cover the medical bill in case of injury resulted from clinical trial participation.

In the phase I respondents, 38% were not sure if they had been appropriately informed about the amount of time participants were supposed to dedicate to the study participation, an answer that correlated with the level of education (r = 0.44, significant at the 0.01 level) and their lack of understanding of the purpose of research and of the study design. The respondents from phase II and III clinical studies considered they understood the time they were supposed to dedicate to the study - 86% of the responders considered they had been appropriately informed in the matter.

In the questionnaire designed for the participants in phase II and III trials, there were some additional questions regarding cancer treatment. 88% of the patients were not sure if there was any other available treatment option aside from the clinical trial participation and 72% of the patients considered that all treatments and procedures from the clinical trial are standard treatment for their type of cancer. Those that considered clinical trial procedures as standard

TABLE 1 Objective understanding

Question	Phase I clinical trials			Phase II and III clinical trials		
	Disagree	*Unsure*	*Agree*	*Disagree*	*Unsure*	*Agree*
When I signed the consent form for my current therapy, I knew that I was agreeing to participate in a clinical trial. **	-	-	-	2%	6%	**92%**
The main reason clinical trials are done is to improve the treatment of future patients.	0%	0%	**100%**	4%	26%	**70%**
I have been informed how long my participation in this clinical trial is likely to last.	0%	38%	62%	4%	26%	**70%**
All the treatments and procedures in my clinical trial are standard for my type of disease. **	-	-	-	4%	24%	**72%**
In my clinical trial, one of the researchers' major purposes is to compare the effects (good and bad) of two or more different ways of treating patients with my type of disease, in order to see which is better. **	-	-	-	4%	20%	**76%**
In my clinical trial, one of the researchers' major purposes is to test the safety of a new drug or treatment.	0%	0%	**100%**	4%	26%	**70%**
In my clinical trial, one of the researchers' major purposes is to find the highest dose of a new drug or treatment that can be given without causing severe side effects.	0%	**50%**	**50%**	4%	20%	**76%**
In my clinical trial, one of the researchers' major purposes is to find out what effects (good and bad) a new treatment has on me [and my disease]. ##	0%	28%	**72%**	4%	18%	**78%**
The treatment being researched in my clinical trial has been proven to be the best treatment for my type of disease.	-	-	-	0%	0%	**100%**
In my clinical trial, each group of participants receives a higher dose of the treatment than the group before, until some participants have serious side effects.	0%	**56%**	44%	4%	20%	**76%**
After I agreed to participate in my clinical trial, my treatment [investigational medication] was chosen randomly (by chance) from two or more possibilities. ^^	0%	4%	**96%**	4%	26%	**70%**
Compared with standard treatments for my type of disease, my clinical trial does not carry any additional risks or discomforts.	-	-	-	0%	**42%**	58%
There may not be direct medical benefit to me from my participation in this clinical trial.	0%	0%	**100%**	**24%**	**40%**	**36%**
By participating in this clinical trial, I am helping the researchers learn information that may benefit future patients.	0%	0%	**100%**	2%	10%	**88%**
Because I am participating in a clinical trial, 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.	0%	0%	**100%**	2%	**84%**	14%
My doctors did not offer me any alternatives besides treatment in this clinical trial. **	-	-	-	0%	**88%**	12%
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 clinical trial.	0%	0%	**100%**	0%	**76%**	24%
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 clinical trial.	0%	0%	**100%**	0%	**72%**	28%
If I had not wanted to participate in this clinical trial, I could have declined to sign the consent form.	0%	0%	**100%**	0%	**76%**	**24%**
I will have to remain in the clinical trial even if I decide someday that I want to withdraw.	**100%**	0%	0%	32%	68%	0%

** - applicable only for Phase II and III clinical trials
- text in „[...]" for Phase II and III clinical trials
^^ - text in „[...]" for Phase I clinical trials

and were not sure that there were other available treatments were more likely to be less educated (r = 0.59, significant at the 0.01 level). Also, they were more likely to answer "not sure" to questions regarding the objective assessment of the purpose of the research or study.

3.2 | Subjective understanding

All participants from the phase I studies understood very well that the clinical study they were about to enroll in implied research, whereas only 76% of the participants from phase II and III clinical

TABLE 2 Subjective understanding

Question	Phase I clinical trials					Phase II and III clinical trials				
	A	*B*	*C*	*D*	*E*	*A*	*B*	*C*	*D*	*E*
The fact that your treatment involves research	0%	0%	0%	0%	**100%**	4%	4%	2%	14%	**76%**
What the researchers are trying to find out in the clinical trial.	0%	0%	16%	30%	**54%**	4%	14%	**34%**	26%	22%
How long you will be in the clinical trial.	0%	0%	0%	0%	**100%**	2%	4%	8%	40%	**46%**
The treatments and procedures you will undergo.	0%	0%	0%	38%	**62%**	0%	6%	22%	26%	**46%**
Which of these treatments and procedures are experimental.	0%	0%	0%	40%	**60%**	0%	6%	22%	26%	**46%**
The possible risks and discomforts of participating in the clinical trial.	0%	0%	16%	40%	**44%**	0%	4%	**32%**	16%	**48%**
The possible benefits to you of participating in the clinical trial.	0%	0%	0%	0%	**100%**	0%	0%	10%	12%	**78%**
How your participation in this clinical trial may benefit future patients	0%	0%	0%	0%	**100%**	0%	2%	10%	0%	**88%**
The alternatives to participation in the clinical trial. **	-	-	-	-	-	2%	2%	**84%**	0%	12%
The effect of the clinical trial on the confidentiality of your medical records.	0%	0%	0%	0%	**100%**	0%	4%	**76%**	6%	14%
Who will pay for treatment if you are injured or become ill because of participation in this clinical trial.	0%	0%	0%	0%	**100%**	0%	4%	**66%**	6%	24%
Whom you should contact if you have questions or concerns about the clinical trial.	0%	0%	0%	0%	**100%**	2%	6%	**54%**	10%	28%
The fact that participation in the clinical trial is voluntary.	0%	0%	0%	0%	**100%**	0%	8%	**50%**	20%	22%
Overall, how well did you understand your clinical trial when you signed the consent form?	0%	0%	0%	**56%**	**44%**	0%	2%	**74%**	14%	10%

** - applicable only for Phase II and III clinical trials
A – I didn't understood at all
B – I understood a little
C – I somewhat understood
D – I understood well
E – I understood very good

trials had the same perception (2 of the respondents considered that they did not understand anything). Almost all participants believed they had a good understanding regarding the duration of the study (100% of the responders from phase I and 90% of the responders from phase II and III rated their understanding as "very good").

Regarding the purpose of research, 54% of the responders from phase I clinical trials considered that they had completely understood the purpose of that specific study, whereas 16% answered that they "somewhat understood" and 30% that they "understood well". While this assessment did not correlate with the number of previous clinical study participations or with the participant's education, those that did not completely understand the purpose of research were the same responders that were not sure about the risks and discomforts associated with participating in the clinical study and were uncertain if their study entailed using increasingly larger doses of the study drug. However, all participants believed they fully understood that their participation in the clinical study will help future patients.

The percentage of participants that considered to have a good understanding of the purpose of research was lower in the phase II/III clinical trials respondents - 18% declared that they understood little or nothing about the aim of the study (none of these responders had finished high school; r = 0.72, significant at the 0.01 level). The level of understanding also correlated with answering "not sure" to questions about the aim of the research, research design and risks and benefits in Part A of the questionnaire. However, almost all phase II/III participants considered that they perfectly understood that their clinical trial participation will benefit future cancer patients (88%).

Regarding risks and benefits of the clinical study, most phase I participants felt they had at least a good understanding of the procedures and treatments that they were about to undergo (100% of the respondents) and were able to separate experimental treatments and procedures from the standard approach (40% believed that they "understood well" and 60% "completely understood"). Benefits were clearly explained to everyone in the study (100% - completely understood). Some of the

participants only understood to a certain extent possible risks and discomforts that could arise from participating in the clinical study (16%) and 40% stated that they "understood well" potential risks. Subjective understanding of the risk significantly correlated with objective understanding of the risk (r = 0.81, significant at the 0.01 level).

Only 62% of the participants from phase II/III clinical trials felt they had a good/excellent understanding of the procedures and treatments that they were about to undergo. Additionally, the respondents had lower levels of understanding when it came to distinguishing between standard and experimental procedures (28% declared they understood the procedures "to a certain extend" or "a little"). This correlated with the level of education (r = 0.80, significant at the 0.01 level). Potential risks and potential benefits were better understood, with 80% and respectively 90% of the respondents declaring they considered they had a good/excellent understanding of the two.

Other issues, such as confidentiality of medical information, the voluntary quality of participating in the clinical study, who will pay for medical care in case of injury secondary to clinical trial participation and who to contact in case of additional questions, were rated as "completely understood" by all of the respondents from phase I trials. Only 30-40% of the respondents from phase II/III trials considered they had a good/excellent understanding of confidentiality of medical information and who will pay for medical care in case of injury secondary to clinical trial participation. However, a larger part of the respondents considered they had a good understanding of the voluntary nature of the clinical study (74%) and declared they knew who to contact in case of additional questions (90%).

One question specifically designed for phase II/III participants assessed whether the respondents understood their other treatment options (aside from clinical trial participation). 84% of the patients considered a partial understanding of their alternatives and 4% considered that they had little to no understanding of the alternatives. This significantly correlated with education (r = 0.70, significant at the 0.01 level) and with agreeing to objective statements regarding the design and the aim of the clinical study.

All in all, 56% of the participants from phase I clinical trials felt that they had a good understanding of the clinical study and 44% declared that they "completely understood" it. Most respondents from the phase II/III clinical trials felt they partly understood the clinical study (74%), with only 10% considering they completely understood the clinical trial. The level of perceived understanding correlated with the answers given in the objective assessment (questions regarding study design and potential risks) and with subjective perception regarding understanding of the purpose of the research, the procedures and potential risks.

4 | DISCUSSIONS

Informed consent documents have to contain specific elements meant to help clinical studies participants in making an informed decision.[15] Although a lot of research has recently focused on different methods of improving participants' understanding of clinical trials, several aspects of the informed consent form, such as risks, potential discomforts, benefits and confidentiality are still considered "uninformed".[16] Additionally, a lot of the existing informed consent documents do not meet validated standards for encouraging good decision making[17]] and several studies report that clinical trial participants do not truly understand what a clinical trial entails.[18]

The present study aimed to assess both objective and subjective participant's understanding of the clinical trial by using a modified version of the Quality of Informed Consent scale (QuIC). Two types of responders were asked to complete the questionnaire – healthy volunteers participating in phase I clinical studies and cancer patients participating in phase II/III clinical studies. The two populations were significantly different – phase I participants were more educated, younger and had previously participated in at least one other phase I clinical study, whereas phase II/III participants were older, participated for the first time in a clinical trial and were less educated. These results concur with available data[19] - mean age in phase I clinical trials participants usually varies between 20 to 40 years[20,21,22,23] whereas cancer trial participants tend to be older, mostly due to the increase on cancer incidence with age.

Regarding the gender of the participants, some studies report that phase I volunteers are mostly female while others reported high percentages of male participants (similar to our results).[24] The gender of cancer clinical trials participants (phase II and III clinical studies) highly depended on the type of cancer assessed (gender-specific cancers such as endometrial or prostate cancer trials have only female or male participants) and on its incidence in males and females (lung cancer is still more frequent in males, for example).

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Our study showed that the most important predictive factor for a good subjective and objective understanding of the clinical trial was the level of education – more educated participants were more likely to understand the purpose of research, the study design, risks and benefits and other clinical trial information. The role of education in understanding a clinical trial is controversial – while some studies report no direct correlation between the two[25,26] others[27,28,29] suggest that education influences understanding and/or consenting to participate in clinical trials in general.[30] It can be presumed that people with superior education better appreciate their role as clinical trials participants and are more willing to do their share of participation.

In Romania, all clinical trials must have the approval of the National Drug Agency and by an Institutional Review Board (IRB) and informed consent forms (ICF) are similar to those available in other European countries. The ICF must contain details regarding the potential risks and benefits, the aim of the clinical trial, study design, confidentiality, insurance and contact details in case of additional questions. Although all this information is routinely included in the ICF, few clinical trial participants truly understand it. A part from educational issues, one possible explanation for the lack of understanding resides in the physician's paternalistic attitude in the medical practice, more common in developing countries, where doctors are the ones that most often make the decisions for their patients, in spite of the signed informed consent forms. This attitude can also be found in clinical studies where the physicians explains briefly what the clinical study is about and the patient immediately signs the informed consent form, without questioning the doctor. This is understandable, especially since most informed consent forms have a length that exceeds 30 A4 pages and, in spite of permanent efforts of simplification, remain quite difficult to understand. A recent study performed in a Turkish hospital assessed the quality and extent of informed consent for invasive procedures and found that most patients did not properly read the consent form since they trusted their physician.[31]

A possible solution for this problem could be editing a simpler version of the ICF form, which would increase readability and understanding. For instance, a recent study performed among cataract surgery patients found that concise informed consent information sheets at lower reading grade levels were easier to read and understand.[32] Similarly, videotapes and/or animated cartoons have been found to significantly increase understanding and recalling in all patients.[33] We found no correlation between the age of the participants or their gender and clinical trial subjective or objective understanding. This finding is in accordance with available literature data.[34] We thought that geographical residence (urban versus rural) would significantly influence understanding, but no significant correlation was found. This can be explained by the selection bias - all participants from phase I studies came from an urban area as well as more than half of the phase II/III clinical trials participants - that is a consequence of study requirements (weekly or bimonthly visits to the hospital/research unit).

Participating in more than one clinical study was associated with a better understanding of potential risks in phase I clinical trial participants. While we did not find similar results in the literature, this finding can be interpreted as being asked to read similar informed consent forms more than once. Although each ICF is unique, they all describe a common set of risks that are better understood and remembered after one has read the ICF more than once. The most important finding in our study is that all the respondents from phase II and III trials (100%) believed that the treatment they were receiving was known to be the best for their cancer, thus indicating that they did not understand the experimental nature of the research and they did not take into account the fact that the experimental drug might prove to be a failure. This feature - understanding the risks, but not being able to differentiate between standard and experimental treatment - is quite common in all clinical trial participants[35] and is often included under the "therapeutic misconception" umbrella. Also, therapeutic misconception wasn't influenced by the level of the education or other factors that were analyzed in our study. Song et al. showed that pharmaceutical companies financially benefits the most from enrolling this type of participants[36], perpetuating the problem. As specified above, there is a need for a better version of ICF, one that is more specific regarding the therapeutic misconception. Another contextual factor that can influence this concept is the access to cancer treatment, Cherny et al.

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found that in countries from Eastern Europe, including Romania, there is a lack of availability for many anticancer medicines.[37]

A lot of participants did not understand that their treatment was experimental and that they would not receive individualized therapy, but would be randomly assigned to one of the treatment arms. Also, our results indicate that 88% of the patients (phase II and III clinical trials participants) were not sure if there was any other available treatment option aside from the clinical trial participation. This is not surprising - on the one hand, we have found that Romania still favors a paternalistic attitude towards medical treatments and procedures and on the other hand, we must take into account the specific pathology treated in these clinical trials. Worldwide, oncologists are encouraged to enroll all cancer patients in clinical trials and the National Comprehensive Cancer Network (NCCN) guidelines clearly state that "NCCN believes that the best management for any cancer patient is in a clinical trial" (https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf). As such, oncologists tend to encourage (or even "nudge") their patients to enter a clinical trial, which may contribute to the subjective perception of a cancer patients that he/she did not completely understand what the trial was about.

5 | CONCLUSIONS

This study is one of the first empirical papers in Romania that investigates the participants' understanding of the information provided by the researchers before enrolling them in biomedical research, using the adapted Quality of Informed Consent (QuIC) questionnaire.

In general, the results are similar to those usually found in this type of studies, namely that although the informed consent forms (ICF) contain all the information (such as potential risks and benefits, the aim of the clinical trial, study design and confidentiality) needed for an informed decision, few clinical trial participants truly understand the information provided. But some issues, such as lack of understanding of voluntary nature in Phase II or III clinical trials participants and therapeutic misconception in Phase I clinical trials participants, stand out as especially interesting.

The results shows that the most important predictive factor for a good subjective and objective understanding of the clinical trial was the level of education and also that previous experience of participation in CT was related to better understanding.

Our study suggests that researchers should consider putting more effort in order to help clinical trials participants achieve a better understanding of the informed consent. In this way they will ensure that participants' decision-making is meaningful and that their interests are protected.

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How to cite this article: Alexa-Stratulat T, Neagu M, Neagu A-I, Alexa ID, Ioan BG. Consent for participating in clinical trials - Is it really informed?. *Developing World Bioeth*. 2018;18:299–306. https://doi.org/10.1111/dewb.12199