

VILNIUS UNIVERSITY

— ASTA ČEKANAUSKAITĖ —

INFORMEDNESS ABOUT  
CLINICAL TRIALS OF PATIENTS  
PARTICIPATING IN  
PLACEBO-CONTROLLED  
CLINICAL TRIALS  
IN LITHUANIA

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Summary of Doctoral Dissertation

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Biomedical Sciences, Public Health (09 B)

Vilnius, 2013

The Doctoral Dissertation was prepared at Vilnius University in 2005–2012.

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VILNIAUS UNIVERSITETAS

— ASTA ČEKANAUSKAITĖ —

PACIENTŲ, DALYVAUJANČIŲ  
PLACEBU KONTROLIUOJAMUOSE  
KLINIKINIUOSE VAISTINIO  
PREPARATO TYRIMUOSE LIETUVOJE,  
INFORMUOTUMAS APIE  
KLINIKINIUS TYRIMUS

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Daktaro disertacijos santrauka

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Biomedicinos mokslai, visuomenės sveikata (09 B)

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# 1. INTRODUCTION

## 1.1. The research question and relevance of the study

Informed consent is one of the fundamental principles of modern medical ethics, entrenched by national and international laws as well as codes of ethics. It is one of the best known but also one of the most-debated ethical principles in the context of both clinical practice and biomedical research because its implementation still raises practical problems. Informed consent is an important principle in medical ethics because it guarantees a person's right to self-determination and a decision based on an awareness and understanding of the facts is also important in terms of the safety of patients.

The field of clinical trials is an especially delicate one because here, as opposed to ordinary, everyday clinical practice we encounter the use of human beings, their biological tissue and personal information not for treatment or prevention, but for research purposes, that is, not to improve a person's health but to advance scientific knowledge. It is for this reason that an individual's informed and free decision to take part in such a process is especially important.

In order for the consent to be considered credible and valid, several conditions must be met – consent must be given by a competent individual (or their legal representative), consent must be given of free will and before consent is obtained, the individual must be presented with all of the relevant information which could be significant when making a decision about participating in the trial. Despite the fact that this requirement has been in effect for many years, the results of studies reveal that individuals participating in clinical trials often do not understand the key information about the clinical trial.

It is important to note the specifics of clinical trials in Lithuania – the main sponsors of clinical trials are international pharmaceutical companies<sup>1</sup>, which is why the majority of the informed consent forms used in Lithuania are translated from English. It is also important to note the differences of sentential structures, grammatical forms and terminology used in Lithuanian and English, therefore it could be that translated texts are even more difficult to comprehend. However, this premise needs further study.

An analysis of the scientific literature allows us to conclude that it is not intellectual aptitude alone which determines understanding of the information about clinical trials, the difference between medical research and clinical practice, or the choice to participate in a clinical trial. A number of emotional, social, economical, cultural, psychological and individual factors are also important, namely, the ‘therapeutic’ environment of clinical trials, confidence in healthcare, the culturally determined public perception of physicians, the investigators’ own beliefs and values and even the resources allocated to healthcare. Some of these factors are especially relevant in Central and Eastern European countries due to the legacy of the paternalistic physician-patient relationship model and because of a relative scarcity of healthcare resources.

Despite the fact that the provision of informed consent for biomedical research has been enshrined at the legal level in Lithuania since 2000, informed consent policy and its practical implementation in the context of biomedical research in Lithuania (and in the region of Central and Eastern Europe) has not yet been researched.

**The aim of the study** is to assess the informedness<sup>1</sup> about clinical trials of patients participating in placebo-controlled clinical trials in Lithuania.

### **Objectives of the study**

1. To describe the context of the implementation of informed consent in clinical trials using an original model of contextual analysis.
2. To determine problematic areas of informedness about clinical trials of patients participating in placebo-controlled clinical trials.
3. To determine the correlation between overall informedness and informedness about clinical trial design along with informedness about the rights of clinical trial participants.
4. To reveal how patients participating in placebo-controlled clinical trials evaluate the information provided about clinical trials, their motives for participating in clinical trials as well as their opinion about the scientific methods used in clinical trials (placebo-control, double-blindness, and randomisation).

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<sup>1</sup> For the purposes of this text we use the term “informedness” – which is a derivative of the adjective “informed” – defined as *based on an understanding of the facts of the situation*. See Oxford English Dictionary: <http://oxforddictionaries.com>.

### **Theses to be defended in the dissertation:**

1. The legal framework sets the basis for adequate informedness about clinical trials, however, patients participating in placebo-controlled clinical trials are insufficiently informed about them.
2. Patients participating in placebo-controlled clinical trials are better informed about the rights of clinical trial participants than about clinical trial design, however, informedness about design is a more important condition for overall informedness than informedness about participants' rights
3. The majority of placebo-controlled clinical trial participants do not understand at least one of the three key methodological elements used in clinical trials (placebo-control, double-blindness, randomisation) and they tend to interpret the scientific methods used in clinical trials therapeutically.

### **1.2. Novelty of the study**

- An analysis of the literature allows us to state that this is the first scientific study conducted in Lithuania and Central and Eastern Europe in which informedness of clinical trial participants has been examined combining qualitative and quantitative research methods.
- This study aims to reveal the most important issues regarding informedness of placebo-controlled clinical trial participants, with an emphasis on informedness about clinical trial design (placebo-control, double-blindness, randomisation). Informedness about clinical trial design is emphasised because understanding that the objectives of research are fundamentally different from individualised care is considered to be key when giving informed consent to participate in a medical research. Therefore, if the research participant does not understand the investigational nature of the activity, comprehension of the rest of the information provided is distorted.
- The study contains a comparison of placebo-controlled clinical trial participants' informedness about clinical trial design and other clinical trial topics along with the correlation between them.
- The methodology and instrument (questionnaire) which have been created for the purposes of this study can be applied to evaluate the in-

formedness of double-blind, placebo-controlled clinical trial participants for both research and practical purposes (they may be recommended to ethics committees, investigators or sponsors).

### **1.3. Practical significance of the study**

The study aims to elucidate the problematic areas regarding informedness of clinical trial participants, which would enable the improvement of both the formal requirements and the procedure of informing participants in order to achieve the most important objective – to ensure that participants' consent is both informed and voluntary.

This is the first survey of clinical trial participants conducted in Lithuania in a variety of healthcare establishments, its implementation scheme may be useful for scientists and practitioners analysing this problem in the future.

The instrument which has been devised may be applied (or adapted according to the design of a specific clinical trial) in future research about placebo-controlled, double-blind clinical trials in Lithuania. This instrument may be important to investigators, whose competence and responsibility is to ensure suitable informedness of participants and ethics committees who may be evaluating the suitability of consent procedures, consent forms and the safeguarding of clinical trial subjects' rights.

## **2. MATERIALS AND METHODS**

The study is composed of three parts. The first part comprises an analysis of the scientific literature, normative documents and other secondary sources, the second – the development of a research instrument and methodology, and the third – the empirical study (a survey of clinical trial participants).

### **2.1. Population and sample size**

Adults (over 18 years old, who can independently provide informed consent) participating in randomised, double-blind, placebo-controlled clinical trials in Lithuania were invited to participate in the survey.



Considering that the general population is unknown and that it is difficult to access the target group, a 95% confidence level was chosen for statistical analysis of the data with an error margin of less than 10%. In the design of the study where population parameters (population size and variance) are unknown, the minimum sample size is 97.

In total, 430 questionnaires were distributed. Of these – 330 to investigators (96 questionnaires were returned, one of these – not completed, return rate – 29.3%). The statistical database consists of 195 questionnaires (45.3% of all questionnaires distributed). The data was analysed with 95% confidence, within a 7% error margin.

## **2.2. Organisational aspects**

The survey was conducted in March-July, 2012 in 13 healthcare institutions in Lithuania in which placebo-controlled clinical trials were being conducted.

According to the public registers of clinical trials (State Medicines Control Agency and Lithuanian Bioethics Committee), 209 clinical trials were performed at the time of our survey in Lithuania and 72 of them met the inclusion criteria of our research project.

Having obtained approval from the Vilnius Regional Biomedical Research Ethics Committee, invitations to collaborate were sent to 23 companies sponsoring (or representing sponsors of) clinical trials in Lithuania. 8 companies conducting 36 clinical trials agreed to collaborate, 10 trials were inactive (e.g., they had not started, had been stopped or patients were no longer visiting the trial centre), of the remaining 26 trials – either the sponsors (or their representatives), heads of the healthcare institutions or all the investigators in the trial refused to collaborate.

During the course of the study, 54 investigators from different healthcare institutions in Vilnius, Kaunas, Klaipeda, Siauliai and Kedainiai agreed to collaborate. Permission to conduct the survey was received from the heads of the healthcare institutions.

It is important to note that contacting the respondents in the study was especially complex because the essential condition for reaching them is the physician-investigator's agreement and intermediation.

**Limitations of the study:** 1) Limited information about clinical trials currently taking place and the number of patients participating in them; 2) Limited and complicated reachability of respondents (a few intermediaries: clinical trial sponsors (representatives), the administration of healthcare institutions, physicians-investigators).

### 2.3. Data collection

In order to attain the goals of the study, a combination of qualitative and quantitative data collection methods were used. Using the instrument of the study (questionnaire), the survey was conducted in two ways:

1. The interview was conducted by the author of the study herself, or
2. The questionnaire was given to the respondents by a physician-investigator, who explained the principles of completing and returning it.

Physicians-investigators determined whether an interview was conducted or a self-completion questionnaire was provided as only less than a half of investigators agreed to let the author communicate with respondents.

Before the author of this study conducted an interview with a respondent, a physician-investigator received the respondent's consent to participate in the survey. Interviews usually lasted about 25 minutes.

If the questionnaire was presented by a physician-investigator, respondents completed the questionnaire themselves, neither the author nor a physician-investigator were involved in its completion.

There were no statistically significant differences between answers obtained through different data collection methods (factor independence in control groups was analysed applying an  $X^2$  criterion) so all questionnaires are considered to be suitable for statistical analysis.

The study database consists of 76 interviews and 195 questionnaires.

### 2.4. The study instrument

Having evaluated the experience of similar studies and considering the local legal requirements for informed consent and the wording of informed consent forms used in Lithuania, the study instrument (anonymous questionnaire) was created by the author. The questionnaire consists of 4 parts:

1. An introductory section in which respondents are introduced to the background and objectives of the survey (comprehensive information about the survey was provided separately);
2. A section containing closed questions which have several possible answers containing questions about motives for participating in the clinical trial, rating of information about the clinical trial in terms of its significance to the respondent and evaluation of the purpose of the informed consent form, certain design aspects of the clinical trial along with the time devoted to – and nature of – the consent procedure.
3. A section of closed statements with three possible answers – ‘yes’, ‘no’, ‘difficult to say’, where statements are provided which reflect informedness about the main clinical trial design elements and the rights of participants.
4. A section about the socio-demographic characteristics of respondents in which the gender, age, education, family status, occupation, place of residence, monthly income and clinical trial field are indicated.

The reliability of the instrument was evaluated during the pilot study with 21 respondents, participating in 5 different placebo-controlled clinical trials in 4 healthcare institutions. The final questionnaire consisted of 39 closed questions and 9 questions about socio-demographic characteristics.

## 2.5. Data analysis

Interviews with respondents were recorded onto a digital sound storage device and transcribed. Respondents’ answers were grouped together according to topic. The data was systematised within topics, revealing opinion models and searching for the links between them. In order to meet the objectives of the study, a combination of quantitative and qualitative data analysis methods were used. Quantitative data were analysed in terms of individual (question) and aggregated (grouped data on the basis of correct answers) levels.

In order to calculate indicators of informedness<sup>2</sup> about the clinical trial,

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<sup>2</sup> For the purposes of our research, we distinguished between 3 indicators of informedness, namely: 1) indicator of overall informedness about clinical trial, 2) indicator of informedness about clinical trial design, and 3) indicator of informedness about rights of clinical trial participants. The *Informedness indicator* denotes the average estimate of correct answers expressed in a percentage.

21 questions were chosen from the questionnaire (modified questionnaire) which have a correct answer (that is, questions which are not intended to find out opinions, views, or factual circumstances about participation in the trial). A correct answer was assigned a value of 1, while an incorrect one – 0 (options “*it is difficult to say*”, “*I do not know/have an opinion*”, “*none of the options provided are applicable*” were counted as incorrect answers). In order to simplify the evaluation of data, the data are provided on a scale of 1-100 and expressed as a percentage. 100% informedness consists of 21 correct answers.

Questions were divided into two thematic blocks – informedness about clinical trial design (11 elements) and informedness about the rights of clinical trial participants (10 elements). 4 topics were singled out in the first block: placebo (4 elements); blindness (3 elements); randomisation (3 elements) and side effects of the investigational product (1 element). In the second block, 6 topics, namely: voluntariness (4 elements); confidentiality (1 element); knowledge of where to seek help (1 element); compensation of expenses (1 element); authorisation of the competent authorities (1 element) and compensation for damage (2 elements).

The survey data was processed and analysed using the IBM SPSS 20.0. statistical analysis software package. Descriptive and multivariate statistical analysis methods were applied to analyse the results. Crosstabs were used when analysing the dispersion of answers by socio-demographic groups and the interdependence of individual questions from the questionnaire. Attribute independence was checked using an  $X^2$  criterion and an independent proportions z-test. (a coefficient of  $X^2$  and  $\phi$  was applied to 2X2 frequency tables). Correlational analysis was used to analyse the link between the direction and strength of variables. The Spearman correlation coefficient  $\rho$  was used to study the link between non-parametric (rank order scale) variables. Links between continuous variables were analysed applying Pearson's  $r$ . A T-test was used to analyse dependency of aggregated element group averages on socio-demographic factors. A factor analysis (of the main components) was used to verify the choice and grouping of elements from the modified questionnaire. The Cronbach  $\alpha$  criterion was used to verify the internal consistency of the modified questionnaire.

## 3. RESULTS

### 3.1. Characteristics of the survey population

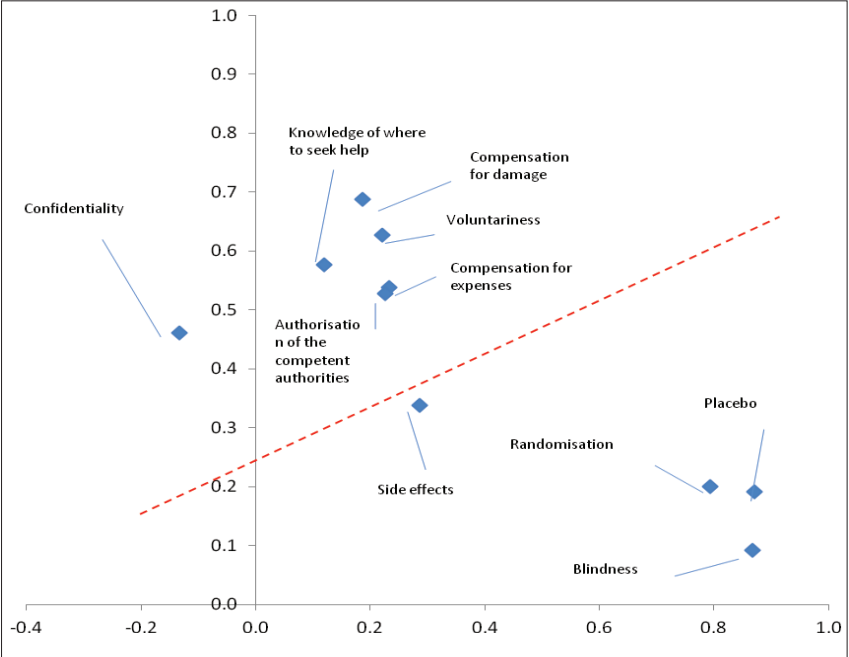
103 women (52.8%) and 92 men (47.2%) were surveyed, average age – 62.9 (median – 65.0). 47.7% of those surveyed had a secondary or a advanced vocational education, 45.6% – higher education, 6.7% – primary or basic education. 63.1% of those surveyed were married, 19.5% – widowed and the rest – either unmarried or cohabiting. 62.6% of those surveyed were not working because they were pensioners due to their age or a disability. Most respondents were living in cities (92.3%), 7.2% – in rural areas. Respondents were divided into four groups according to income, the largest was composed of respondents whose monthly net income was between 801-1000 Lt (28.6%), 24.6% had an income of up to 800 Lt, 16.9% had an income of 1001-1400 Lt and 18.5% – over 1400 Lt. Of those surveyed, most were participating in clinical trials in the fields of endocrinology, oncology and cardiology. The distribution of these fields corresponds to general tendencies of distribution of clinical trials according to medical field in Lithuania.

### 3.2. Evaluation of respondents' informedness about the clinical trial: general tendencies

To calculate informedness indicators about the clinical trial, 21 questions were chosen from the original questionnaire (modified questionnaire), which have a correct answer (that is, questions which are not intended to find out opinions, views, or factual circumstances about participating in the trial). Questions were divided into two thematic blocks: informedness about clinical trial design (11 elements) and informedness about the rights of clinical trial participants (10 elements). 4 topics were selected in the first block: placebo (4 elements); blindness (3 elements); randomisation (3 elements) and side effects of the investigational product. In the second block – 6 topics: voluntariness (4 elements); confidentiality (1 element), knowledge of where to seek help (1 element); compensation of expenses (1 element); authorisation of the competent authorities (1 element) and compensation for damage (1 element).

It has been determined that the internal consistency of the modified questionnaire is high (Cronbach's  $\alpha=0.86$ ), so this instrument may be applied in practice and in future scientific research.

Factor analysis (main components) confirmed that questions may justifiably be divided into two blocks (Fig. 1).



**Fig. 1: Principal component factor loadings**

Analysis of the quantitative data shows that, on average, respondents answered 66.3% of questions correctly (overall informedness indicator – 66.3%)

The data also shows that respondents are better informed about the rights of clinical trial participants (indicator of informedness about the rights of clinical trial participants – 74.7%), than about clinical trial design (indicator of informedness about clinical trial design – 58.6%) (Table 1).

While examining the quantitative data at the aggregate level, it has been determined that, of the information about clinical trial design, information

**Table 1: Average estimates of elements of informedness indicators\***

	Element	Average estimate (%)*	Topic (aggregated data)	Average estimate (%)	Thematic block (aggregated data)	Informedness indicator (%)
1	Placebo definition	60,5	Placebo	58,5	<b>Informedness about clinical trial design</b>	58,6
2	Purpose of a placebo	50,8				
3	Some patients might get a placebo	66,7				
4	Some patients might get an inactive medication	55,9				
5	Patients can distinguish investigational products	70,8	Double-blindness	68,2		
6	Patients know which investigational product they get	63,6				
7	Physician knows which investigational product is administered to the patient	70,3				
8	Who makes the decision regarding the investigational product	55,4	Randomisation	47,5		
9	Principle of selection of investigational product	40,5				
10	Grouping of patients	46,7				
11	Side effects of the investigational products	64,1	Side effects	64,1		
12	Right to compensation of expenses	67,2	Compensation of expenses	67,2	<b>Informedness about rights of clinical trial participants</b>	74,7
13	Right to alternative treatments	83,6	Voluntariness	90,8		
14	Right to refuse to participate in the clinical trial	94,4				
15	Right to withdraw from participation in the clinical trial	90,8				
16	Right to get a copy of the informed consent form	94,4				
17	Accessing private information	52,8	Confidentiality	52,8		
18	Right to compensation for damage	61,0	Compensation For Damage	54,9		
19	Knowledge of who to contact to be compensated for damage	48,7				
20	Knowledge of where to seek help	89,7	Knowledge of where to seek help	89,7		
21	Competent authorities which have issued permission for the clinical trial	64,1	Authorisation of the competent authorities	64,1		
					<b>Overall informedness</b>	66,3

\* Average estimate corresponds to the percentage of correct answers

about double-blindness was best understood (average estimate – 68.2%), while randomisation was the worst understood (47.5%). In the block containing information about the rights of clinical trial participants the voluntary nature of participation was best understood (average estimate – 90.8%), and the worst – confidentiality (average estimate – 52.8%) (Table 1).

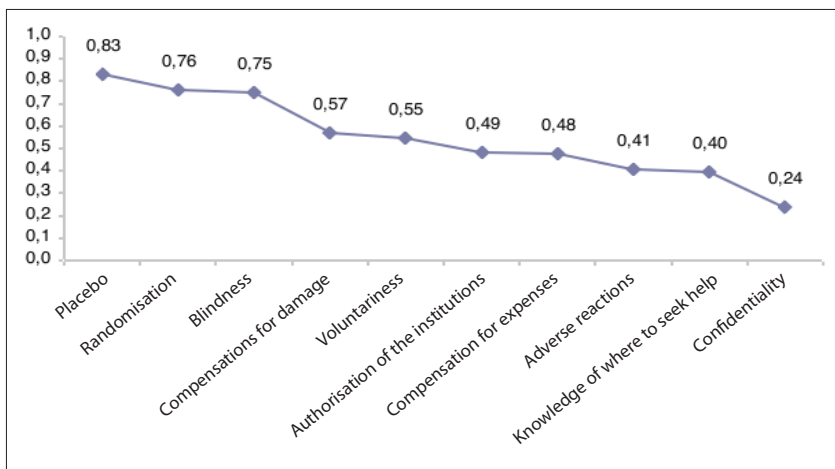
It is also important to note that only 5 respondents correctly answered all the questions, 20 – all the question in the design section and 26 – all the questions about participant rights.

While examining informedness at the level of separate design elements, it has been determined that respondents were best informed about the fact that patients cannot distinguish a placebo from other investigational products (average estimate – 70.8%), while they were worst informed about the principle of randomisation (average estimate – 40.5%). In the block containing information about the rights of clinical trial participants, information about the right to refuse to participate in the trial and the right to receive a copy of the informed consent form was best understood (average estimate – 94.4%), while the worst understood was information about confidentiality (average estimate – 52.8%) (Table 1).

While examining the aggregated (summed groups of elements) data, a strong direct correlation was determined between knowledge about clinical trial design and overall informedness (Pearson's  $r$  ranges from 0.75 to 0.83;  $p < 0.01$ ). Knowledge of the rights of clinical trial participants is less related to overall informedness (Pearson's  $r$  ranges from 0.24 to 0.75;  $p < 0.01$ ) (Fig. 2). This shows that informedness about clinical trial design is likely to be a more important condition for higher overall informedness than informedness about the rights of clinical trial participants.

The study also showed that the most important socio-demographic characteristics related to respondents' informedness are gender, education, income and occupation. Women (69.95%), respondents who had obtained a higher education (74.26%), those currently in employment (71.62%) and with a monthly income above 1400 Lt (77.78%) had a superior rate of overall informedness. Respondents in these groups were also better informed about clinical trial design. A correlation between informedness about the rights of clinical trial participants and respondents' socio-demographic characteristics was not determined.





**Fig. 2: Correlation between topic and overall informedness indicator (Pearson r,  $p < 0,01$ )**

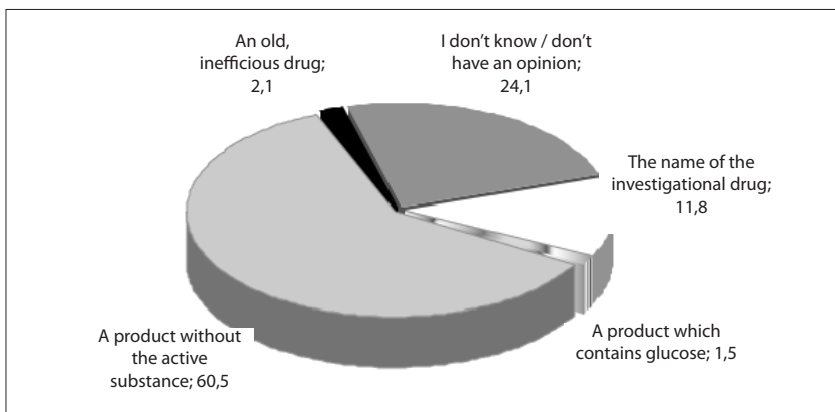
The next section contains comprehensive analysis of qualitative and quantitative data.

### 3.3. Respondents' informedness about clinical trial design: placebo, double-blindness and randomisation

#### 3.3.1. Placebo

Analysis of quantitative data shows that 60.5% of respondents answering the question, "What is a placebo?" chose the most accurate option (Fig. 3). 24.1% of respondents specified that they do not know the meaning of the word or do not have an opinion, 11.8% stated that 'placebo' is the name of the new investigational drug.

During the interview, when respondents were asked to describe how they understood the idea of a placebo in their own words, they did not use the "official" terminology most frequently used on consent forms and generally associated a placebo with deception ('cheat tablet', 'cheat medicine', 'imitation', 'prop'), emptiness ('empty sweet'), ineffectiveness, having no effects or no negative effects ('harmless tablet') or autosuggestion. The majority of respondents characterised a placebo as water or liquid ('coloured water', 'dis-



**Fig. 3: Distribution of answers to the question, “What, in your opinion, is a placebo? (percentage)**

tilled water’, ‘saline’, ‘holy water’, ‘experimental liquid’). We provide one quote which reflects the predominate terminology.

*“The doctor told me that it could be a prop or dummy. I asked the doctor what ‘placebo’ means. Like I said, it is like a sweet wrapped in a wrapper which may contain a completely different sweet. I can give it to you straight – instead of the active ingredient, you get some starch or whatever else. It is a product without the active ingredient. Human consciousness can do a lot if I want to get better and believe that the drug will help. I am sure that I will get better even if I do not get the real drug.”* (60 year old male, special secondary education)

In attempting to explain the concept of a placebo, respondents also referred to starch, chalk, sugar (‘powdered sugar pressed into a tablet’), vitamins (‘a mixture of vitamins’), or compared a placebo to homeopathic drugs.

An analysis of the quantitative data also shows that 24.1% of respondents could not explain the meaning of the word ‘placebo’. However, qualitative data show some respondents who were unable to identify the word ‘placebo’ and claimed to not know its meaning, gave the correct answer when asked if all the patients participating in the trial took the same drugs.

**Respondent:** I can't say. The word is too specific, so I didn't pay attention... there were many medical terms [on the consent form].

**Interviewer:** *But you mentioned earlier that there are two groups of patients and they receive different investigational products. If one group of patient gets a new drug, what does the other group get?*

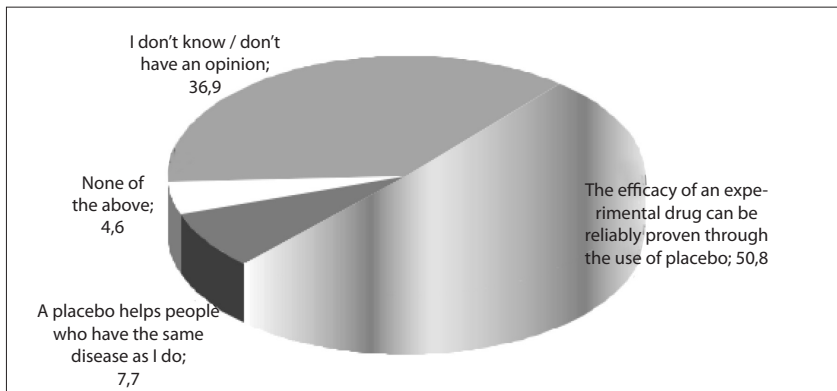
**Respondent:** An imitation. As far as I understood, those pills look the same – the coat and colour are the same“. (84 years old male, higher education)

However, some respondents were completely unable to answer the question, even when additional questions were posed, and several interviewees claimed during the interview that a placebo is the new investigational drug being studied or provided surprising answers, for example, “*Placebo... a familiar word... something... related to the state of the internal organs?*”

Aiming to elucidate a deeper understanding of the concept of a placebo, respondents were asked to not only indicate the appropriate meaning of the concept, they were also asked about the potential inconveniences or risks related to the use of a placebo as well as the reasons for using a placebo.

#### ***Reasons for using a placebo***

An analysis of the quantitative data shows that 50.8% of respondents chose the correct answer when asked about the reasons for using a placebo (“*The efficacy of an experimental drug can be reliably proven through the use of a placebo*”), 39.6% could not answer the question (fig. 4).



**Fig. 4: Distribution of respondents' answers to the question, "Why, in your opinion, is a placebo used in clinical trials?" (percentage)**

Interviews with respondents reveal that the question about the reasons for using a placebo was one of the most difficult to answer in the context of clinical trials. The majority of respondents found it difficult to explain the necessity of using a placebo. Even respondents who commented on other questions quite accurately hesitated or were unable to answer this question. A quote from an interview with a respondent who coherently answered and commented on other placebo-related questions is provided below.

**Interviewer:** *Why, in your opinion, is a placebo used in clinical trials?*

**Respondent:** So that it would help psychologically. If a person feels better psychologically, he gets better. But generally, I see no reason for giving a placebo.

**Interviewer:** *In that case, maybe some patients could not be given any product at all?*

**Respondent:** No, they could give the drug to everyone. I don't really know why a placebo is necessary [...] Purely so that psychologically... It could actually help." (30 year old male, higher education)

Many respondents used concepts such as 'science', 'scientific reasons', 'scientific study', 'rules', 'standards' in order to describe the reasons for using a placebo but could not provide with a more accurate explanation. It would seem that the word 'science' was used as a code allowing to define arguments within a complicated field which the respondents, not being experts, did not aim to define or understand. Often, they simply stated, "But this is a scientific work" or, "A scientific study is a scientific study."

It should be noted that respondents who correctly identified the scientific reasons for using a placebo sometimes interpreted them in somewhat surprising ways. For example, lowering costs of clinical trials (drugs are expensive and a placebo is cheap), to allow the identification of patients participating in the trial whose illnesses arose due to psychological reasons, in order to determine the real cause of the illness (somatic or psychological) or to help people participating in the trial (in this case patients interpreted the expected therapeutic effect as a scientific reason).

However, the majority of respondents, even after having identified the scientific bases for using a placebo emphasised the healing power of placebos – that the use of a placebo would prepare the body for using the real drug, stimulate the body's vital powers or the sub-consciousness, mobilise the body for the fight against an illness. For example,

*“You need to prepare the body. I am saying what I think here. The way I see it, you need to prepare the body if it is exhausted. If there is a lack of any kind of substance, the drug will not be absorbed, or it will not be effective.”* (46 year old female, higher education)

Studying the aggregated quantitative data, it was noticed that there is a very strong correlation (strongest when comparing with the other topics) between informedness about placebo and overall informedness (Pearson’s R 0.83;  $p < 0.01$ ) (Fig. 1). This shows that understanding the concept, purpose and other aspects of a placebo is potentially a precondition for understanding other elements of clinical trial design (double-blindness and randomisation) as well as general informedness about clinical trials. For this reason, it seems that more attention should be devoted to explaining what a placebo is, reasons for using it and associated risks or discomfort on informed consent forms.

### **3.3.2. Double-blindness**

Analysis of the quantitative data shows that a majority (63.6%) of respondents are informed that during the trial, patients cannot know which product (placebo or investigational drug) and what dosage they are using. When asked whether patients can distinguish a placebo from a product containing the active substance, most (70.8%) respondents answered that they cannot. However, attention should be drawn to the fact that a third (29.2%) of respondents did not know the answer or claimed that they can distinguish which product they are using. Most respondents who had confirmed that a patient can recognise that they are using a placebo indicated that the patient himself can feel it (41.2%), a smaller percentage – that the patient was told about the product being used by the physician (23.5%).

Analysis of the qualitative data reveals that, despite the fact that most respondents correctly identified that patients cannot know which product they are using, this question raised some doubts. This is demonstrated by the frequent usage of words like ‘don’t know’, ‘something’ and similar. Sometimes respondents voiced their doubts about the official information given on informed consent forms. Respondents guessed and were unsure about this question:

*“Well, there isn’t anything written there because that drug is coded. Ask me something simpler. I really don’t remember.” (71 year old female, higher education)*

Analysis of the quantitative data shows that half (50.3%) of respondents knew that the physician conducting the clinical trial does not know which product the patients are using and disaffirmed the statement, *“The physician conducting the clinical trial does not know, for the entire duration of the trial, which investigational product (placebo or investigational drug) or what dosage the patients are taking.”* 29.7% of respondents believed that the physician conducting the clinical trial knows which investigational product (placebo or trial drug) and what dosage the patients were being given, and 20% had doubts.

Respondents surveyed during interviews also divided into two almost even groups, those who very firmly and clearly stated that physicians do not know which product is being administered to patients and those who were uncertain about the answer or were certain that physicians knew.

During interviews, respondents who firmly asserted that the physician knows which product is being administered to patients during the clinical trial, made the argument that it is a physician’s professional duty to treat patients, take care of their health and wellbeing and also that there is a potentially higher associated risk due to the experimental nature of clinical trials. For example,

*“Of course they know what they are administering. <...> You know, the doctor is not motivated to administer some rubbish to you. If he is motivated to cure me, then he is motivated to cure me and not to pass on some kind of substitute to you, I personally believe in that doctor, that is to say, my doctor. I don’t know about the others, but I can tell you about mine with 100% certainty. The doctor is very responsible, he knows his job.” (58 year old male, primary education)*

It can again be noted that just like the other questions related to clinical trial design, the question whether the physician knows about the product being administered to patients raises doubts and a large part of respondents lacked self-assurance.

*“If the description is to be believed, then the doctor must not know. But I personally think that he has to know, 100%. [...] I think he can feel it. He has to feel it. [...] I don’t know whether he knows or doesn’t know. How could I know?” (65 year old male, higher education)*

When asked, “*Why is it important for patients to not know which product (placebo or investigational drug) is being administered to them?*” the answers of respondents with whom interviews were conducted could be split into two groups: some emphasised that if patients knew which product they were using they would not agree to participate in the trial, others claimed that not knowing is a necessary condition for the therapeutic (diagnostic) effect of the placebo.

Most respondents, when explaining the importance of applying the blindness method in clinical trials, gave the justification that patients who do not know that they ended up in the placebo group would simply refuse to take part in the trial.

*“But then there would be no reason for having a placebo, if they knew. The ones that would have to take the placebo would not take it, there would be no motivation for it. For example, if that happened to me, I wouldn’t want the placebo. And now there is a likelihood of 2/3 that I am receiving the medicine. That motivates. And I definitely wouldn’t sacrifice myself for a pharmaceutical company.”* (34 year old male, higher education)

Another evident group of respondents – those who thought that not knowing is related to the therapeutic (diagnostic) effect of a placebo, that is, if the patients know which product they are using, they would not get the positive effect on their health because not knowing is a prerequisite for believing in the efficacy of the product being administered (mobilisation of the body), which would encourage the process of self-healing.

*“So as I said, if you know that it’s a placebo, it can’t even affect you psychologically. You automatically know that you are not taking medicine, so then nothing will help you. Then there’s no point in taking part.”* (30 year old male, higher education)

One of the main reasons indicated by respondents as to why the physician is not allowed to know which product is being administered to patients – scientific objectivity and impartiality, for example:

*“I think that there are certain rules for researching and approving drugs. [...] A doctor may also alter the results according to his own subjective opinion – this would bring in the additional opinion of the doctor.”* (64 year old male, higher education)

Many respondents directly or indirectly tried to justify the physician's not knowing about the product being administered by making the argument that it is for the prevention of corruption and also by explaining that the physicians cannot know because they could abuse the privilege and, either of their own accord or influenced by a patient, start administering products to patients who are grateful or who they like more.

*"They are not allowed to know due to objectivity. And rightfully so. For example, so that it would be objective, so that, quite simply, there wouldn't be any, excuse me, corruption. [...] And without any doubt, if the doctors or nurses knew then the majority would come and definitely ask for the drug. Then they could give the drug to acquaintances or someone else, or they could simply give the drug instead of that placebo for some other reason."* (64 year old female, higher education)

Although it was uncommon, when answering this question some people were of the opinion that the physician cannot know because it is only in this way that he could determine the real cause of the illness.

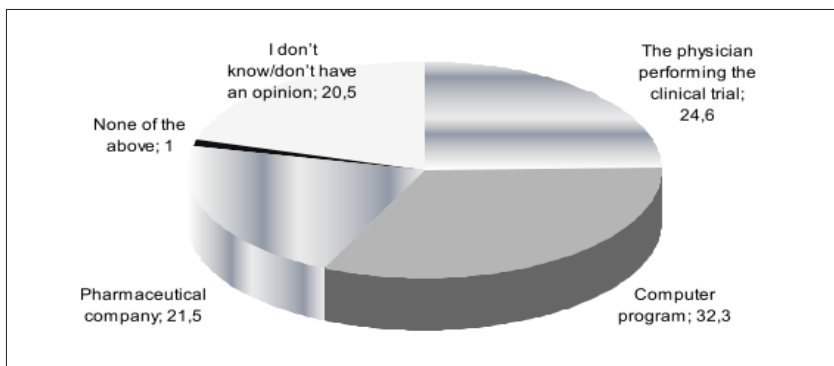
*"Maybe to preserve objectivity in diagnosing the illness – do I need to take drugs or does my psychological state need to be restored. Maybe I need the help of a psychologist? [...] I'm telling you, 70-80% here are psychological issues"* (65 year old male, higher education)

Some of the respondents interviewed indicated that physicians are not allowed to know which product is being administered to patients so that they would not reveal this information to patients.

### **3.3.3. Randomisation**

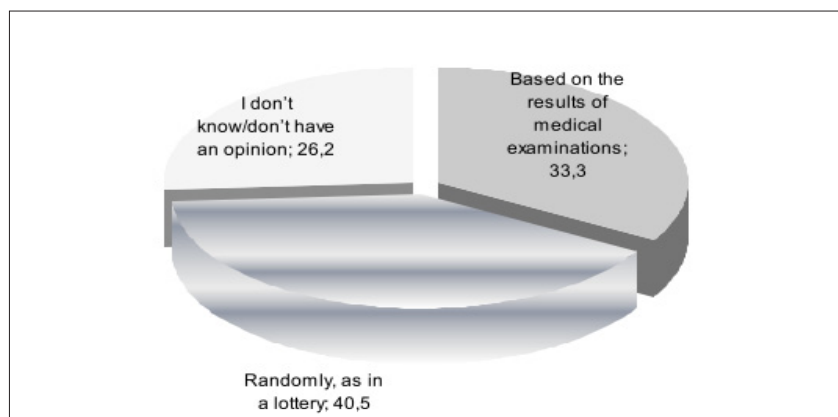
When asked who decides which product is to be administered to patients, respondents were asked to choose one of three answers: physician, computer program or pharmaceutical company. Analysis of the quantitative data shows that 32.3% of respondents chose the most accurate answer (the product is chosen by a computer program), 24.6% stated that it is done by a physician, 21.5% – that it is the pharmaceutical companies and 20.5% of respondents could not answer the question (fig. 5).





**Fig. 5: Distribution of answers to the question, “Who decides which investigational product (placebo or investigational drug) is administered to you during the trial?” (percentage)**

Analysis of the quantitative data also shows that 40.5% of respondents correctly answered the question about the principle behind the selection of an investigational product (“lottery”) and 59.5% chose an incorrect answer, either that the choice is based on the results of medical examinations or they could not answer the question (fig. 6).



**Fig. 6: Distribution of answers to the question, “In your opinion, how is the decision made about which investigational product (placebo or investigational drug) should be administered?” (percentage)**

It should be noted that interviews with respondents revealed that among those who chose the correct answer, that the choice is made by a computer program, there were those who asserted that a computer is the most able to choose a suitable product because the results of all diagnostic tests and information about patients' health is kept on a computer, for example,

*“I think a computer program, because for a pharmaceutical company to delve into every person... God knows... Maybe some data is entered, indications, and the computer chooses what to give and what not to give.”* (48 year old male, higher education)

It should be noted that there were more respondents who correctly answered the question regarding the principle behind the selection of a product (which is a key question, revealing an understanding of randomisation) (40.5%) as compared to those who chose the correct answer to the question about whose area of competency is the distribution of products (32.3%). Analysis of the quantitative data shows that there is a direct correlation between these two variables – respondents who understood the random distribution of products were more likely to correctly identify that the decision about which drug is administered is depersonalised (paired comparisons, Pearson's  $X^2 = 59.57 > 9.48$ ,  $df = 4$ ,  $p = 0.00 < 0.05$ ) (table 2).

**Table 2: Paired comparison of respondents' answers to questions about randomisation**

			In your opinion, how is it decided which investigational product (placebo or investigational drug) should be administered?		Total:
			Incorrect	Correct	
Who decides which product (placebo or investigational drug) is administered to you in the course of the clinical trial?	Physician	N	46	2	48
		%	95,8%	4,2%	100,0%
	Computer program	N	19	<b>44</b>	63
		%	30,2%	<b>69,8%</b>	100,0%
	Pharmaceutical company	N	20	22	42
		%	47,6%	52,4%	100,0%
	None of the above	N	0	2	2
		%	0,0%	100,0%	100,0%
	I don't know/don't have an opinion	N	31	9	40
		%	77,5%	22,5%	100,0%
Total:	N	116	79	195	
	%	59,5%	40,5%	100,0%	

The tendency for respondents who understand that the product is administered randomly, to more adequately comprehend the depersonalised choice of a product was also evident during interviews with respondents. It should be noted that when asked to answer an open question – who makes the decision about which product is to be administered – respondents sometimes used concepts which do not correspond to the official terminology but which reflected the essence – ‘fate’, ‘luck’, ‘God’, and ‘scientific institute’.

A quote from an interview with a respondent who chose the correct answer, answering the open question, “*Who decides which product (placebo or investigational drug) is going to be administered to you during the trial?*”:

*“Good question [smiles]. Logically, I would say that if they are endeavouring to be objective, then a computer program should be the one to choose, the human factor should not be involved. At least that’s how I would want it to be.”* (34 year old male, higher education)

There is a clear tendency among respondents’ answers which is confirmed by a quantitative analysis of the data – respondents incorrectly or hesitantly answered at least one question about randomisation, that is, they either did not understand that it is not the competency of the physician to choose which product to administer, or they did not understand that the decision is based on chance and not based on their individual needs or the state of their health. For example,

*“This one I really do not know. I don’t think that it is decided by a doctor. <...> maybe someone is deciding over there [in a country sponsoring the trial], because they [local investigators] sent out all of our tests and also videos, echoscopies and so on. So maybe someone could decide who has what and how serious the illness is. Maybe with the help of a computer? Because in this trial, in order to be allowed to participate, the illness needs to be somewhat serious. Those who have light illnesses are not allowed to participate. [...] Maybe they look at the age of participants, at the trial information? If they see, for example, that there are several patients who are 30 years old, then they decide to give one of them a placebo. For example, to the group which has the most members. [...] I would like to think that is not random.”* (30 year old male, higher education)

It should also be noted that respondents sometimes confused the intention of the investigator to conduct comprehensive tests, interviews, collect anamneses in order to evaluate the patient's suitability to participate in the trial or because it is necessary according to the protocol of the trial patients with the interpretation that this is done because of individualised care or treatment.

*"I believe so, I believe that they chose it [product] according to my body to some extent. Because they said that others cannot use it, for example, there were women who said they would not be included."* (69 year old female, special secondary education)

### **3.4. Respondents' informedness about the rights of clinical trial participants: the voluntary nature of participation, compensation of expenses and damage, and confidentiality**

#### ***Voluntary nature of participation***

Analysis of the quantitative data allows us to state that respondents are very well informed about the voluntarily participation in the trial both before and during the trial – 94.4% and 90.8% correctly affirmed the correct statements. A similar percentage of respondents affirmed the statement, *"All patients participating in clinical trials have the right to receive an informed consent form"* (94.4%) and also confirmed that they have a copy of the informed consent (95.9%), which leads to the conclusion that patients are well informed also about these procedural issues.

It is important to note that respondents were especially confident in answering and commenting on questions about the voluntary nature of participation. Majority of respondents noted during the interviews that this information was emphasised by the investigator during a discussion or they themselves noticed it while reading the consent form (e.g. *"Obviously if I have a bad feeling about it, why do I have to take part? That's what was written in the papers for me."* (58 year old male, primary education)).

#### ***Right to compensation of expenses***

Analysis of the quantitative data shows that most respondents (67.2%) are informed about the right to receive compensation of expenses incurred due to participating in the trial, although they do not consider this information

to be significant – 10 respondents declared it to be important, although no one claimed it was the most important (fig. 8). The fact that respondents do not consider the right to compensation of expenses to be important was also confirmed through the opinions expressed in interviews with respondents.

Analysis of the qualitative data reveals that respondents affirmed the statement, *“If I have incurred expenses due to participating in the clinical trial (e.g. travel expenses), I have the right to be compensated for these expenses”* even when they claimed that they had not been informed about it either verbally or in writing, they intuitively felt that they have such a right. For example,

*“Of course I should have it [compensation], if I’m the guinea pig, they should compensate my expenses”* (58 year old male, primary education)

The respondents interviewed usually identified the right to compensation of travel and, in some cases, healthcare expenses. Having identified travel expenses, respondents usually associated their compensation with the centre’s being further away from their place of residence (e.g. *“That’s what they told us, they’ll compensate those who are commuting from further away. We gave them our receipts.”* or *“Well, no, except if someone is travelling from far away.”*)

During interviews, respondents who denied the existence or relevance of compensation of expenses usually made the argument that this information is not provided on the informed consent form, the expenses are insignificant or that patients who have made a decision and have signed up to participate in the trial also make certain commitments and that travel or food expenses are a part of these commitments. For example,

*“Well, not really, I myself signed [the form] and agreed to participate, so what is the need for making complaints”* (59 year old male, general secondary education)

Some respondents stated that despite the existence of a formal right to compensation of expenses, it is difficult to accomplish in practice.

### ***Right to compensation for damage***

Analysis of the quantitative data shows that 61.0% of respondents affirmed the statement, *“If my health suffered as a result of participating in the trial, I have a right to be compensated for the damage.”* 48.7% of respondents stated that they would know whom to contact to be compensated for damage. At the same time, it is important to note that about a third of respondents could not provide an answer to either question (30.8% and 35.0% respectively).

The uncertainty of respondents regarding the issue of compensation for damage becomes evident when analysing the qualitative data too – only some of those interviewed answered this question without hesitating or pointed out that this information was provided on the informed consent form or it was mentioned by a physician. The most assured answers still contained the words ‘I believe’ or ‘probably’, indicating a certain sense of doubt. For example, *“Theoretically yes, but in reality, I don’t know, even though it’s supposed to be specified there,”* or *“I believe that is true. If I’m not mistaken, it was specified in the contract.”*

Several respondents who denied that the right to compensation for damage exists, claimed they do not know about such a right and made the argument that their decision to participate in the trial means they agree to accept the consequences arising from it (*“Well, no, I don’t have any right like that, I agreed to it myself and that’s it.”*)

### ***Confidentiality of private information***

This survey was not intended as a means of investigating all of the issues concerning informedness about the collection and processing of personal data – the intention was only to answer the question – do respondents know that their personal information can be accessed not only by medical personnel but also persons looking after or controlling the clinical trial.

Analysis of the quantitative data shows that 52.8% of respondents confirmed the statement, *“Persons not directly involved with my treatment (e.g. ethics committees or the pharmaceutical company who ordered the trial) will be able to access the information collected during this clinical trial,”* however informedness about the safeguarding of confidentiality is lowest in the context of informedness about other rights.

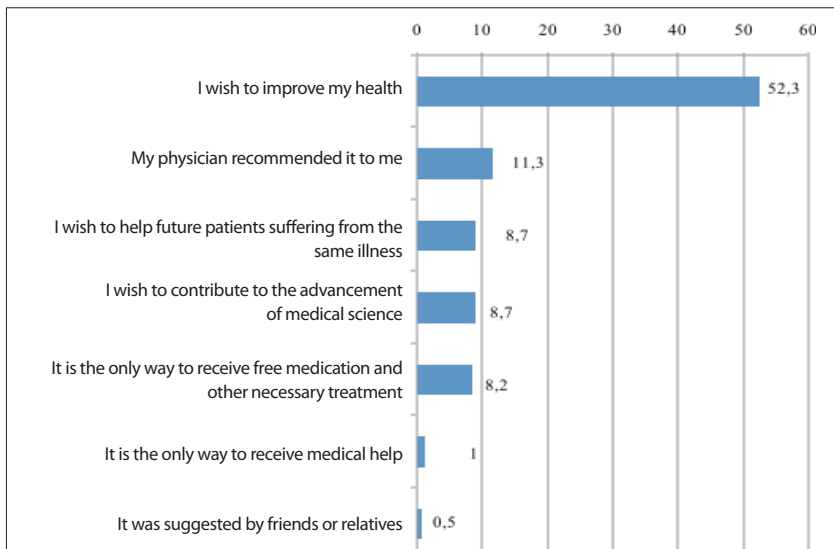
Respondents’ answers during interviews also clearly showed that they are driven more by intuition than information that had been provided by their physician or they themselves had read. Both respondents who affirmed and those who disaffirmed the statement that the information collected during the trial can be accessed by persons who are not directly involved in their treatment used words such as ‘probably’, ‘I believe’, ‘I think’. To many, the question about confidentiality of personal information was clearly new, so they tried to form their opinion on the question during the interview, for example,

*“I think that it would be best if only my doctor knew.”* (58 year old male, primary education)

*“Other can probably access it too, not just the doctor. Somehow I didn’t really pay attention to that.”* (76 year old female, higher education)

### 3.5. Respondents’ motives for participating in the trial and the relationship between evaluating the significance of the information provided and informedness

Analysis of the quantitative data reveals that the most important reason determining participation in the clinical trial was a desire to improve one’s health (indicated as the most important by 52.3% of respondents). 11.3% of respondents specified ‘physician’s recommendation’ as most important. The third most commonly cited reason was a desire to help future patients with the same illness (9.2% of respondents chose this as the most important) (fig. 7). A statistically significant correlation between the most important motive for participating in the trial and socio-demographic characteristics of the respondents has not been determined.



**Fig. 7: The distribution of answers to the question, “Why did you agree to participate in the trial?” (percentage)**

Qualitative data also confirm this tendency – during interviews respondents usually mentioned a desire to recover or improve their health and the importance of a physician’s opinion, less often – a desire to contribute to the process of creating a new drug which will be beneficial to future patients (“*I feel a sense of public duty, I like it*”).

Both quantitative and qualitative data analysis also reveals that respondents are not inclined to consult friends or family (the advice of friends and family was specified as the most important by only 2 respondents).

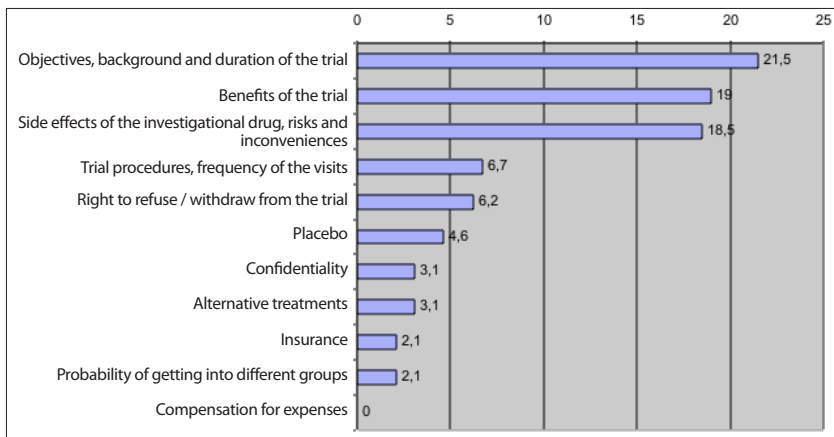
During interviews, respondents answering the open question, “*Why did you agree to participate in the clinical trial?*” also specified reasons such as the opportunity to receive free medication and diagnostic tests, more attentive healthcare (“*My doctor suggested that I participate in the trial and said that if I participate, I will get all the medication that I get now for free*”), a tendency for trying new things (*‘adventurousness’*) as well as the fact that taking part in a clinical trial helps with discipline and regulation of taking medication.

### ***Respondents’ assessment of the importance of information about the clinical trial***

Seeking to discover which information about clinical trials respondents consider to be the most important and determine the correlation between informedness and the subjective rating of information in terms of importance, respondents were provided with a list of informational elements usually provided on informed consent forms prepared according to the requirements for informed consent forms confirmed by the Lithuanian Bioethics Committee. Respondents were asked to select 3 of 11 informational elements and rank them in order of importance. Analysis of the quantitative data shows that information about side effects of the trial medication, potential discomfort or harm due to the trial (21.5%), potential benefits of the trial (19%), objectives, justification and duration of the trial (18.5%) were considered to be the most important items of information (fig. 8).

It is important to note that a statistically significant correlation between informedness and ratings of importance has not been determined (correlational analysis, Spearman’s  $\rho$ ). As mentioned earlier, respondents were best informed about the rights of clinical trial participants (voluntariness, compensation for damage, compensation of expenses), although they did not





**Fig. 8: Distribution of respondents' answers to the question, "Which information about the clinical trial is the most important to you?" (percentage)**

consider them to be important. In fact, respondents considered side effects of the medication to be the most important, however 35.9% of respondents hesitated or incorrectly disaffirmed the statement, "*The trial medication may cause side effects*".

### ***Issues to be emphasised***

Legislation determines what information must be presented on informed consent forms, and their acceptability is evaluated by the competent authorities (Lithuanian Bioethics Committee, State Medicines Control Agency). According to our research data, respondents confirmed they have their informed consent form (95.9%), the majority read it more than once (73.3%) and discussed it with their physician-investigator for approximately 20 minutes. The research data also show that the majority of respondents do not consider the information provided about clinical trials to be complicated – only 15.9% of respondents indicated that the informed consent forms contained words or statements which were difficult to understand.

It would seem that these circumstances would guarantee informedness of clinical trial participants, however, respondents could not answer a third of questions correctly and only 5 respondents managed to answer

every question correctly. Undoubtedly, the process of receiving and evaluating information and making decisions is influenced by many external and personal factors, which cannot be eliminated completely. For example, analysis of the qualitative data reveals that in terms of almost all of the clinical trial-related questions, respondents declared significant therapeutic expectations which became clear both in answers about placebos, double-blindness, randomisation and when speaking about motives for participating in the clinical trial or the purpose of the trial.

It should also be noted that besides being concerned about their health, respondents specified 'physician's recommendation' as a motive for participating in the trial. Other studies also reveal that a physician is the first source of information about clinical trials for the trial subjects and his or her recommendation is one of the main reasons why patients decide to participate in a clinical trial. Another important factor which was revealed indirectly during general contextual analysis and interviews with respondents – a lack of critical thinking, the reason for which, in our opinion, is insufficient distribution of impartial information about clinical trials and low health literacy skills (or more specifically, clinical trial literacy skills). Open and extensive access to both general information about clinical trials as well as information about a specific clinical trial would help current and future clinical trial participants to critically evaluate the information provided and potentially lower the influence of the stress caused by the situation and other undesirable factors.

## 4. CONCLUSIONS

1. Normative and regulatory documents determine what information must be presented on informed consent forms and their suitability is evaluated by the competent authorities, however 1) there are no instruments which would allow for the readability of health texts in Lithuania to be objectively evaluated; 2) informed consent forms used for clinical trials conducted in Lithuania are more than twice as long (16.6 pages) as the recommended optimal length for these documents (7 pages).

2. A survey of patients participating in placebo-controlled clinical trials shows that their informedness about the clinic trial is average (66.3%) and is seen as insufficient. Respondents were better informed about the rights of clinical trial participants (74.7%) than clinical trial design (58.6%). The highest participants' informedness was about the voluntariness of participation in clinical trials (average estimate – 90.8%), the lowest – about randomisation (average estimate – 47.5%).
3. Informedness about clinical trial design is a more significant precondition for higher overall informedness (Pearson's  $r$  ranges from 0.75 to 0.83;  $p < 0.01$ ), than informedness about the rights of clinical trial participants (Pearson's  $r$  ranges from 0.24 to 0.57;  $p < 0.01$ ). A strong statistically significant correlation (strongest when comparing with other topics) has been determined between informedness about placebos and overall informedness (Pearson's  $r$  0.83;  $p < 0.01$ ).
4. Most respondents positively evaluated the information provided about the clinical trial (they did not consider it to be complicated and indicated that they had read the informed consent form several times, discussed it with their physician and devoted more than 20 minutes to the discussion). Respondents considered information about inconveniences resulting from the trial, potential benefits, objective of the trial, justification and duration of trial to be the most important, however, a statistically significant correlation between respondents' informedness and importance rating of the information has not been determined.  
Most respondents associated participation in clinical trials with personal therapeutic benefits. This shows that some respondents did not fully identify the experimental nature of the clinical trial which is important in order to adequately evaluate its risks and benefits. The therapeutic expectations of respondents are demonstrated not only by answers to questions about the motives for participating in the clinical trial but also answers to questions about clinical trial design (placebo-control, double-blindness and randomisation).
- 4.1. The most important reason for participation in a clinical trial was a desire to improve one's health (52.3%), second – physician's recommendation (11.3%), third – a desire to help patients suffering from the same illness in the future (9.2%).

- 4.2. Double-blindness was the best understood topic in terms of clinical trial design. Informedness about double-blindness is high (average estimate – 68.2%), however the scientific bases for its use specified by respondents lead to doubts about a deeper understanding of this method. Some respondents did not identify the scientific reasons for using this method and relied on advantages to patients' health as an argument (belief produced by not knowing helps to fight the illness, mobilises the organism, allows for the illness to be diagnosed) and also specified practical (prevention of corruption) or social fairness reasons (so that the product would be given regardless of the patients social or personal characteristics).
- 4.3. Although 60.5% of respondents correctly identified the meaning of the term 'placebo' and 50.8% correctly answered the question about reasons for using a placebo, analysis of qualitative data revealed insufficient understanding of this term. Most respondents were more inclined to explain both the notion of a placebo and the purpose for using it not in terms of scientific reasons but therapeutic intentions (healing power of belief, using a placebo may reveal the real cause of an illness, a placebo does not have side effects).
- 4.4. Informedness about randomisation is average (average estimate – 47.5%), but is the lowest not only in the context of informedness about clinical trial design but also overall informedness about the clinic trial. A large part of those surveyed answered at least one question about randomisation hesitantly or incorrectly, that is, they either did not understand that administering of the investigational product is not the physician's competence (correctly answered by 32.3% of respondents), or did not grasp that this administering is based on chance (correctly answered by 33.3% of respondents). This shows that, by participating in the trial, respondents expect their individual healthcare needs to be met.

## 5. RECOMMENDATIONS

1. Educate and train investigators and improve their communicational skills, encourage scientific research about investigators' views on problematic aspects of patients' informedness.
2. Encourage the formation of public critical discourse about clinical trials and the distribution of impartial information about clinical trials:
  - 2.1. Encourage the development and distribution of impartial information about clinical trials via different media of communication. Discussions or conferences among patients (or their organisations), investigators, heads of healthcare institutions, sponsors (CROs) and competent authorities can also be considered an efficient means of raising awareness about medical research. Although information and education about clinical trials is considered to be within the competence of control institutions, there is a demand for more information which could be accessed in more varied ways.
  - 2.2. Encourage the establishment of non-governmental clinical trial organisations (of patients, investigators, scientists).to assist in the distribution of information, the mediation of discourse and in bringing more transparency to the field.
3. Improve the quality of written information (informed consent forms) given to clinical trial participants:
  - 3.1. Emphasise clinical trial design on informed consent forms, forming a uniform notion of the *benefits* (direct and indirect) of clinical trials which is acceptable to the local clinical trial community. Explain the most important design aspects in simpler and more everyday language, avoiding the possibly confusing implications of the notion of treatment. Consistently use terminology appropriate to the research context.
  - 3.2. Shorten the informed consent forms and, if necessary, prepare additional supplements which explain the more complicated information, or information requiring more extensive explanation.
  - 3.3. Develop instruments which enable effective and objective assessment of the readability of (health) texts in Lithuanian.

4. It is suggested that sponsors, investigators, ethics committees and researchers should use the study scheme, methodology and instrument which have been created to evaluate the informedness of patients participating in placebo-controlled clinical trials for practical and scientific purposes.

## LIST OF PUBLICATIONS

1. **Čekanauskaitė A.**, Gefenas E. Gydomo ir mokslinio tyrimo painiavos problema klinikinčiuose tyrimuose. [The problem of therapeutic misconception in clinical drug trials] *Visuomenės sveikata*. 2012;1(56):11-21.
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2. Informuoto asmens sutikimas pacientų saugos kontekste [The role of informed consent in the context of patients' safety]. International congress „Patients' safety in odontology“ . June 5-6, 2009, Trakai, Lithuania.



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## **Education**

From 2005 Vilnius University, Faculty of Medicine, Institute of Public Health, doctoral student

1996–1999 Vilnius University, Faculty of Philosophy, Master's Degree in Philosophy

1992–1996 Vilnius University, Faculty of Philosophy, Bachelor's Degree in Philosophy

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## **Work experience**

2007–2010 Vilnius University, Medical Faculty, Department of Medical History and Ethics, research fellow

From 2001 Lithuanian Bioethics Committee, chief specialist

From 2000 Vilnius University, Medical Faculty, Department of Medical History and Ethics, assistant, lecturer of medical ethics

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## SANTRAUKA

### **Tiriamoji problema ir jos aktualumas**

Informuoto asmens sutikimas yra vienas svarbiausių šiuolaikinės medicinos etikos principų, įtvirtintas tarptautiniuose ir nacionaliniuose teisės aktuose bei etikos kodeksuose. Tai yra ir vienas geriausiai žinomų, tačiau kartu labiausiai diskutuojamų etikos principų tiek klinikinės praktikos, tiek biomedicininų tyrimų kontekste, nes jo įgyvendinimas vis dar kelia nemažai praktinių problemų. Informuoto asmens sutikimas yra svarbus medicinos etikos principas, nes užtikrina asmens apsisprendimo teisę, o informuotumu pagrįstų sprendimų priėmimas svarbus ir pacientų saugos aspektu.

Klinikiniai tyrimai yra ypač jautri sritis, nes čia, skirtingai nei įprastinėje kasdienėje klinikinėje praktikoje, susiduriama su žmogaus kūno, biologinės medžiagos, taip pat privačios sveikatos informacijos panaudojimu ne konkretaus paciento gydymo, profilaktikos ar slaugos, bet mokslinio tyrimo tikslais, t. y., ne konkretaus asmens sveikatos labui, o naujo mokslinio žinojimo plėtojimui. Todėl sąmoningas ir laisvas asmens apsisprendimas ir sutikimas dalyvauti tokiaame procese yra ypač svarbus.

Tam, kad sutikimas būtų laikomas pilnaverčiu, galiojančiu, turi būti įgyvendinta keletas sąlygų – sutikimą turi duoti kompetentingas asmuo (ar teisėtas jo atstovas), sutikimas turi būti duotas laisva valia, o prieš gaunant sutikimą asmeniui turi būti pateikta visa su tyrimu susijusi informacija, kuri gali būti reikšminga priimančiam sprendimui dėl dalyvavimo tyrime.

Nepaisant to, kad šis reikalavimas galioja jau daugelį metų, tyrimų rezultatai atskleidžia, kad klinikiniuose tyrimuose dalyvaujantys asmenys dažnai nesupranta pagrindinės su klinikiniais tyrimais susijusios informacijos, esminių klinikinio tyrimo, kuriame asmuo kviečiamas dalyvauti ar jau dalyvauja, elementų.

Svarbu atkreipti dėmesį į Lietuvos klinikinių vaistinio preparato tyrimų specifiką – pagrindinis tokių tyrimų užsakovas yra tarptautinės farmacijos kompanijos<sup>3</sup>, todėl didelė dalis Lietuvoje naudojamų informuoto asmens sutikimo formų yra vertiniai iš anglų kalbos. Nėra aišku, ar verstiniai tekstai

<sup>3</sup> Lietuvos bioetikos komiteto duomenimis, 2006-2011 metais iš 598 klinikinių vaistinio preparato tyrimų, gavusių Lietuvos bioetikos komiteto pritarimą, tik 9 buvo vadinamieji akademiniai (nekomerciniai) tyrimai.

nėra sunkiau suprantami dėl skirtingose kalbinėse struktūrose naudojamos sakinių darybos, gramatinių formų bei terminologijos.

Iki šiol atlikti du empiriniai tyrimai, kuriais buvo siekiama tyrinėti klinikinių tyrimų dalyvių informuotumą ir požiūrį į dalyvavimą klinikiniuose tyrimuose Lietuvoje. 2003 m. K. Lukauskaitės atliktas tyrimas, anot autorės, rodė rimtas informuoto asmens sutikimo užtikrinimo problemas. Tačiau šio tyrimo viešai prieinami tik labai bendri duomenys. V. Marčiulionienė 2010 m. apgintu magistro darbu siekė išsiaiškinti dalyvavusių ir nedalyvavusių pacientų požiūrį į klinikinius tyrimus, motyvaciją dalyvauti bei kai kuriuos informuotumo aspektus.

**Darbo tikslas** – įvertinti pacientų, dalyvaujančių placebo kontroliuojamuose klinikiniuose vaistinio preparato tyrimuose Lietuvoje, informuotumą apie klinikinius tyrimus.

#### **Darbo uždaviniai**

1. Aprašyti informuoto asmens sutikimo klinikiniuose tyrimuose įgyvendinimo kontekstą naudojant originaliai sukurtą konteksto analizės modelį.
2. Nustatyti pacientų, dalyvaujančių placebo kontroliuojamuose klinikiniuose vaistinio preparato tyrimuose, informuotumo apie klinikinius tyrimus problemines sritis.
3. Nustatyti informuotumo apie klinikinių tyrimų metodologiją ir klinikinių tyrimų dalyvių teises ryšį su bendru informuotumu.
4. Atskleisti pacientų, dalyvaujančių placebo kontroliuojamuose klinikiniuose vaistinio preparato tyrimuose, pateikiamos informacijos apie klinikinius tyrimus vertinimą, motyvaciją dalyvauti klinikiniuose tyrimuose bei nuomonę apie klinikinių tyrimų mokslinius metodus (placebo kontrolę, dvigubą aklumą, atsitiktinį grupių sudarymą).

#### **Ginamieji teiginiai**

1. Teisinis reglamentavimas sudaro prielaidas klinikinių tyrimų dalyvių informuotumui, tačiau pacientų, dalyvaujančių placebo kontroliuojamuose klinikiniuose vaistinio preparato tyrimuose, informuotumas yra nepakankamas.

2. Pacientai, dalyvaujantys placebo kontroliuojamuose klinikiniuose vaistinio preparato tyrimuose, yra geriau informuoti apie klinikinių tyrimų dalyvių teises nei apie klinikinių tyrimų metodologiją, o informuotumas apie klinikinių tyrimų metodologiją yra svarbesnė prielaida bendram informuotumui nei informuotumas apie dalyvių teises.
3. Dauguma pacientų, dalyvujančių placebo kontroliuojamuose klinikiniuose vaistinio preparato tyrimuose, nesupranta vieno ar daugiau iš trijų pagrindinių klinikinių tyrimų metodologijos elementų (placebo kontrolės, dvigubo aklumo, atsitiktinio grupių sudarymo) ir klinikiniuose tyrimuose taikomiems moksliniams metodams yra linkę suteikti terapinę reikšmę.

### **Darbo mokslinis naujumas**

Šis darbas – pirmoji Lietuvoje mokslinė studija, kuria, derinant kokybinį ir kiekybinį metodus, tiriamas klinikiniuose tyrimuose dalyvujančių asmenų informuotumas. Šiuo darbu siekiama atskleisti svarbiausias placebo kontroliuojamuose klinikiniuose vaistinio preparato tyrimuose dalyvujančių pacientų informuotumo problemas, ypatingą dėmesį skiriant informuotumui apie klinikinio tyrimo metodologiją. Literatūros analizė įgalina teigti, kad tai – viena iš nedaugelio studijų pasaulyje ir pirmoji Lietuvoje bei Rytų Vidurio Europoje, kuria, derinant kokybinį ir kiekybinį metodus, tirtas informuotumas apie klinikinio tyrimo metodologiją (dizainą), apimantis trijų svarbiausių klinikinių tyrimų eksperimentinį pobūdį konstituojančių elementų supratimą – placebo, dvigubo aklumo, atsitiktinio tiriamųjų grupių sudarymo ir šių metodų naudojimo priežastis. Šiame darbe metodiškai palygintas placebo kontroliuojamuose tyrimuose dalyvujančių pacientų informuotumas klinikinių tyrimų metodologijos ir informuotumas kitomis klinikinių tyrimų temomis bei jų tarpusavio ryšiai.

Sukurta mokslinio tyrimo metodika bei instrumentas (anketa), kurie gali būti taikomi dvigubai akluose, placebo kontroliuojamuose klinikiniuose tyrimuose dalyvujančių pacientų informuotumui vertinti mokslo ar praktiniais tikslais (rekomenduotini etikos komitetams, tyrėjams, užsakovams).

### **Darbo praktinė reikšmė**

Šiuo darbu siekiama išsiaiškinti probleminius klinikinių tyrimų dalyvių informuotumo aspektus, kurie įgalina kryptingą formalių reikalavimų bei

tiriamųjų informavimo praktikos tobulinimą, siekiant svarbiausio tikslo – užtikrinti laisvą ir informuotumo pagrįstą tiriamųjų sutikimą.

Sukurtas instrumentas gali būti taikomas (arba adaptuojamas atsižvelgiant į konkretaus klinikinio tyrimo metodologijos specifiką) tolimesniuose dvigubai akluose placebo kontroliuojamuose tyrimuose dalyvaujančių pacientų informuotumo moksliniuose tyrimuose Lietuvoje. Šis instrumentas gali būti reikšmingas tiek tyrėjams, kurių kompetencija ir atsakomybė yra užtikrinti tinkamą tiriamųjų informavimą, tiek etikos komitetams, vertinantiems informuoto asmens sutikimo formų ir procedūrų tinkamumą bei tiriamųjų teisių užtikrinimą. Tyrimo įgyvendinimo schema gali būti naudinga mokslininkams ir praktikams, nagrinėjantiems šią problemą ateityje.

### **Metodika**

Mokslinį darbą sudaro trys dalys – teorinė dalis (mokslinės literatūros sisteminimas ir analizė), tyrimo instrumento bei metodikos sukūrimas ir empirinis tyrimas (klinikinių tyrimų dalyvių apklausa). Įvertinus ankstesnių panašių tyrimų patirtį ir atsižvelgus į specifinius Lietuvos teisinius reikalavimus informuoto asmens sutikimui ir Lietuvoje naudojamų informavimo formų formuluotes, pacientų apklausai taikytas anoniminis autorės sukurtas tyrimo instrumentas – anketa. Dalyvauti apklausoje buvo pakviesti suaugę asmenys (18 metų ir vyresni respondentai, galintys savarankiškai duoti informuoto asmens sutikimą), kurie apklausos metu dalyvavo Lietuvoje vykstančiuose dvigubai akluose atsitiktinio tiriamųjų grupių sudarymo placebo kontroliuojamuose klinikinuose vaistinio preparato tyrimuose. Apklausai gautas etikos komiteto leidimas.

Tyrimo tikslams pasiekti buvo derinamas kokybinis ir kiekybinis duomenų rinkimo metodai. Tyrimo duomenų bazę sudaro 76 interviu ir 195 anketos.

Interviu su respondентаis buvo įrašyti į skaitmeninę garso laikmeną ir transkribuoti taip suformuojant pirminę tyrimo medžiagą. Respondentų atsakymai buvo sugrupuoti pagal temas. Medžiaga buvo sisteminama temos viduje, išskiriant požiūrių modelius ir ieškant jų ryšio bei susiformavimo prielaidų kitose temose. Kiekybiniai duomenys buvo analizuojami individualiu (klausimo) ir agreguotu (grupuoti teisingų atsakymų duomenys) lygmeniu. Duomenys apdoroti ir analizuoti IBM SPSS 20.0. statistinės anali-

zės programine įranga. Kiekybinių duomenų analizei naudoti aprašomosios ir daugiamatės statistinės analizės metodai.

### **Išvados**

1. Teisės aktai ir kiti norminiai dokumentai nustato, kokia informacija turi būti pateikta Informuoto asmens sutikimo formose, o jų tinkamumą įvertina kontroliuojančios institucijos, tačiau 1) nėra instrumentų, leidžiančių objektyviai įvertinti sveikatos tekstų lietuvių kalba skaitomumą (suprantamumą); 2) Lietuvoje vykdomų klinikinių tyrimų vidutinis Informuoto asmens sutikimo formų puslapių skaičius daugiau nei du kartus (16,6 psl.) viršija rekomenduojamą optimalią šių dokumentų apimtį (7 psl.).
2. Apklaustų placebo kontroliuojamuose klinikiniuose tyrimuose dalyvaujančių pacientų informuotumas apie klinikinius tyrimus yra vidutiniškas (rodiklis 64,6 proc.) ir vertintinas kaip nepakankamas. Respondentai buvo geriau informuoti apie klinikinių tyrimų dalyvių teises (rodiklis 74,7 proc.), nei apie klinikinio tyrimo metodologiją (rodiklis 56,2 proc.). Aukščiausias buvo respondentų informuotumas apie dalyvavimo klinikiniuose tyrimuose laisvanoriškumą (vidutinis įvertis 90,8 proc.), žemiausias – apie atsitiktinį tiriamųjų grupių sudarymą (vidutinis įvertis 47,5 proc.).
3. Informuotumas apie klinikinio tyrimo metodologiją yra svarbesnė prielaida aukštesniam bendram informuotumui (Pirsono r svyruoja nuo 0,75 iki 0,83;  $p < 0,01$ ), nei informuotumas apie klinikinių tyrimų dalyvių teises (Pirsono r svyruoja nuo 0,24 iki 0,57;  $p < 0,01$ ). Nustatytas stiprus statistiškai reikšmingas ryšys (stipriausias lyginant su kitomis temomis) tarp informuotumo placebo tema ir bendro informuotumo (Pirsono r 0,83;  $p < 0,01$ ).
4. Dauguma respondentų pozityviai vertino pateikiamą informaciją apie klinikinį tyrimą (nelaikė jos sudėtinga, nurodė skaitę Informuoto asmens sutikimo formą pakartotinai, aptarė ją su gydytoju ir aptarimui skyrė daugiau nei 20 min). Svarbiausia respondentai laikė informaciją apie klinikinio tyrimo nepatogumus, planuojamą naudą ir jo tikslą, pagrindimą bei trukmę, tačiau statistiškai reikšmingas ryšys tarp respondentų informuotumo ir informacijos svarbos vertinimo nenustatytas.

Dalyvavimą klinikiniuose tyrimuose dauguma respondentų siejo su asmenine terapine nauda, kas rodo, kad dalis respondentų nepilnai identifikavo mokslinį-tiriamąjį klinikinio tyrimo pobūdį, kuris yra adekvataus klinikinio tyrimo naudos ir nepatogumų (rizikos) santykio vertinimo prielaida. Respondentų terapinius lūkesčius liudija ne tik atsakymai į klausimą apie dalyvavimo klinikiniame tyrime motyvaciją, bet ir atsakymai į klausimus apie klinikinių tyrimų metodologiją (placebo kontrolę, dvigubą aklumą ir atsitiktinių grupių sudarymą).

- 4.1. Svarbiausia priežastis, lėmusi respondentų sprendimą dalyvauti klinikiniame tyrime, buvo noras pagerinti sveikatą (52,3 proc.), antroji pagal reikšmingumą buvo gydytojo rekomendacija (11,3 proc.), trečioji – noras padėti ateities pacientams, sergantiems ta pačia liga (9,2 proc.).
- 4.2. Dvigubas aklumas buvo geriausiai suprantama tema klinikinių tyrimų metodologijos kontekste. Informuotumas apie dvigubą aklumą yra aukštas (vidutinis įvertis 68,2 proc.), tačiau respondentų nurodomos šio mokslinio metodo naudojimo priežastys verčia abejoti gilesniu jo esmės supratimu. Dalis respondentų neidentifikavo mokslinių šio metodo taikymo priežasčių, o pasitelkdavo naudos pacientų sveikatai argumentaciją (nežinojimo sukuriamas tikėjimas padeda kovoti su liga, mobilizuoja organizmą, leidžia diagnozuoti ligą) bei nurodydavo praktinį (korupcijos prevencija) ar socialinio teisingumo aspektą (kad preparatas būtų skiriamas neatsižvelgiant į paciento socialines ar asmenybės charakteristikas).
- 4.3. Nors 60,5 proc. respondentų teisingai nurodė termino „placebas“ reikšmę, o 50,8 proc. teisingai atsakė į klausimą apie placebo naudojimo priežastis (informuotumas vidutiniškas), kokybinių duomenų analizė atskleidė šio termino supratimo trūkumą. Dauguma respondentų tiek placebo sąvoką, tiek placebo naudojimą klinikiniuose tyrimuose buvo linkę aiškinti ne mokslinėmis priežastimis, o terapinėmis intencijomis (tikėjimas gydo, placebo naudojimas gali leisti nustatyti tikrąsias ligos priežastis, placebas nesukelia pašalinių poveikių).
- 4.4. Informuotumas apie atsitiktinių tiriamųjų grupių sudarymą yra vidutiniškas (vidutinis įvertis 47,5 proc.), tačiau žemiausias ne tik

klinikinių tyrimų metodologijos, bet ir bendrame informuotumo apie klinikinius tyrimus kontekste. Didelė dalis apklaustųjų neteisingai ar abejodami atsakė bent vieną iš atsitiktinio grupių sudarymo klausimų, t. y. arba nesuprato, kad tiriamojo preparato skyrimas nėra gydytojo kompetencija (teisingai atsakė 32,3 proc. respondentų), arba nesuvokė, kad šis skyrimas grindžiamas atsitiktinumu (teisingai atsakė 40,5 proc. respondentų). Tai rodo, kad respondentai iš dalyvavimo tyrime tikisi individualizuotos sveikatos priežiūros, jų asmeninių sveikatos poreikių tenkinimo.