EARLY PHASE CLINICAL RESEARCH AS VIEWED BY HEALTHY VOLUNTEERS

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Early phase clinical research is an essential step in the development of novel medicinal products. Its main subjects are healthy volunteers. The research quality and outcomes directly depend on how and among whom healthy volunteers are selected and how well the volunteers follow the requirements. Selection of healthy volunteers for participation in early phase clinical research can be influenced by a number of various factors and ethical problems. Better comprehension of volunteer's expectations, potential fears, limiting factors and motives will promote adherence to respective ethical standards and, as a rule, result in qualitative research practice. In this article, authors have tried to analyze the attitude of healthy volunteers towards various aspects of participation in clinical research using own research experience and available literature data. Surveys of healthy volunteers, individual observations and interviews of researchers with participants represented data to be analyzed. Basic variables of interest included the social and demographic portrait of a healthy volunteer, motivation and barriers to research participation, perception of risks by volunteers and their attitude to adverse events, and financial aspects.

Keywords: early phase clinical research, healthy volunteers, ethics, motivation to participation, payment, perception of risks and benefits, adverse events, 'professional' volunteers

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Compliance with ethical standards: voluntary informed consent was obtained from every participant. Questioning was conducted on a voluntary basis.

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КЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ РАННИХ ФАЗ ГЛАЗАМИ ЗДОРОВЫХ ДОБРОВОЛЬЦЕВ

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Клинические исследования ранних фаз являются важнейшим этапом разработки новых лекарственных препаратов. Основные субъекты таких исследований — здоровые добровольцы. Качество проведения и соответственно результаты исследований напрямую зависят от того, как и среди кого осуществляется отбор здоровых добровольцев, насколько добросовестно добровольцы соблюдают предъявляемые к ним требования. Сам процесс отбора здоровых добровольцев для участия в исследованиях ранних фаз может подвергаться влиянию ряда достаточно разнообразных факторов и проблем этического характера. Приобретение лучшего понимания ожиданий добровольцев, их потенциальных страхов, сдерживающих факторов и мотивов позволит обеспечить соблюдение соответствующих этических норм и, как следствие, качественное проведение исследований. В настоящее статье авторы попытались проанализировать отношение здоровых добровольцев к различным аспектам участия в клинических исследованиях, опираясь на собственный исследовательский опыт и данные доступной литературы. Материалами для анализа послужили проведенные опросы здоровых добровольцев, отдельные наблюдения и беседы исследователей с участниками. Основными переменными интереса являлись: социально-демографический портрет здорового добровольца, мотивация и барьеры к участию в исследованиях, восприятие добровольцами рисков и отношение к нежелательным явлениям, финансовые аспекты.

Ключевые слова: клинические исследования ранних фаз, здоровые добровольцы, этика, мотивация к участию, вознаграждение, восприятие риска и выгоды, нежелательные явления, «профессиональные» добровольцы

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Соблюдение этических стандартов: добровольное информированное согласие было получено от каждого участника. Анкетирование проводилось на добровольной основе.

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Ethical aspects of participation of healthy volunteers continue to be a key issue of early phases of clinical research (CR) that can't be solved with standard benefit/risk approaches due to the lack of a suggested therapeutic effect and, as a consequence, social benefit for subjects along with potential health risks of various degrees. In this respect, it is necessary to mention significant efforts and success of the society regarding safety and well-being of subjects of the CR reflected in regulatory documents. All experienced researchers are well aware of these and stick to them in daily routine.

However, a subjective attitude of CR participants to regulatory requirements and their actual performance remains a grey area. Systemic examination of its characteristics is not paid enough attention yet, and such studies are sparse. Dichotomic division of

healthy volunteers into 'good' and 'bad' ones, which is habitual in modern practice, is no longer in line with the latest trends and makes us review this issue in detail. Taking into account the available literature data and own more than 15 years of experience at centers of early phases of CR on the basis of public health institutions, the authors tried to analyze and comprehend the attitude of healthy volunteers to various aspects of participation in CR.

Data to be analyzed involved periodic interrogations with anonymous questionnaires, individual observations and interviews of volunteers by investigators. Basic variables of interest included the social and demographic portrait of phase I research participant, motivation and barriers to research participation, awareness about the trial, subjective assessment of its safety, attitude to adverse events (AE), readiness to report them and financial aspects of participation in CR.

MOTIVATION TO PARTICIPATE IN CR

What is the basic motive that urges people to take part in CR as healthy volunteers? This question has been examined and analyzed by foreign researchers for a long time. It is expected that according to many papers, the majority of volunteers decide to participate because of financial compensation. Many of them are commonly people with low income and low level of education [1,2].

A similar fact was established by Russian authors as well. They state that the main motivating factor of participation in bioequivalence studies among healthy volunteers, especially among men, was financial compensation [3].

After a more in-depth analysis, Indian researchers have found a wide list of factors that influence taking a positive decision about participation in phase I clinical research: 29–38 years, being a male, being married, living in urban slums, big family, low income, lack/low level of education, experience in participation [4]. In another work, composed with support of Pfizer, healthy volunteers from the USA, Belgium and Singapore primarily focused on the amount of payment. No significant association with a social and demographic factor has been detected [5].

The described results increasingly become a subject for discussion by specialists dealing with recruiting ethics of economically disadvantaged volunteers, as low income or unemployment can be the reason for insignificant assessment of all risks by volunteers.

It is true that payment wasn't the principal factor in all trials devoted to examination of volunteers' motivation. Thus, Berg et al. (US) found out that altruism was the basic motive to participate in trials of novel drugs among the majority of participants (72%) [6]. Interest in science and medicine, curiosity, social connections and access to free medical aid are commonly considered as secondary motivators [7], which are widely spread among Chinese healthy volunteers [8]. Moreover, over 80% of participants of Pfizer-supported trial reported competence and friendliness of researchers, contribution to science and aid for future patients as additional factors, which are significant while taking decisions [7].

To make a certain portrait of healthy volunteers visiting our research center, anonymous surveying was performed. The survey consisted of several blocks: social and demographic characteristics (gender, age, education, employment, marital status, number of children), activity of participation in clinical research (employment period, number of trials per year, etc.), motivating factors and barriers while taking a solution about participation in the research, and system of payment *payment.*

The survey involved 83 subjects with 37 females and 46 males. The mean age was 34.8 and 33.4 years respectively. 56.5% had higher education; 53.0% held steady employment; 9.6% were unemployed; 30.1% had a common-law marriage; 80.6% had children. Detailed social and demographic characteristics were described in table.

Speaking about motives of healthy volunteers to participate in research, financial compensation was the principal motive (94.0% of survey participants). Secondary motives involved as follows: being useful for the society (76.8%), free medical examination (64.2%), additional communication and expansion of horizons (55.6%).

In some aspects, the obtained results are concordant with the data from the foreign publications mentioned above, i. e. motivation of our volunteers does not differ from the one of volunteers from other countries.

BARRIERS TO PARTICIPATION IN CR

While taking decisions about participation in clinical research, healthy volunteers can commonly come across barriers which seem important to them. The reasons why people do not want to participate in CR have been studied for over 30 years. Thus, it is believed in some old publications that intervention-based health risks, adverse effects and burden in the form of lost time can be considered as barriers to taking a decision about participation [9–11].

Table. General social and demographic characteristics of survey participants (*n* = 83).

Type of data	Parameter, unit of measurement	Value
Demography	Men,%	44.6
	Women,%	55.4
	Age, M±SD, years	34.01±6.99
Social status	Education,% – Higher – Higher, not completed – Secondary, completed (11 classes) – Secondary, not completed (9 classes)	 56.5 24.1 8.4 10.8
	Married,%	30.1
	Children,% – none – 1 – 2 – 3 and more	 19.4 9.6 10.8 60.2
	Employment,% – Have a permanent job – Unemployed – Self-employed – Freelancer	 53.0 9.6 19.3 18.1

According to the results of more modern trials, risks associated with participation and possible adverse effects of the examined medicine were also taken as more significant barriers that prevailed over such motivation factors as 'aid for future patients' [5]. There are also data stating that volunteers were not ready for a more complex trial [7,12–14], in particular, for the ones that suggested performance of invasive procedures such as bone marrow biopsy and lumbar puncture. Only the minority agreed to change their decision when the amount of compensation is increased [15].

Healthy volunteers were rather ready to take a decision about participation if possible adverse effects included loss of hair, increase of weight, moderate pain within an hour and vomiting during a day. At the same time, such adverse events as one-in-a million chance of death, a small chance of renal failure and effect on consciousness were significant barriers to research participation. Among Chinese volunteers, an unexpected reason for refusal was a possibility to let relatives and friends know about participation in clinical research, and i/v administration of medicine [8].

During the mentioned survey of volunteers from our center, barriers that influenced taking a decision about participation included research schedule (87.7%), adverse effects of the examined medicine (87.3%) and a clinical center where the research is held (68.4%).

Particularly interesting was a response of volunteers regarding such a barrier as a clinical center. It can be supposed that conditions of staying and perhaps attitude to volunteers are quite different in every center, as this factor could be the reason for refusal from participation in CR almost in 70% of volunteers.

RESEARCH BURDEN AS VIEWED BY VOLUNTEERS

As far as the degree of safety for a healthy volunteer goes, protocols of CR can commonly be different from each other and include first-in-human administration of medicines, dose escalation study, finding dose-limiting toxicity, examination of medicines with possible immune-mediated adverse events that occur long-term (8–10 weeks) [16], trials conducted at later stages of drug development process, for instance, to assess effects of food, drug interaction, bioequivalence of medicines and biosimilars.

It has been established in the study by Jill A. et al. that the majority of participants can classify phase I research by a degree of risk (moderate, high or extremely high). However, the majority believes that they are personally protected from harm [17].

We were also interested how the nature of Phase I trial influences the decision of volunteers about participation. It has been found during the survey of 79 subjects that 88.3% of those interviewed paid attention to the nature of the research and its potential harm; it is of no importance for 11.5% of people. Those who responded 'yes' were subdivided into two almost equal groups in terms of gender composition (50.7% of males, 49.3% of females) with the mean age of 34.5±7.1 years. The majority of them had a high level of education (59.4% had a higher education, 21.7% had incomplete higher education, 10.4% had secondary education, 8.7% had incomplete secondary education (9 classes)) and no family (66.7%).

SOURCES OF INFORMATION ABOUT CONDUCTED CR — WHAT INFLUENCES THE CHOICE OF A VOLUNTEER?

It is no secret that healthy volunteers have a social network of their own where they exchange data about regional CR, nature of examined medicines regarding their potential tolerability and adverse events that developed (or not developed) among those who have already participated in hospitalization and have been on outpatient supervision. The information is commonly essential when potential volunteers (including beginners) decide about screening at a respective center.

When healthy volunteers were introduced into the database of our center in 2022, over 90% mentioned social network when answering a standard question about the source of data about our institution and conducted study (until coming across the form of informed consent by those volunteers who have already undergone screening). Others mentioned relatives, family members and friends.

Candidates commonly prefer to participate not in the beginning of the trial but following results of the first hospitalizations. Thus, we have found out an interesting fact indirectly confirming as follows: we analyzed qualitative composition (as related to these parameters) of participants who underwent screening from the first (a half of the set of participants of the entire protocol) and subsequent cohorts during the research of 2022.

39 subjects who visited the center for the first time underwent the screening. 14 subjects (10 women and 4 men with the mean age of 31.9 years) wanted to participate in 2 first cohorts, whereas 21 younger (with the mean age of 26.8 years) women (14 subjects) and men (7 subjects) took part in two subsequent hospitalizations. During the interview prior to signing an informed consent form it has been found out that almost all candidates for participation at the start (13 subjects out of 14) had the experience of participation in CR, knew about inclusion of volunteers from social networks into research, and in 70.9% of cases asked an investigator about potential risks of the examined medicine. 2 participants explained their motivation saying that 'if women are involved, the research can't be harmful' and that 'what safety we are talking about if we are mothers of 2 children and have a mortgage?'.

During the interview with volunteers who wanted to take part in cohorts 3 and 4 it has been found out that in 80.9% of cases they have already been told about good tolerability by previous research participants from social networks, whereas only 47.6% of people asked an investigator about the potential danger of the research. All volunteers also had experience of participating in CR at other centers.

Survey of the last candidates (4 subjects) for hospitalization into small cohort 5 who were first-time visitors of our center is remarkable. They made a conscious decision to participate as their husbands (2 women with experience in taking part in CR having 4 and 3 children respectively) and friends (1 woman with no experience and 1 man with experience in participation in CR having no children) took part at early stages of the research. Only a candidate with no experience in participation in CR was really interested in detailed research procedures and safety of a medicine.

ADVERSE EVENTS AS VIEWED BY VOLUNTEERS

In the light of examination of safety of medicines, another, more significant problem arises. It is about reporting of any symptoms developed among volunteers during phase I research. Meta-analysis of the research has shown that adverse effects represent a common phenomenon in similar trials almost in two-thirds of healthy volunteers; many of AE are moderate and/or disappear rather rapidly [18].

Actual adverse effects of the studied medicine can be distorted when healthy volunteers failed to fulfill their obligations prior to the research [19,20], without reporting the AE. It has also been established that almost 30% of the participants either postponed reporting or totally concealed the AE from the

research personnel [21]. The reasons for concealing information about AE included as follows: volunteers forget/poorly remember their symptoms, have difficulties with verbalization of changes within their body, fear of being excluded from the research if they report the AE [22,23]. Healthy volunteers are commonly difficult to understand whether their decision about termination of participation in the research is an adequate reaction to AE for the purpose of own safety.

The reasons for AE underreporting primarily included the participants who undermined the process of clinical research due to their financial motivation [24–26], as healthy volunteers who registered in clinical research to obtain compensation could hardly report an AE if these can result in early discharge or partial payment only.

Based on experience obtained in our center, we also came across a problem when a volunteer could be excluded from a trial when COVID-19 was reported. This aspect was not mentioned in the informed consent form. Many participants regretted that they were frank about the disease they had. They also said that if the informed consent form contained the condition about non-payment of the remaining part of compensation in case of the disease, they would conceal the fact about the disease or report it during the last visit only.

On the other hand, lack of proportional payment can make participants fabricate or exaggerate the rate of AE to leave the research early with full compensation. This is true for the volunteers who wanted parallel participation in several studies.

VOLUNTEER'S DIARY: SHOULD IT BE FILLED OR NOT?

At our center, 64 participants were interviewed when the diary was issued to detect their attitude to the document. Based on the survey, all volunteers were subdivided into the following groups:

1. Those who won't' fill in the diary (5 subjects).

2. Those who would rather fill in the diary (6 subjects).

3. Those who will definitely fill in the diary (53 subjects).

Two participants from the first group believed that 'the diary was useless paper', three of them said that 'they had never had or could have an AE'.

When participants of the second group were asked in what cases they would still make a record in their diaries, 13 people responded that they would report only those events that were significant in their opinion, whereas 6 of those interviewed provided an unexpected response: 'It depends on a clinical research center. It happens that reporting an AE can make an investigator disappointed as he or she doesn't want to fill it in'.

6 people tried not to make written notes without a preliminary interview with an investigator. One woman who took part in CR multiple times laughingly said that 'she is hardly a writer, so she shouldn't be given a diary'. She meant previous participation in a protocol when she left the following note: 'heel scratching'. She just wanted to reveal all available information for the purpose of scientific research.

Many of those from the third group were aware of their liability towards validity of data about the examined preparation (18 subjects) and fulfillment of labor obligations to the Sponsor (35 subjects).

Interview results of 131 healthy volunteers from the USA described their experience with AE including the reasons why they reported or failed to report symptoms [27]. The interviewers found out that the participants had three basic justifications of their behavior when AE reports were composed: economic, health- and data integrity-oriented. The results of the clinical trial display that behavior of those who reported the results is more complex that it was assumed with the previous portraits of healthy volunteers. In the majority of cases, they are ready to refuse from full compensation if, according to them, reporting their symptoms threatens their own safety or research validity.

PAYMENT FOR PARTICIPATION IN CR

It is already common practice both in our country and abroad that healthy volunteers who participate in early phase clinical research are provided financial compensation. The amount of financial compensation is one of the main objects of ethical expertise in early phase CR. Determining the volume of respective payment that would allow to attract enough participants and be proportionate to the provided load, on the one hand, and avoid excessive effect (pressure) while taking a participation decision, on the other hand, is quite controversial. It is the subject of loud discussions in mainly foreign publications devoted to bioethics or clinical research [28–30].

In Russia, the practice of ethical committees and research centers almost lacks any consistency with regard to this matter. Regulatory recommendations are lacking as well. For instance, recommendations to calculate an amount of compensation considering the research design and scope of procedures, recommendations regarding the procedure for paying payment in case of early termination of participation due to various reasons. In fact, every research center calculates the amount of payment taking into account its own ideas and experience with volunteers.

We witnessed situations when the amount and procedure of payment within the same research in various centers of the same city were significantly different.

Russian investigators of early phase CR are well aware of phase 1-related recommendations of the British guidance [31], when it is established that the amount of compensation should correspond to the duration of stay of a volunteer in early phases, number of visits, and rate of research-associated discomfort. Meanwhile, the amount of payment should not depend on the degree of assumed risk associated with participation in CR. However, the question regarding if all our research centers follow the recommendations remains open.

It is interesting that the available literature contains very little data regarding how volunteers assess the adequacy of payments and what their expectations are based on. American authors suggested that volunteers should independently determine the amount of payment for several hypothetical trials and substantiate the decision. It was found out that apart from logistic aspects and temporary load, volunteers mentioned the degree of risk as a key factor that determines the amount of compensation [32]. We are well aware of recommendations of specialists in ethics as far as the issue goes, as the amount of payment should not depend on risk.

There is little evidence of actual amount of compensation for healthy volunteers. Thus, publication by Fisher JA et al. contains data about payments to healthy volunteers in the USA. Thus, payment per one research amounted from 150 to 13,000 US dollars. Meanwhile, less than 2,000, from 2,000 to 4,000, and over 6,000 US dollars were offered for participation in 22.9%, 42.3% and 14.7% of trials respectively. The median of annual earning among volunteers was 4,200 US dollars [33]. The authors concluded that the funds were not enough for adequate existing to rely upon participation in CR as the principal source of income.

Based on experience of conducted research at our center during the last year, it has been shown that volunteers could earn maximum 160,000 rubles each visiting our center only and

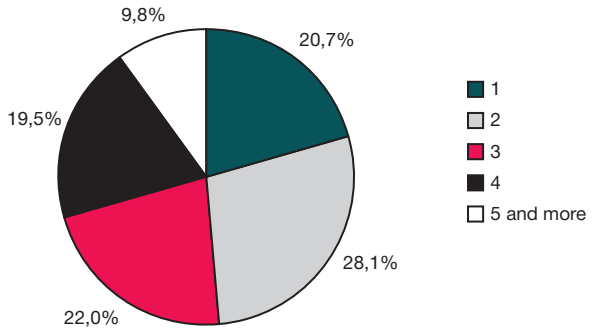

Fig. 1. The structure of replies to the following question 'How many times during a year do you averagely participate in clinical research?'

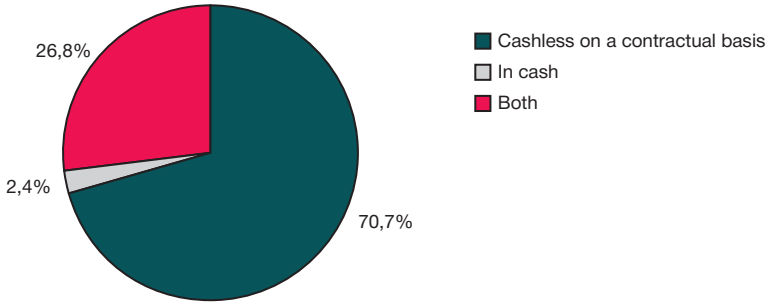

Fig. 2. The structure of replies to the following question 'How do you get your payment?'

observing the recommended timeframes between the trials. It is obvious that the conclusion made was similar to the one of American colleges.

Nevertheless, it is known that some volunteers misuse their participation by referring to (commonly even simultaneously) different early phase centers, trying to earn money with CR only [34] and becoming the so-called 'professional' volunteers. As a rule, the term is used by researchers in negative context.

PROFESSIONAL VOLUNTEERING

In the previous work, we described the over-volunteering and associated risks both for developers of novel medicines, and for volunteers, and ways of struggle with this phenomenon. We were also talking about the measures and procedures used in our research center to detect these cases [35]. Unfortunately, Russian researchers of early phase CR increasingly come across 'professional' volunteers and episodes of misused participation in phase I and bioequivalence CR. Our experience confirms the fact.

28.1% of those interviewed gave 4 and more replies to the following question: 'How many times during a year do you averagely participate in clinical research?' (fig. 1). This raises certain questions because as per recommendations of the Ministry of Health of the Russian Federation [36]*, which are basically followed by all developers while writing CR protocols, the washout period should constitute at least 3 months. In other words, almost one-third of volunteers misuse participation in CR. Men do it more frequently than women (55.4% vs 44.6% respectively, p=0.014).*

The reply to the question 'How do you get your payment*?' was revelation. In accordance with fig. 2, 29.2% of volunteers mentioned that they were* payment *in cash. In this context, conversation with a volunteer, who referred to the Pension Fund upon reaching a certain age to trace tax deductions, was remarkable. He was unpleasantly surprised that in some cases the deductions were absent.*

In our opinion, payment to volunteers should be paid based on the concluded agreement (contract). Apart from the necessity to follow the tax legislation, it can also prevent misuse of participation in CR by volunteers. Contractual relationships emphasize the seriousness and importance of following by volunteers of all requirements and limitations associated with early phase CR.

Thus, efforts to prevent misuse of CR participation by professional volunteers are enough to change the situation in future. We have to state that the problem of over-volunteering has the only effective solution. Unified registries of healthy volunteers (at least at the regional level) have to be created, which was actively reflected in some foreign regulatory documents [31,37]. If the Russian regulatory agency and developers of medicines are not ready to take the initiative as far as the issue goes, the leading (most authoritative) ethical committees and investigators can do it instead. However, the idea can hardly be supported by research subjects presenting a novel view on the problem by healthy volunteers.

CONCLUSION

It is necessary to conclude that the sector of volunteers' participation in early phase CR in Russia is currently in the state of early development. It acquires characteristics, which are inherent to mental features of our population. Tendencies to professionalism are combined with the Russian happy-go-lucky attitude, whereas scrupulous examination of an informed consent form is associated with sympathy towards an investigator and trust in the entire healthcare system. Philosophical perception of life is hardly blended with the common standard operational procedures. This is due to the lack of systemic principles of regulating motivation of CR participants.

There is only one conclusion. As an impossibility to create novel effective medicines without participation of healthy volunteers is an axiom, systemic examination of subjective factors of CR and methods of their influencing constitutes a pressing need of today.

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