https://doi.org/10.54500/2790-1203-2024-3-122-27-35
UDC 614; 614.2; 614:33
IRSTI 76.75.75

Original article

Insurance Management in Clinical Trials (International and Domestic Experience)

Gulnara Kulkayeva [1], Margarita Graf [2], Valentina Tarassova [3], Adlet Tabarov [4]

[1] *Chairman of the Board, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan, E-mail: gulnara1412@mail.ru*

[2] *Head of Clinical Development Center, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan. E-mail: m.graf@nrchd.kz*

[3] *Clinical Development Center Project Manager, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan. E-mail: v.tarasova@nrchd.kz*

[4] *Vice chairman of the Board, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan. E-mail: a.tabarov@nrchd.kz*

Abstract

The issue of insurance for clinical trial participants is one of the important factors in creating a "safe" research ecosystem. Clinical trials may encounter adverse outcomes, and researchers are focused on maintaining a balance between the safety of study participants and the bureaucratic obstacles in the legal aspect of the path to scientific discoveries

Objective. *Develop recommendations for improving Kazakhstan's clinical trials insurance system based on the analysis of best practices conducted.*

We have conducted an analysis of the experience of 14 countries on issues of insurance of clinical trials according to 3 parameters: stability of the insurance institution; regulation of the insurance issue; mechanism for reimbursement of insurance payments; and tariff policy.

Each country has its own standardized protocols and requirements for clinical trial insurance. Some countries make insurance "mandatory" by enshrining it in law (most European countries), while others make it advisory (USA, UK). Two forms of research insurance are practiced: "liability" of initiators and "accident" insurance for participants. Approaches to determining insurance limits also differ - some cover only insurance payments upon completion, while others set minimum coverage for an insured event. In Kazakhstan, a norm is regulated that obliges participants in clinical trials to be insured, but there is no mechanism, rules, or requirements for the process. The lack of clear requirements for the content of the document on life and health insurance for research participants is a barrier for sponsors.

Conclusion*. Based on the experience of international practices, it is necessary to consolidate a national model of insurance for clinical trials in Kazakhstan. The key aspects for promoting the clinical trials insurance system at the political level in Kazakhstan are the definition of insurance, insurance event, amount of insurance payments, insurance rates, the procedure for paying the insurance premium, the procedure for concluding the contract and its term, rights, and obligations of the parties to the contract and insured persons, the procedure for making insurance payments.*

Keywords: clinical research, subject insurance system.

Corresponding author: Graf Margarita, Head of Clinical Development Center, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan.
Postal code: Z05K5M0
Address: Kazakhstan, Astana, Mangelik El Avenue, 20
Phone: +7 7172 570-951 (1060), +7 701 915 9222
E-mail: m.graf@nrchd.kz

2024; 3 (122): 27-35
Recieved: 01-08-2024
Accepted: 09-09-2024

Introduction

Insurance is a critical component in clinical research, serving both as a regulatory requirement and a safeguard for participants. According to the Declaration of Helsinki, established by the World Medical Association, the welfare of participants in research involving human subjects is paramount. This principle mandates that researchers take all necessary measures to minimize potential adverse effects on participants' physical, mental, and social well-being [1].

In today's global environment, with the observed growth of clinical trials (from 2,408 trials in 1999 to 54,952 in 2022), insurance plays a pivotal role in establishing a "safe" research ecosystem. This growth underscores the necessity of ensuring that the principle of benefit outweighs risk for study participants [2]. Clinical trials may encounter adverse outcomes, as, for example, in studies with fialuridine drugs (NIH, USA, 1993), TGN1412 (TeGenero, UK, 2006), the results have significantly influenced changes in the rules and procedures governing clinical trials [3-4].

Countries are focused on developing affordable clinical research insurance systems that balance participant safety with legal and bureaucratic challenges in pursuing scientific discoveries. Sustainable insurance, which ensures the protection of research subjects' rights in cases of harm, has been shown to impact patient recruitment and boost interest in participation positively. The approach to clinical research insurance; the level of regulation of the issue; the amount of insurance payments, premiums; the judicial mechanism, and the claim process differ from country to country. On the one hand, countries implementing a national insurance system demonstrate a commitment to the development of the clinical research market, on the other hand, this is a barrier to international research, leading to financial costs on the part of the sponsor.

For Kazakhstan, the clinical research insurance system is not fully regulated, and today sets an important task for the country's politicians – to create sustainable conditions for the promotion of clinical research, including international ones. While Kazakhstan's legislation mandates life and health insurance for participants in clinical research, the mechanisms for implementing this requirement remain underdeveloped. This gap hinders the creation of a robust environment for clinical research and limits the country's ability to attract and facilitate international studies.

The objective of the review is to develop recommendations for improving the clinical trials insurance system in Kazakhstan based on the analysis of best practices.

Methodology

The clinical trials insurance systems of the USA, European countries (Germany, Sweden, Switzerland, Sweden, France, etc.), Russia and others (n=14) were analyzed. The assessment was carried out following the analytical scheme based on a set of relevant (significant) parameters: sustainability of the clinical trials insurance institute; regulation of the clinical trials insurance issue; mechanism for reimbursement of insurance payments with the establishment of presentation periods; and tariff policy in terms of determining the amount of insurance payments. The study materials were national regulatory legal acts, industry standardizing documents, and original articles on the issue under study over the past 3 years.

International practice of clinical trial insurance

In alignment with the standards of good clinical practice (GCP) in conducting clinical trials, countries adhere to the implementation of insurance policies at the national level. Each country has its standardized procedures for insurance and liability coverage related to clinical trials (Table 1). Some countries give insurance a "mandatory" ("permitted") character, securing it at the legislative level, as in most European countries, other countries – a recommendatory ("non-admission") (USA, UK). Two forms are practiced: – insurance of "liability" of the initiators of the study (sponsor, research team) and "from accidents" of the participants in the study. Approaches to determining insurance limits also vary – some require the initiators of the study to cover only insurance payments upon the fact, while others establish minimum coverage levels for insured events.

1/3 of the clinical trials market is in the United States and remains one of the main sources of global research [5-6]. In the United States, clinical trials insurance is not mandatory ("non-admitted") and is provided within the framework of the existing health insurance system (Affordable Care Act), and covers routine costs of medical care (visits to health workers, standard treatments, laboratory tests, supportive therapy, etc.) [7]. Since 2020, the Clinical Treatment Act (H.R. 913) has been passed in the United States, which requires all federal programs to cover routine costs associated with qualifying clinical trials (Phase I, II, III, or IV) that are conducted in connection with the prevention, detection, or treatment of cancer or other life-threatening conditions [8].

According to experts (D. Brettler et al., 2022), clinical trials conducted in the United States have a certain flexibility in the development of insurance programs. [9]. Typically, insurance policies are issued for 12 months, covering the anticipated activities of the sponsor within that timeframe. US companies conducting clinical trials involving humans outside the country face several problems: differences in insurance regulations, insurance payment mechanisms, and other processes in countries with their insurance systems. An important problem for the US insurance system is the lack of national standards for compensation for damage associated with clinical trials, which leads to denials of insurance for clinical trial subjects because the service "clearly does not meet the established standard of care."

Some U.S. states (including Pennsylvania and New Jersey) have "comparative negligence" statutes that 1) limit the amount of damages a research subject can recover if the research subject is partially responsible for the damages; and 2) allow a research subject to sue a party that is only minimally responsible for the damages [10].

The European experience of insuring subjects of clinical trials is related to the adoption in 2014 of the European Union Regulation on Clinical Trials No. 536/2014, which notes the responsibility of EU Member States (Article 76) for compensation for any harm caused to a subject as a result of his participation in a clinical trial conducted on their territory [11]. Along with this Regulation, individual national standards for insurance systems have been defined in the EU Member States. Approaches to ensuring participants in clinical trials vary, despite the general principles. This variation can be a barrier to conducting international clinical trials, as the lack of a unified insurance mechanism increases bureaucracy and extends the time

required to obtain necessary permits. Characteristic features of the insurance system in the EU Member States are the mandatory availability of insurance coverage for study participants [12]. Insurance is intended to provide compensation for any harm caused to the subject's health as a result of his or her participation in a clinical trial, and in practice insurance companies pay compensation only for specific damages incurred – the cost of treatment and loss of ability to work. Exclusions include worsening of pre-existing health problems unrelated to participation in a clinical trial; intentional harm to health caused by participants or the research team; and the event of withdrawal from the trial.

The insurance must cover the period from the inclusion of the first patient (screening) to the last visit, and also take into account the extended reporting period – the period during which the insurance company can be notified of harm caused to the research subject (in Germany – up to 10 years, in other countries - from 3 months to 10 years, and for studies involving children – more than 10 years).

The cost of clinical trial insurance is not set at a flat rate but varies based on several factors: risk (studies using non-invasive medical devices have lower costs than studies involving surgical interventions); duration of the clinical trial; number of study subjects; cohort of subjects (children and subjects with severe pre-existing diseases increase the cost). The cost of insurance is estimated from 5 to 30 thousand euros per clinical trial (average value – 17.5 thousand euros).

In Germany, Austria, and the Netherlands, participants in clinical trials are subject to compulsory accident insurance, while the systems of the Czech Republic, France, Greece, Portugal, Spain, and Poland are based on compulsory "liability" insurance for those conducting the trial, although the amount of insurance is often not fixed by law. In the UK, the insurance mechanism is voluntary, but in practice accident insurance is always required regardless of fault.

One of the first countries in the European Union to introduce insurance in clinical trials is Germany (since 1978), compared to all EU countries (since 1985). Insurance in Germany is issued in favor of the participant in the clinical trial with an insurance company authorized to operate in an EU member state. Insurance issues are regulated by the German Pharmaceutical Products Act (AMG) for medicinal products and the German Medical Devices Act (MPG) for medical devices [13]. Many sponsors also issue insurance for cases for which insurance is not required by law, for example, for new methods of examination and treatment [14]. A mandatory condition is a reasonable proportionality of the volume with the risks associated with the clinical trial (in the event of physical injury, deterioration in health, and death), and the minimum insured amount is 500 thousand euros per subject and at least 5 million euros per study protocol. Germany is also one of the EU countries that provides insurance for research using radioactive materials. The amount of the insurance premium is determined taking into account the medicinal product, the phase of the clinical trial, the number of study subjects, and the amount of the insurance sum, and ranges from 30 to 400 euros per volunteer [15].

Since the adoption of the Federal Law on Research Involving Human Participants (HRA) in Switzerland in 2014, the minimum insurance amount is set depending on the categorization of research projects involving humans depending on the degree of expected risk to the participants (A, B and C): for risk class A (registered medicinal products, bioequivalence) no payments are made, for class B the amount for an accident (bodily injury) is 250 thousand euros (3 million euros per protocol), and for class C (for unregistered medicinal products) - 1 million euros (per protocol - 10 million euros) [16,17]. Damage that occurs during the term of the insurance policy is subject to insurance, and the extended coverage period is 120 months after the termination of the clinical trial. The amount of insurance premiums in Switzerland varies and depends on the number of participants, in the study, while the minimum value always remains reserved [18,19].

The Austrian clinical trial insurance system is regulated according to the industry standard Medicines Australia Guidelines for Compensation for Injury Resulting from Participation. This system, akin to practices in other countries, determines the amount of insurance compensation based on the nature, severity, and persistence of the harm sustained. The minimum insured amount for an accident under the protocol is 3.5 million euros per study protocol or 500 thousand euros for study participants [20].

The insurance system in Spain (Art Royal Decrece 561/1993) makes the sponsor responsible for taking out civil liability insurance, according to which, in the event of failure to fully cover damages, all participants in the study (the clinical trial organizer, the principal investigator, and the head of the clinical site) are jointly and severally liable, regardless of fault, for damage caused to the health of the clinical trial subject (during the study and for one year after its completion), as well as for economic damage directly arising from such damage [21,22]. Limitations on compensation are noted in relation to harm caused to the health of the subject if it is inherent in the pathology being studied or is part of the side effects of the drug prescribed for the specified pathology, as well as the development of the disease itself as a result of the ineffectiveness of the treatment. The minimum insured amount of civil liability in Spain is 30 million monetary units of the local currency (equivalent to 1,775.0 thousand dollars) for each study subject, in the form of a one-time compensation [23]. In the event that such compensation is established as a permanent or increasing annual income, the coverage limit of such insurance will be no less than 3 million monetary units of the country's currency per year (177.5 thousand dollars) per subject of the clinical trial.

A difference is the Swedish experience, where there is no statutory regulation on insurance, but the Swedish Medicines Association provides sponsors with insurance through a group mechanism [24]. This mechanism provides insurance limits on a group basis, so that companies share the limits within the pooling agreement, rather than having a specific limit for their specific trial. With this approach, insurance payments depend on an adequate policy for setting limits available at the time of the claim. This approach may result in claims against the sponsor of one clinical trial leaving other sponsors without sufficient protection.

In the UK, clinical trial insurance policies are optional and are available in two ways: Fault Policies – legal costs, expenses, and compensation awarded to litigants as a result of negligence or lack of due care; and Non-Negligent Harm – compensation is paid following guidelines to participants who have suffered harm [25]. This insurance must demonstrate a causal relationship to the harm. The Association of the British Pharmaceutical Industry (ABPI) has published guidance setting out the distinction between compensation for Phase I (healthy volunteers) clinical trials and Phases II, III, and IV.

These guidelines apply to all clinical trials since 2015. For Phase I clinical trials that do not involve direct therapeutic benefit to the subjects (healthy volunteers and patient volunteers not suffering from the target disease), warranties and legal obligations to pay compensation in the event of harm arising from participation in the clinical trial are required. Compensation is provided for personal injury arising from negligence on the part of the research team, defect in service (failure to meet safety expectations), and other causal relationships. The amount of compensation is calculated based on the amount of damages normally awarded for similar harm by an English court if liability is accepted. Compensation may be reduced to the extent that the volunteer is partly responsible for the harm (or if the volunteer has received equivalent payment for such harm under any insurance policy taken out by the company in favor of the volunteer). The recommended minimum level of insurance cover (since 2012) is set at £5 million in total per protocol for first-in-human studies, reducing this to a minimum of £2,5 million in total per protocol for other types of studies [26]. The standard for the duration of insurance coverage (recommended) is up to 3 years after completion of the study.

For Phase II, III, and IV trials, the Association of the British Pharmaceutical Industry advocates a simple and expeditious procedure for the provision of compensation for harm arising from participation in clinical trials [276]. Although there is no legal obligation, compensation should be paid to trial subjects who suffer physical injury (including death). Compensation should be paid if, on the balance of probabilities, the harm was attributable to the administration of the investigational medicinal product (except in Phase IV) or to any clinical intervention or procedure covered by the trial protocol, and only for the more serious harm of a long-term and disabling nature (including exacerbation of existing disease), and not for temporary pain or discomfort or less serious or treatable complaints. Compensation should also be paid to a child who suffers harm in utero when the subject's mother participates in a clinical trial. It is stipulated that compensation should not be paid (or should be reduced) where there are significant departures from the trial protocol; in the event of a wrongful act or default by a third party, including the failure of a physician to adequately respond to adverse reactions; as well as due to the negligent behavior of the patient himself. The mechanism for determining the amount of compensation is flexible, which can be reduced or excluded taking into account the seriousness of the disease, the degree of likelihood of adverse reactions, etc.; as well as taking into account the risks and benefits of the established treatment compared with known or investigational drugs, and requires taking into account the circumstances of the individual patient.

The Brazilian experience in terms of compensation for damages resulting from clinical trials, which is also enshrined in law, is interesting. As specified in PANDRH-GCP, the sponsor is responsible for providing insurance coverage for any unforeseen damage to study participants [28]. Normative documents do not limit liability and compensation for damages, even in cases where this is provided for in the Clinical Trial Agreement (CTA) [29]. Insurance provides for two types of compensation: free comprehensive medical care (immediate and deferred, with the term for the latter not regulated), as well as compensation for damages (for physical and psychological injuries). The investigator, sponsor, and clinical site are fully responsible for medical services during the study, while liability for compensation for damages is not defined [30]. Brazilian legislation does not establish economic losses, the mechanism for receiving insurance payments, or the amount of compensation. The insurance system does not distinguish between “no-fault” compensation. It also defines the possibility and participation of subjects in the study without insurance coverage or by determining an alternative insurance option. But in this case, the research subject bears a double burden - the risk of participating in the study and insurance against possible economic losses.

Despite the rapid growth of the clinical research industry in India (7-10 thousand annually), which is also associated with the possibility of recruiting a large number of research subjects (16% of the world's population lives in this country), the clinical research insurance system is poorly developed [31]. Professional liability insurance for researchers is a common practice, but it does not protect health workers from compensation for claims related to participation in a clinical trial. The system sets minimum and maximum limits, and the insured amount averages from 1 to 20 million, and both the costs of protection and claims are paid under the policy within the policy limits. The insured amount, as in the EU countries, depends on a number of factors, including the size of the study, the phase of the study, the financial stability of the organization conducting the study, the type of drug or device being studied, and the demographic characteristics of the subjects on whom the studies will be conducted [32].

In the report by K. Sridharan et al. (2016), the results of the assessment of insurance documentation by the Ethics Committees of India were presented, in which many shortcomings were found - lack of coverage for the entire duration of clinical trials; the presence of provisions that make it difficult to pay compensation to study participants, etc., identifying these areas as priority areas for improvement in these issues [33].

According to Chinese law, clinical trial insurance is mandatory to cover treatment costs and provide appropriate compensation for subjects harmed by the study drug. However, there is no requirement for local insurance for this purpose (Chinese companies have not offered such services until recently), and it is carried out within the framework of global clinical trial insurance, which includes China [34-35]. This approach to the insurance system has expanded the horizons of clinical trials, with 27,7% of global clinical trial activity in 2022 occurring in China [36].

In Latin America, clinical trial insurance is also not mandatory, but many bioethics committees, especially in Argentina, occasionally request proof of insurance as part of their document review when approving clinical trials. The increased demand for insurance has led to an increase in clinical trial insurance in local markets.

In Australia (eg NSW Public Health Organisations), insurers must be approved by the Australian Prudential Regulation Authority, or an overseas insurer with a minimum Standard and Poor's (or equivalent) credit rating of A- or above. The policy must provide coverage for study subjects for at least A$20 million per occurrence and in aggregate per year [37, 38]. The policy must not include a deductible or self-insurance amount exceeding A$25,000 for each claim or series of claims arising from the same underlying cause.

Russia has taken the path of building a system of compulsory insurance for clinical research. The Law on the Circulation of Medicines defines the object of insurance as the property interest of the insured person associated with harm to his life or health as a result of clinical trials of a medicinal product [39].

Insured events are the death of the insured person or deterioration of his health, including those leading to the establishment of disability, if there is a causal relationship between the occurrence of this event and the participation of the said person in the clinical trial. When researching a biomedical cell product, the initiators of the research refer to the relevant law [40].

The standard rules establish the amount of insurance payments - in the event of the death of the insured person - 2 million rubles (22.5 thousand US dollars), in the event of deterioration of health resulting in the establishment of disability from 500 thousand to 1.5 million tenge (3.5 - 17 thousand US dollars) depending on the disability group, and also in the event of deterioration of health, but not resulting in the establishment of disability - no more than 300 thousand rubles (3.5 thousand US dollars) [41]. The amount of the insurance tariff is determined depending on the purposes of the clinical trial, for example, to establish the safety of a drug for patients from among healthy volunteers - 9.811 rubles (US), to select optimal dosages and course of treatment - 3.804 rubles (US), etc. The rules also regulate insurance coefficients, which differ depending on the number of patients and are built on the principle - the higher the number of patients, the lower the coefficients, for example, when insuring up to 50 patients - 1.0, and when insuring over 800 patients - 0.7. The insurance premium is determined depending on the insurance tariff.

The insurance payment under the contract is made regardless of payments due under other types of insurance, including compulsory insurance, as well as in the order of social security and compensation for damage (patients' demands for compensation for damage in the form of a property claim following the civil legislation of the Russian Federation).

Kazakhstan's realities in building an insurance system for conducting clinical trials

In Kazakhstan, the insurance of subjects of clinical trials is carried out in practice within the framework of general insurance activities; there are no rules regulating the insurance of subjects of clinical trials [42]. The Code of the Republic of Kazakhstan "On Public Health and the Healthcare System" defines the mandatory condition for conducting interventional clinical trials as the execution of documents on the life and health insurance of the research participant (civil liability insurance contract, Insurance Policy). Responsibility for the insurance of research subjects is determined by the GCP Rules, which also guarantee legal and financial support from the sponsor to researchers or a medical organization in the event of claims related to the study, except for those claims that arose as a result of intent or negligence on the part of the researcher or members of the research team [43]. The formation of a policy on insurance activities in the field of clinical trials does not lie within the competence of the authorized representative in the field of health.

The Rules for Conducting Clinical Trials regulate the provision of a Standard for the Activities of Bioethics Commissions, which defines the content of a document on life and health insurance for a research participant - but this document has not yet been developed [44]. The lack of clear requirements for the content of a document on life and health insurance for research subjects is a barrier for sponsors (especially when conducting international clinical trials). The industry needs to develop requirements for the process of insuring research subjects - from determining the size of the insurance rate and the insurance amount in the event of death, deterioration of health, resulting in disability, etc.; to a mechanism for determining cause-and-effect relationships and rules for compensation by insurance companies.

The imputed system of professional liability insurance for healthcare professionals does not include the issue of "insurance of the liability of researchers and protection of their interests." This regulatory document specifies responsibility for failure to perform, improper performance of professional duties of healthcare professionals, resulting in varying degrees of severity of health and death, as well as mechanisms for protecting their interests, without taking into account the specifics of research activities [45].

The clinical research system of Kazakhstan requires regulation of the issue of insurance (of participants in clinical research), in the construction of which it is rational to refer to the experience of countries with stable systems in the global community.

The key areas for creating a clinical research insurance system in Kazakhstan are as follows. It is rational to create it within the framework of the existing research infrastructure of the country through regulation by national rules. Countries are given the competence to establish national rules for insurance conditions - definition of the concept of "insurance" and "insured event", the number of insurance payments, insurance rates, the procedure for paying the insurance premium, the procedure for concluding the contract and its term, the rights and obligations of the parties to the contract and the insured persons, the procedure for making insurance payments.

Today, the definition of "clinical research insurance" is understood as "a risk transfer instrument in which one organization (the policyholder) transfers its risks (with exceptions) to another entity (the insurer) through an agreed payment and contractual agreement." In turn, an exception is understood as "an instrument by which the insurer limits the amount of risk that the policyholder can transfer to it." The essence of this insurance is to provide the policyholder with a reserve against claims from patients who suffered during a clinical trial.

This conceptual apparatus defines all the components of the process that must be included when building an insurance system and includes:

- Defining the vector to which the insurance coverage will be directed - insurance of damage suffered by the subject of a clinical trial and/or insurance of the professional liability of the researcher. Several countries adhere to the second type, implying that it covers all the risks of a clinical trial.

- Defining the type of compensation to which the subject of a clinical trial is entitled - medical care in the event of adverse effects (except for short-term ones) or financial compensation for psychological, social, and economic damage.

- Setting the limit of coverage of an insurance event in the current practice can be based on the approach of "legal liability" (as in the USA) or "no-fault" (some EU countries). It is necessary to set these limits by the risks, as well as the criteria for setting the limits of these amounts (standard compensation amounts). A number of insurance systems have developed a special fair approach, according to which the amount of payments is calculated depending

on risk factors (age of the patient, his health condition at inclusion and the phase of the study, etc.). When determining the compensation mechanism, stakeholders often rank financial costs based on the phase of the clinical study - the amount of insurance payments for the early phases of the study is often higher. It is believed that subjects of phases 3 and 4 studies are exposed to less risk.

- Establishment of the insurance period - an extended reporting period, which determines the period after the expiration of the policy, during which the cause-and-effect relationships of damage as a result of the clinical study can be identified, and insurance payments are covered. In many countries, the definition of the extended insurance period is regulated by law, and in practice ranges from 3 months to 10 years (on average for the countries analyzed in this article up to 3 years).

- A list of the standard package of documents required to settle claims.

One of the important factors in building a clinical research insurance system is the overregulation of judicial practice - the mechanism for establishing causal relationships between the resulting harm or death (which may be caused by the natural progression of a disease) as a consequence of the actions of a medicinal product and medical device, or the negligent attitude of the research team when implementing the research protocol. It is rational to also provide for a "no-fault" compensation option when it is impossible to establish the fact of negligence/error on the part of the research team.

For the effective implementation of the clinical research insurance system, it is necessary to create a stable institutional basis - insurance companies operating in this area (registered or licensed in the country). Insurance companies must not only guarantee that the policies they provide are broad and comply with local and national rules (for international ones), but also be able to protect the interests of participants in the research process. Following international practice, several external factors are of great importance for insurance companies - a qualified research environment (researchers, medical organizations), the responsibility of study participants, a well-established legislative system, a legal basis for regulating activities, and requirements for insurers.

The system of compensation (payments) to subjects of clinical trials in court proceedings in many countries is considered through tort liability. In practice, this legal procedure, especially in cases of negligence on the part of health professionals, has disadvantages: high legal costs and labor-intensive process; compliance of the amount of compensation with the level of damage caused; high transaction costs; unknown level of risks and uncertainty in conducting research, etc.

The tendency of sponsors to attract multi-center, international clinical trials dictates the need to create a flexible legal framework for the formation of insurance conditions during clinical trials. Historically, the practice aimed at securing insurance issues following national regulations has become a certain obstacle to the conduct of international multi-center trials.

Conclusions

By adhering to the standards of good clinical practice (GCP), countries guarantee insurance for participants in clinical trials. Each country has its standardized protocols and requirements for how insurance is carried out and for covering liability associated with the conduct of clinical trials.

Based on the experience of international practices, Kazakhstan needs to establish a national insurance model for clinical trials. Key aspects to address in developing and promoting this system at the political level include the definition of insurance, insurance event, amount of insurance payments, insurance rates, the procedure for paying the insurance premium, the procedure for concluding an agreement and its terms, rights, and obligations of the parties to the agreement and insured persons, the procedure for making an insurance payment.

Conflict of interest. We declare that we have no conflict of interest.

Funding. It was carried out within the framework of the research project BR18574198 "Development of new approaches to the organization and conduct of clinical trials in the Republic of Kazakhstan. Creation of a unified system for coordination of clinical trials

Authors' contributions. Conceptualization – M.G.; methodology – M.G.; verification – V.T.; formal analysis – G.U., M.G., V.T.; writing (original draft preparation) – M.G., T.V.; writing (review and editing) - G.U., M.G., V.T., A.T.

References

1. Declaration of Helsinki of the World Medical Association, 1964 (with clarification 2008). Website. [Cited 10 Aprl 2024] Available from URL: https://www.mediasphera.ru/upload/medialibrary/Declaration_of_Helsinki.pdf?ysclid=lwmf727jpj782953421

2. WHO International Clinical Trials Registry Platform. Website. [Cited 11 Aprl 2024]. Available from URL: https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-trial-registrations-by-year-location-disease-and-phase-of-development

*3. Kaur R.J., Singh S., Sidhu P., Sharma P.K. TGN-1412 and BIA-2474 Trials with Tragic End: Lessons Learnt To Make Clinical Trials Safer. Rev Recent Clin Trials 2018; 13(4): 252-256. [*Crossref*]*

*4. Eddleston M., Cohen A.F., Webb D.J. Implications of the BIA-102474-101 study for review of first-into-human clinical trials Br J Clin Pharmacol 2016; 81(4):582-6. [*Crossref*]*

5. Statista (COPE). Website. [Cited 17 May 2024]. Available from URL: https://www.statista.com/statistics/732954/global-clinical-registered-studies-by-location/

6. Zhuravlev K, Nayanova O. Clinical Trials in the USA, 2019. Website. [Cited 17 Aprl 2024] Available from URL: https://accellclinical.com/clinical-trials-in-usa/

7. Clinical trials handbook. United States of America, Baker & McKenzie 2019:20. Electronic resource. Access mode: https://www.bakermckenzie.com/-/media/files/insight/publications/2019/healthcare/america/dsc125067_clinical-trials-handbook--us.pdf

8. Clinical Treatment Act. H.R.913 - 116th Congress (2019-2020): January 30, 2019. Electronic resource. Access mode:

https://www.congress.gov/bill/116th-congress/house-bill/913

9. Brettler D. For Global Human Clinical Trials. Insurance&Risk Management: For Global Human Clinical Trails, 2018: 6. Electronic resource. Access mode: https://www.connerstrong.com/wp-content/uploads/2018/03/1468CSB-LS-Clinical-Human-Trial-Article.pdf

10. Kregler J., Butler L. Global Effort: Navigating the Intricacies of Insuring International Clinical Trials, 2022:4. Electronic resource. Access mode: https://www.chubb.com/content/dam/chubb-sites/chubb-com/us-en/business-insurance/global-clinical-trials/documents/pdf/Chubb_Multinational_LS%20Advisory_051622.pdf

11. Regulation (EC) No 536/2014 of the European Parliament and of the Council on clinical trials of medicinal products for human use, 16 April 2014. Available from URL: https://mknc.ru/contents/posts/9260000/9260079/document9260079.pdf?ysclid=lwdvsyx36x961985735

12. Private Vs Public Health Insurance In Germany [English Guide], 2024. Website. [Cited 5 Aprl 2024] Available from URL: https://www.johner-institute.com/articles/johner-institute/insurance-for-clinical-investigations/#:~:text=In%20Germany%2C%20the%20minimum%20sum,compensation%20for%20pain%20and%20suffering

13. Federal Law Gazette. Medicinal Products Act (Arzneimittelgesetz – AMG): 19 July 2023, №197. Electronic resource. Access mode: https://www.gesetze-im-internet.de/englisch_amg/

*14. Renner M., Anliker B, Sanzenbacher R, Schuele S. Regulation of Clinical Trials with Advanced Therapy Medicinal Products in Germany. In: Galli M., Serabian M. (eds). Regulation Aspects of Gene Therapy and Cell Therapy Products. Advances in Experimental Medicine and Biology, 2015; 871. [*Crossref*]*

15. Federal Institute for Drugs and Medical Devices. Website. [13 May 2024]. Available from URL: https://medical-journal.kz/index.php/mua/Template-for-a-review-article

16. Global Experiences from Regulatory Sandboxes. Finance, Competitiveness and Innovation Global Practice. The World Bank Group, 2020; 8:87. Electronic resource. Access mode: https://documents1.worldbank.org/curated/en/912001605241080935/pdf/Global-Experiences-from-Regulatory-Sandboxes.pdf

17. Schott M., Grossniklaus Jan, Bär & Karrer. Clinical Trials: Overview (Switzerland), Thomson Reuters Practical Law, Global Guide, 2024: 24. Electronic resource. Access mode: https://uk.practicallaw.thomsonreuters.com/w-039-1860?transitionType=Default&contextData=(sc.Default)&firstPage=true

18. Kristina M.L. Acri née Lybecker, Barua B. Universal Insurance for Pharmaceuticals in Switzerland and the Netherlands, 2019: 62. Electronic resource. Access mode: https://www.fraserinstitute.org/sites/default/files/universal-insurance-for-pharmaceuticals-in-switzerland-and-the-netherlands-execsum.pdf

19. Caniza V., Hobson J., Livne O., Calderón C. Life Sciences 2024: Switzerland: Chambers and Partners, 2024. Website. [17 May 2024]. Available from URL: https://practiceguides.chambers.com/practice-guides/life-sciences-2024

20. Hebenstreit S., Cepic M, Kröpfl M. Life Sciences 2024. Website. [17 May 2024]. Available from URL: https://practiceguides.chambers.com/practice-guides/life-sciences-2024/austria

21. Decree Governing Clinical Trials of Medicinal Products, Ethical Committees for Medicinal Products Research and the Spanish Register of Clinical Trials (Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos): 2015, 1090/2015. Electronic resource. Access mode: https://www.boe.es/buscar/doc.php?id=BOE-A-2015-14082

22. Gerboles A, Bailach J., Gonzalo C., Martinez J. Life Sciences 2024. Website. [18 March 2024]. Available from URL: https://practiceguides.chambers.com/practice-guides/life-sciences-2024/spain

23. Rowena Byrne-Jones. Clinical Trials Liability Insurance. A detailed review of cover and impact, 2020:9. Electronic resource. Access mode: https://assets.crawco.com/docs/uk-resource-2020-q3-Report-Clinical-Trials.pdf

24. Sweden Clinical Trials Support Service Market Analysis. Website. [18 March 2024]. Available from URL: https://www.insights10.com/report/sweden-clinical-trials-support-service-market-analysis/

25. Leadley J., Gillert J. Clinical trials handbook: United Kingdom, 2019:10.

26. Guidance on insurance and compensation in the event of injury in Phase I clinical trials. Guidance developed by the Association for the British Pharmaceutical Industry, the BioIndustry Association and the Clinical Contract Research Association in consultation with the Department of Health and the National Research Ethics Service, 2015: 10. Electronic resource. Access mode: https://www.abpi.org.uk/publications/insurance-and-compensation-in-the-event-of-injury-in-phase-i-clinical-trials/

27. Clinical Trial Compensation Guidelines. Association of the British Pharmaceutical Industry. 2014, 8. Electronic resource. Access mode: https://www.abpi.org.uk/publications/clinical-trial-compensation-guidelines/

*28. Chingarande G.R., Moodley K. Disparate compensation policies for research related injury in an era of multinational trials: a case study of Brazil, Russia, India, China and South Africa. BMC Medical Ethics, 2018; 19: 8. [*Crossref*]*

29. Kashiwabara P., Trojan V., Vicenti G., Mezher G. Life Sciences 2024. Website. [18 March 2024]. Available from URL: https://practiceguides.chambers.com/practice-guides/life-sciences-2024/brazil

30. Brazil Clinical Trials Support Service Market Analysis, 2024: 37.

*31. Kalikar M.V, Dakhale G.i, Sinha V., Giradkar A. Analysis of clinical trial agreement and insurance policy submitted to the ethics committee of a tertiary care teaching institute in central India. Perspectives in Clinical Research, 2021: 13(3): 151-154. [*Crossref*]*

*32. Vennu V., Saini P. P. India's Clinical Trial Regulatory Changes, Indian Researcher?s Awareness of Recently Changed Regulations, and the Impact of the New Drugs and Clinical Trial Rules: A Review. Indian J Pharm Sci, 2020; 82(5): 726-740. [*Google Scholar*]*

*33. Sridharan K., Deshpande S. at el. Knowledge about clinical trial agreement and clinical trial related insurance among Ethics Committee members: A cross-sectional survey. Perspectives in Clinical Research, 2016; 7(4): 191. [*Crossref*]*

34. Clement Ngai, Elva Yao. Clinical trials handbook: China. Baker McKenzie, 2019:11. Electronic resource. Access mode: https://www.bakermckenzie.com/-/media/files/insight/publications/2019/healthcare/ap/dsc125067_clinical-trials-handbook--china.pdf?la=en

35. Zhang Shu, Zhu Dongyun, Qin Jie. Study on the rights and interests of subject in clinical trials. Public Policy and

Administration Research, 2019; 12(9). [Crossref]

36. China accounts for 27.7% share of global clinical trial activity in 2022. Website. [January 10, 2023]. Available from URL: https://www.clinicaltrialsarena.com/marketdata/china-accounts-for-27-7-share-of-global-clinical-trial-activity-in-2022/

37. Clinical Trials - Insurance and Indemnity. NSW Health, 2024: 22. Electronic resource. Access mode: https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2011_006.pdf

38. Global Clinical Trial Support Services Market by Service (Administrative Staff, Clinical Trial Site Management, Data Management), Phase (Phase I, Phase II, Phase III), Study Design, Indication, Sponsor - Forecast 2024-2030, 2024: 192. Website. [January 10, 2023]. Available from URL: https://www.asdreports.com/market-research-report-646182/clinical-trial-support-services-global-forecast

39. Federal Law of the Russian Federation. On circulation of medicines: 2010: 61-FZ. Website. [January 10, 2023]. Available from URL: https://wipolex-res.wipo.int/edocs/lexdocs/laws/en/ru/ru239en.html#:~:text=This%20Federal%20Law%20regulates%20relations,the%20Russian%20Federation%2C%20export%20from

40. Federal Law of the Russian Federation. About biomedical cell products: 2016: 180-FZ. Website. [January 10, 2023]. Available from URL: https://cis-legislation.com/document.fwx?rgn=86404

41. Об утверждении Типовых правил обязательного страхования жизни и здоровья пациента, участвующего в клинических исследованиях лекарственного препарата. Постановление Правительства РФ от 13 сентября 2010, №714. Режим доступа: https://base.garant.ru/12178762/

Ob utverzhdenii Tipovyh pravil objazatel'nogo strahovanija zhizni i zdorov'ja pacienta, uchastvujushhego v klinicheskih issledovanijah lekarstvennogo preparata. Postanovlenie Pravitel'stva RF (Model rules for compulsory life and health insurance of a patient participating in clinical trials of a medicinal product. Resolution of the Government of the Russian Federation) [in Russian], ot 13 sentjabrja 2010, №714. Rezhim dostupa: https://base.garant.ru/12178762/

42. On insurance activities. The Law of the Republic of Kazakhstan dated 18 December, 2000, No. 126.43. Available from URL: https://adilet.zan.kz/eng/docs/Z000000126_#:~:text=This%20Law%20shall%20define%20the,peculiarities%20of%20opening%2C%20licensing%20regulation%2C

44. On approval of the rules for conducting clinical trials of drugs and medical devices for diagnostics outside the living organism (in vitro) and the requirements for clinical bases and the provision of the state service "Issuance of permission to conduct a clinical trial and (or) testing of pharmacological and medicinal products, medical devices". Order of the Minister of Health of the Republic of Kazakhstan. : December 11, 2020, No DSM-248/2020. Available from URL: https://adilet.zan.kz/eng/docs/V2000021898/compare

45. On Amendments and Additions to Certain Legislative Acts of the Republic of Kazakhstan on Health Issues. Resolution of the Government of the Republic of Kazakhstan. On the draft Law of the Republic of Kazakhstan: dated June 29, 2022, No. 444. Electronic resource. Access mode: https://www.wto.org/english/thewto_e/acc_e/kaz_e/wtacckaz50a1_leg_3.pdf

Клиникалық зерттеулер жүргізу кезінде сақтандыру мәселелерін басқару (халықаралық және отандық тәжірибе)

Кулкаева Г.У. [1], Граф М.А. [2], Тарасова В.М. [3], Табаров А.Б. [4]

[1] Салидат Қайырбекова атындағы Ұлттық ғылыми денсаулық сақтауды дамыту орталығының Басқарма төрайымы, Астана, Қазақстан, E-mail: gulnara1412@mail.ru
[2] Клиникалық даму орталығының басшысы, Салидат Қайырбекова атындағы Ұлттық ғылыми денсаулық сақтауды дамыту орталығы, Астана, Қазақстан. E-mail: m.graf@nrchd.kz
[3] Клиникалық даму орталығы жобасының жетекшісі, Салидат Қайырбекова атындағы Ұлттық ғылыми денсаулық сақтауды дамыту орталығы, Астана, Қазақстан. E-mail: v.tarasova@nrchd.kz
[4] Басқарма төрайымының орынбасары, Салидат Қайырбекова атындағы Ұлттық ғылыми денсаулық сақтауды дамыту орталығы, Астана, Қазақстан. E-mail: a.tabarov@nrchd.kz

Түйіндеме

Клиникалық зерттеулерге қатысушыларды сақтандыру мәселесі «қауіпсіз» зерттеу экожүйесін қалыптастырудағы маңызды факторлардың бірі болып табылады. Клиникалық зерттеулер қолайсыз нәтижелерге тап болуы мүмкін және зерттеушілер зерттеуге қатысушылардың қауіпсіздігі мен ғылыми жаңалықтар жолындағы құқықтық аспектідегі бюрократиялық кедергілер арасындағы тепе-теңдікті сақтауға бағытталған.

Зерттеудің мақсаты: үздік тәжірибелерді талдау негізінде Қазақстанның клиникалық зерттеулерін сақтандыру жүйесін жетілдіру бойынша ұсынымдар әзірлеу.

Клиникалық зерттеулерді сақтандыру мәселелері бойынша 14 елдің тәжірибесін келесі 3 параметр бойынша талдау жүргізілді: сақтандыру институтының тұрақтылығы; сақтандыру мәселесін реттеу; сақтандыру төлемдерін өтеу тетігі және тарифтік саясат.

Әр елдің өзінің стандартталған хаттамалары мен клиникалық зерттеулерді сақтандыру талаптары бар. Бірқатар елдер сақтандыруға «міндетті» сипат беріп, оны заңнамалық деңгейде (Еуропа елдерінің көпшілігі), ал басқа елдер ұсыным бекітеді (АҚШ, Ұлыбритания). Зерттеуді сақтандырудың екі түрі қолданылады: бастамашылардың «жауапкершілігі» және қатысушылардың «жазатайым оқиғалардан» сақтандыру. Сақтандыру лимиттерін анықтаудағы тәсілдер де ерекшеленеді - кейбіреулері тек сақтандыру төлемдерін жабады, ал басқалары сақтандыру жағдайының минималды қамтуын белгілейді. Қазақстанда клиникалық зерттеулерге қатысушыларды сақтандыруды жүргізуді міндеттейтін норма реттелген. Алайда процесске тетік, ережелер мен талаптар бүгінгі таңда әлі де қарастырылмаған. Зерттеуге қатысушылардың өмірі мен денсаулығын сақтандыру құжатының мазмұнына нақты талаптардың болмауы демеушілер үшін кедергі болып табылады.

Қорытынды. Халықаралық тәжірибеге назар аудара отырып, Қазақстанда клиникалық зерттеулер жүргізу кезінде сақтандырудың ұлттық моделін бекіту қажет. Қазақстанда клиникалық зерттеулерді сақтандыру жүйесін саяси деңгейде

ілгерілетудің негізгі аспектілері: сақтандыруды, сақтандыру жағдайын, сақтандыру төлемдерінің мөлшерін, сақтандыру тарифтерін, сақтандыру сыйақысын төлеу тәртібін, шартты жасасу тәртібін және оның қолданылу мерзімін, шарт тараптары мен сақтандырылған тұлғалардың құқықтары мен міндеттерін, сақтандыру төлемін жүзеге асыру тәртібін айқындайды.

Түйін сөздер: клиникалық зерттеулер, субъектілерді сақтандыру жүйесі.

Управление вопросами страхования при проведении клинических исследований (международный и отечественный опыт)

Кулкаева Г.У. [1], Граф М.А. [2], Тарасова В.М. [3], Табаров А.Б. [4]

[1] Председатель правления, Национальный научный центр развития здравоохранения имени Салидат Каирбековой, Астана, Казахстан. E-mail: gulnara1412@mail.ru
[2] Руководитель Центра клинических разработок, Национальный научный центр развития здравоохранения имени Салидат Каирбековой, Астана, Казахстан. E-mail: m.graf@nrchd.kz
[3] Руководитель проекта Центра клинических разработок, Национальный научный центр развития здравоохранения имени Салидат Каирбековой, Астана, Казахстан. E-mail: v.tarasova@nrchd.kz
[4] Заместитель председателя правления, Национальный научный центр развития здравоохранения имени Салидат Каирбековой, Астана, Казахстан. E-mail: a.tabarov@nrchd.kz

Резюме

Вопрос страхования участников клинических исследований является одним из важных факторов при формировании «безопасной» исследовательской экосистемы. Клинические исследования могут сталкиваться с неблагоприятными исходами, и исследователи ориентированы соблюдать баланс между безопасностью участников исследования и бюрократическими препятствиями в правовом аспекте на пути научных открытий.

Цель исследования: Выработка рекомендаций по совершенствованию системы страхования клинических исследований Казахстана на основе проведенного анализа лучших практик.

Проведен анализ опыта 14 стран по вопросам страхования клинических исследований по 3 параметрам: устойчивость института страхования; регуляция вопроса страхования; механизм возмещения страховых выплат; и тарифная политика.

Каждая страна имеет собственные стандартизированные протоколы и требования к страхованию клинических исследований. Ряд стран придают страхованию «обязательный» характер, закрепляя его на законодательном уровне (большинство стран Европы), другие страны - рекомендательный (США, Великобритания). Практикуется две формы страхования исследования: «ответственности» инициаторов и «от несчастных случаев» участников. Различаются и подходы при определении страховых лимитов – одни покрывают только страховых выплаты по факту, другие - устанавливают минимальное покрытие страхового случая. В Казахстане зарегулирована норма обязывающая проводить страхование участников клинических исследования, но отсутствует механизм, правила и требования к процессу. Отсутствие четких требований к содержанию документа о страховании жизнь и здоровью участников исследования является барьером для спонсоров.

Выводы. Ориентируясь на опыт международных практик, в Казахстане необходимо закрепить национальную модель страхования при проведении клинических исследований. Ключевыми аспектами для продвижения на политическом уровне системы страхования клинических исследований в Казахстане выделяется: определение страхования, страхового случая, размера страховых выплат, страховые тарифы, порядок выплаты страховой премии, порядок заключения договора и срока его действия, права и обязанности сторон договора и застрахованных лиц, порядок осуществления страховой выплаты.

Ключевые слова: клинические исследование, система страхования субъектов.