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Research Article

Analysis of regulatory implementation of regulation 536/2014 by European Union countries and Ukraine regarding the examination of clinical trials data and information

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Abstract

The article presents the results of a comparative analysis of regulatory requirements for expertise of clinical trials documentation, submitted for regulatory authority and ethic committees' approval in EU member countries and Ukraine, outlining the main trends, considering the updated Regulation (EU) No 536/2014, which came into effect on January 31, 2023. Among the positive changes are simplification of safety reporting requirements, use of artificial intelligence in the process of clinical trials documentation examination for obtaining regulatory authority and ethic commission approval, introduction of a single portal for submitting materials for clinical trials, and functioning of database for the submission and review of initial Clinical Trial Application documents and obtaining authorization within the EU to facilitate the interaction between applicants and regulatory authority are highlighted. To harmonize Ukraine's regulatory requirements with EU legislation, it is advisable to use a single portal for data exchange and document submission for applicants in regards to clinical trials, regulatory authority and local ethics committees. This will expedite the examination process of clinical trial documentation and simplify the monitoring of document review progress.

Keywords

regulatory requirements, clinical trials, medicinal products, Good Clinical Practice, Regulation (EU) No 536/2014, initial Clinical Trial Application documents

Introduction

In light of the adoption and implementation from 31.01.2023 of the updated version of Regulation (EU) No. 536/2014 of the European Parliament and the Council as of 16.03.2014 on clinical trials of medicinal products for human use (hereinafter – Regulation No. 536/2014) and on the repeal of Directive 2001/20/EC on clinical trials of medicinal products, the study of approaches to optimizing regulatory requirements in the European Union (EU) becomes relevant. This Regulation aims to harmonize and simplify the procedures for conducting clinical trials in

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EU member states. The key tools for ensuring the transparency of clinical trials in the EU in accordance with Regulation No. 536/2014 have become a new portal for submitting data and information relating to clinical trials, a database used for submitting and reviewing applications for conducting clinical trials, as well as obtaining authorization within the EU. The database serves as a source of public information about processed applications for the examination of clinical trials information on the territory of the EU, starting from the moment of the decision to grant permission for its conduct and until the completion of the clinical trial with the inclusion of the obtained results in the database.

Currently, scientists from different countries have already analysed the main provisions and consequences of the adoption of the aforementioned Regulation No. 536/2014 for subjects in the field of medicinal products research. According to the results of research by Di Martino and van der Graaf (2022), it has been proved that non-compliance with the requirements of Regulation No. 536/2014 by EU member states makes it impossible for countries to participate in clinical trials. Since the adoption of Regulation No. 536/2014, most EU countries have amended their national legislation on this issue and related procedures. For example, in the Netherlands, the Declaration of Suitability of the test site has been revised, which is a mandatory document that clearly demonstrates such actions (Di Martino and van der Graaf 2022).

Already in 2023, several scientific articles were published in the German publication "Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz". Thus, Chase et al. (2023) analyze the first experience of implementing the new version of Regulation No. 536/2014, as well as the challenges and opportunities it creates for participants in clinical trials. Sudhop et al. (2023) had studied main characteristics of the new procedure for obtaining permission to conduct drug trials in accordance with the requirements of Regulation No. 536/2014, in particular the application process, including requirements for documentation, ethical aspects and data security. At the same time, the processes that regulate cooperation between EU member states, for example, procedures related to the process of approving applications for conducting clinical trials and exchanging safety data, are being studied in detail. Fuhrmann et al. (2023) outlined the key aspects of the first experience in complying with the requirements of Regulation No. 536/2014 from the point of view of non-commercial academic research, considering changes to the legislation such as documentation requirements, approval of ethics commissions and the possibility of cooperation between countries. Scientists highlight the advantages and disadvantages of updated clinical trial submission processes through the Clinical Trials Information System (CTIS) for the nonprofit academic research community. Raffauf-Seufert C. and Grass G. (2023) analyse the impact of Regulation No. 536/2014 on the evaluation of clinical trials by ethics commissions and the need to harmonize their work.

The modern view of the Ukrainian pharmaceutical community on regulatory requirements for examination of data and information relating to clinical trial is the result of many years of experience in their improvement and practical use both in Ukraine and abroad. Combining the needs of business and the interest of the state requires the introduction of simplified interaction of all participants in the process of clinical trials of new drugs, as well as improving the organization of their conduct in order to provide patients with innovative drugs and, as a result, the appropriate level of medical and pharmaceutical care. Examples of such interaction in the EU countries are the use of an electronic register for the centralized submission of initial Clinical Trial Application (CTA) documents by regulatory authorities, as well as a simplified reporting procedure, which frees sponsors of clinical trials from the need to provide completely identical information to different structures of the EU member states. However, the issue of the impact of new EU requirements from the point of view of the Ukrainian pharmaceutical community, as well as cooperation with the EU, requires additional research.

At the moment, the regulation of clinical trials in Ukraine is carried out in accordance with the requirements of the Law of Ukraine "On Medicinal Products" (1996), Order of the Ministry of Health (MoH) of Ukraine No. 690 as of 23.09.2009 "On Approval of the Procedure for Clinical Trials of Medicinal Products and Examination of Materials for Clinical Trials and the Standard Regulation on Ethics Commissions", as well as the Guidelines of the Ministry of Health of Ukraine CT-H of the Ministry of Health 42-7.0:2008 "Good Clinical Practice".

Ukraine, after the approval on 19.03.1997 by the Resolution of the Cabinet of Ministers of Ukraine No. 244 of "Action Plan for the Implementation of Requirements of EU Directives, Sanitary, Environmental, Veterinary, Phytosanitary Norms, International and European Standards", chose a course to harmonize national legislation with EU legislation. Ukraine also actively cooperates with the EU in the field of regulation for clinical trials conduction, as an example, the 2014 agreement between Ukraine and the EU on association, which provides for the harmonization of Ukrainian legislation with EU legislation, including norms for clinical trials conduction, can be cited as an example. Due to such harmonization, the types of documents to be submitted for approval of a clinical trial do not fundamentally differ in Ukraine and the EU and include: protocol of the clinical trial and the investigator's brochure according Good Clinical Practice (GCP); for researched medicinal product - dossier, batch certificate, GMP certificate and sample labeling of the researched medicinal product; patient's informed consent form, information about the medical centre and responsible investigators.

Considering the above, all innovations and changes in EU regulatory documents need to be implemented in Ukraine as well, therefore the discussion and study of this issue is relevant and socially significant.

The objective of this study is a comparative analysis of the regulatory requirements of EU countries and Ukraine and the outline of trends in the organization of examination of data and information relating to clinical trials in order to optimize such activities in Ukraine.

Study planning (methodology)

To achieve the study objective, a plan consisting of the following stages was developed:

- the first stage – analysis and generalization of regulatory requirements related to the examination of data and information relating to clinical trials in the EU and Ukraine using publicly available sources of information on the official websites of the relevant regulatory bodies of the EU and Ukraine, as well as scientific publications in this area. The analysis of the regulatory requirements of the EU countries and Ukraine was carried out on the basis of relevant legal documents regulating the process of examination of data and information relating to clinical trials;
- the second stage – determining the specifics of the work of the ethics commissions of the EU and Ukraine regarding the examination of clinical trials data and information, using sources of information on the official websites of EU and Ukrainian regulatory bodies, as well as relevant legal documents regulating the process of moral and ethical examination of clinical trials;
- the third stage – conducting an analysis of modern trends and changes occurring in the field of clinical trials in EU countries, assessing the requirements of Ukrainian legislation and developing proposals to improve the efficiency and speed of conducting the examination of data and information relating to clinical trials in Ukraine.

Materials and methods

The following regulatory documents were used as study materials: Directive 2001/20/EU dated 04.04.2001 "On the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use"; Regulation No. 536/2014 (2022); Guidelines for Good Clinical Practice E6(R2), put into effect on 14.06.2017; Directive 2001/83/EC of 06.11.2001 "On the Community code relating to medicinal products for human use" (EUR-Lex 2001); Commission Regulation (EU) 2022/20 of 07.01.2022 establishing the rules of application of Regulation (EU) No. 536/2014; Law of Ukraine "On Medicinal Products" No. 124/96-BP dated 04.04.1996; CT-H of the Ministry of Health of Ukraine 42-4.0:2020 "Good Clinical Practice", approved by order of the Ministry of Health of Ukraine No. 1023 dated 04.05.2020; Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009 "On the approval of the Procedure for conducting clinical trials of medicinal products and examination of materials for clinical trial and the Standard Regulation on ethics commissions" (Ministry of Health of Ukraine 2009).

Following methods of study, such as bibliographic, analytical and comparative, logical analysis and generalization were used.

Results

The process of pharmaceutical legislation and regulatory policy development is aimed at the application of new approaches to improve public health and requires the introduction of regulatory innovations to ensure the flexibility of the regulatory framework to support the access of health care entities to new treatment technologies (Tsang and Kerr-Peterson 2023). For example, the COVID-19 pandemic has increased the need for regulatory adaptability to optimize regulatory input mechanisms for clinical trials conduction, for the timely use of necessary health care resources without compromising patient safety and without compromising the quality and efficacy of drugs, and this position now resonates all over the world (European Medicines Agency 2015).

The pharmaceutical strategy of the European Commission (EC), the European Medicines Agency (EMA), the Council of the Heads of Medical Agencies (HMA), published in the first quarter of 2023 were provided in order to reform the general pharmaceutical legislation of the EU, taking into account the shortcomings that have appeared under the pressure of the COVID-19 pandemic. The proposals made, relate to improving patient access to medicines, reviewing the licensing system, and finding new antimicrobials in light of the global problem of antibiotic resistance. In addition, it is planned to revise the patent legislation by 2026 to ensure a balance between stimulating innovation on the one hand and market competition on the other.

An important aspect of the pandemic has been the rapid introduction of virtual interaction between doctors and patients to ensure the continuity of the treatment process. Among the advantages, it should be noted that it allowed to simultaneously maintain social distancing, thanks to the availability of technologies for connecting to the Internet almost everywhere, keeping electronic records of the patient's health, holding video conferences in real time, developing health applications for smartphones and using remotely connected data monitoring devices that are becoming more and more accurate and affordable. At the same time, in parallel with the adoption of "virtual medicine", the interest of sponsors in the possibilities of decentralized clinical trials, in which "virtual elements" are widely used, is growing, accelerating changes in the design of clinical trials (Van Norman 2021). The first fully web-based clinical trial was conducted by Pfizer in the REMOTE study (Research on Electronic Monitoring

of Overactive Bladder Treatment Experience) within the Investigational New Drug program back in 2011. During REMOTE, research participants did not visit the clinical trial site at all, their recruitment was conducted by researchers via the Internet, online questionnaires, electronic diaries and delivery of the study drug directly to the patient's home were used in the process (Orri et al. 2014).

In addition, as part of the modernization of GCP requirements, EU and US regulatory authorities recognize opportunities for innovative designs and new clinical trial methodologies. EMA, in accordance with the requirements of Regulation No. 536/2014, has developed a regulatory policy for complex tests, including advanced approaches to biostatistics and data processing. It is anticipated that the patient screening process may also change with the use of electronic informed consent as an option and new technologies to identify eligible participants in clinical trials, as well as new ways of collecting data during clinical trials (Clinical Trials 2023).

Taking into account the specificity of multicenter clinical trials, the increasing frequency of use of large volumes of data from various sources to make and support decisions by the regulatory authorities of EU member states, as well as the corresponding decisions on the access of new drugs to the EU markets, the quality of such data sources should be subject to a more thorough review to determine the reliability of the information used. During 2023–2026, the regulatory authorities of the EU member states plan to create the European Health Data Space (EHDS) – an ecosystem that will fully harmonize the electronic medical records of patients throughout the EU and facilitate the transfer of patient data between EU member states. The proposal regarding EHDS was made on 03.05.2022. It is assumed that access to this colossal database can be obtained both for the purpose of providing medical care to patients and for the implementation of secondary purposes, such as the development of health care policies, as well as conducting various types of research on the pharmaceutical market, etc. The proper functioning of EHDS in the near future requires the formation of clear rules for its use, general standards and practices, necessary infrastructure, rational approaches to management, requirements for data security and confidentiality (European Commission 2022b).

Changes are also expected to the process of clinical development and management of health data sources. In the previous version of Regulation No. 536/2014 dated 16.03.2014, the problem of creating an electronic register for the centralized submission of clinical trial results for consideration by regulatory bodies was updated. Whereas now this norm has become mandatory from 31.01.2023, according to the updated version of the Regulation. Regulation No. 536/2014 states that the EU database "shall be publicly available, unless one or more exceptions apply". Such exceptions relating to clinical trials are:

- protection of personal data;
- protection of confidential and commercial information, in particular with regard to the registration certificate of the medicinal product, may be justified in the case where there is no priority of public interest;
- protection of confidential communication between EU member states during clinical trial assessment;
- protection of the clinical trials supervision process by the EU member states (Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC 2022).

It should be noted that before the entry into force of the latest version of Regulation No. 536/2014, permission to conduct clinical trials could be obtained only in one individual EU member state, which led to an increase in the terms of consideration of data and information relating to clinical trial. Currently, it is possible to submit initial CTA documents for clinical trials to all EU countries for examination at the same time. Therefore, there is a constant improvement of the system of regulation of the drugs quality (Orri et al. 2014). It is obvious that the active development of the regulatory and legal environment in accordance with the urgent needs of citizens will in the long run have a positive impact on patients' timely access to efficient treatment.

EMA, EC and HMA, on the basis of a joint statement dated 25.01.2023 regarding Regulation No. 536/2014, confirmed the date of implementation of CTIS and discussed its impact on the process of conducting clinical trials in the EU (Clinical Trials Regulation (EU) No. 536/2014 in practice 2023). According to the previously published EC Decision 2021/1240 (EUR-Lex 2021) on compliance of CTIS and EHDS with the requirements set forth in Regulation No. 536/2014, after 31.01.2023 sponsors must submit initial applications for obtaining permission to hold clinical trials only through CTIS. It should also be noted that all current tests approved under the old requirements will be governed by the Regulation as amended in 2014, but in two years, by 31.01.2025, must also be transferred to CTIS. It should also be noted that using CTIS, sponsors will be able to apply for authorization to 30 EU countries with just one application.

One of the key innovations of Regulation No. 536/2014 is the use of artificial intelligence to conduct both the clinical trials and the examination of data and information relating to clinical trials for obtaining permission to conduct them. As part of the EU strategy on artificial intelligence, the EC has proposed for use a first-of-its-kind regulatory framework on artificial intelligence, which includes:

1. Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act) and amending certain union legislative acts as of 21.04.2021 (European Commission 2021);
2. Proposal for a Directive of the European Parliament and of The Council on adapting non-contractual civil liability rules to artificial intelligence (AI Liability Directive) as of 28.09.2022 (European Commission 2022a).

The proposed EC Regulation on harmonized rules for artificial intelligence (2021) highlights the features of the use of artificial intelligence in various cases, which may result in unacceptable risk, high or low/minimal risks. In the case of high-risk AI, such systems will need to meet complex requirements, including data management, record-keeping, transparency, accuracy and security. The use of low/minimal risk AI will only require compliance with transparency obligations. In turn, the Directive on non-contractual civil liability relations related to the use of artificial intelligence (2022) aims to provide companies with legal certainty regarding their liability, while ensuring that the legal framework corresponds to the process of digitalization of the economy. Also, the above-mentioned Directive forms uniform rules for access to evidence of damage caused by artificial intelligence systems, thus establishing a broader protection for the injured party to seek compensation. This Directive (AI Liability Directive 2022) also introduces a presumption of causation against the developer, supplier or user.

At the time of Regulation No. 536/2014 adoption, the United Kingdom left the EU, so the new requirements will not apply, and it is currently unknown whether this country will bring its legislation into line with the updated Regulation. In turn, in the United Kingdom, the Medicines & Healthcare products Regulatory Agency (MHRA) held public consultations on updating the national legal framework for conducting clinical trials (Consultation Outcome 2023). Unlike the EU, the United Kingdom currently follows a decentralized approach to regulating the use of artificial intelligence. An example is the MHRA's Software and AI as a Medical Device Change Program – Roadmap (gov.uk 2023), which details 11 work packages covering elements such as regulatory requirements, as well as testing before and after the devices enter the market.

It should also be noted that the requirements for safety reports are significantly simplified in EU countries. Thus, on 07.01.2022, Commission Implementing Regulation (EU) 2022/20 (Publications Office of the European Union (2022)) was adopted, and it establishes the rules of cooperation between EU member states during the assessment of safety information provided in accordance with the Regulation No. 536/2014 in the 2014 edition. The aforementioned document provided for a 1-year transition period (until 30.01.2023) during which clinical trial sponsors could still choose how to apply for clinical trial authorization under Directive 2001/20/EC of 04.04.2001 (The European Parliament And The Council Of The European Union 2001) (hereinafter – Directive 2001/20/EC) or through CTIS. It is also worth noting that clinical trials, that are currently ongoing and are approved on the basis of Directive 2001/20/EC may continue to be regulated by this Directive until 31.01.2025.

In addition to Regulation No. 536/2014, EMA together with the EC and the HMA announced in January 2023 a new initiative called "Accelerating Clinical Trials in the EU" (European Medicines Agency 2022a) (hereinafter – ACT EU), and also developed the Work Plan for the period 2022–2026 for the acceleration of clinical trials in the EU (European Medicines Agency 2022b), which aims to use the provisions of Regulation No. 536/2014 and CTIS to further improve EU environment in order to attract more clinical trials to EU countries. The ACT EU (2022) strategic document provides for ten priority actions, namely:

1. To develop a road map of existing initiatives and a strategy to rationalize management by coordinating the actions of various experts and working groups in the European Medicines Regulatory Network (EMRN) and the infrastructure for evaluating ethical and moral-legal aspects of clinical trials.
2. To develop key performance indicators, data visualization tools to track the performance of the European clinical trial environment and facilitate more international research, especially in the academic environment.
3. To create a Clinical Trials Information System (CTIS), which will be able to provide information to patients as well.
4. To introduce the modernization of GCP based on the development of guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Humans (ICH).
5. To conduct clinical trials data analysis using academic, non-profit, European and international initiatives, supporting evidence-based decision-making and increasing the effectiveness of policy-making and research funding.
6. To launch a targeted communication campaign to involve all possible participants in the process of accelerating clinical trials in the EU, including data protection specialists, academic institutions, enterprises of various forms of ownership, investors, health technology assessment bodies, as well as health care specialists.
7. To improve the interaction between scientific consultants on issues of approval and design of clinical trials and the working group on methodology, as well as to improve their coordination.
8. To develop and publish key methodological guidelines, in particular for clinical trials using AI and machine learning, complex trials, decentralized trials, and define the process of interaction between the supply of test systems and clinical trials.
9. To create a system for monitoring the safety of clinical trials both during clinical trials and after the drug is placed on the market.
10. To develop a training program on clinical trials, which will include modules on drug development and regulatory requirements, with the involvement of universities and enterprises of various forms of ownership.

Another important aspect, without which the clinical trials conduction is impossible, is the evaluation of clinical trial data and information for their compliance with ethical and moral-legal principles. According to Regulation

No. 536/2014 the ethical review shall be performed by an ethics committee in accordance with the law of the EU Member State concerned. Based on the results of the analysis, it was established that there are a number of differences in this process in different EU countries. Thus, in about half of the studied countries, documents to ethics commissions must be submitted by the sponsor, while in other countries this duty is delegated to the researcher, it is also possible to use both of these options (Table 1).

Table 1. Differences in the legislation of EU countries and Ukraine regarding the submission of applications for examination of clinical trials data and information to ethical commissions.

Country	Clinical trial applicant		
	sponsor (or its representative)	researcher	researcher or sponsor (or representative of the sponsor)
Austria	+	-	-
Belgium	-	+	-
Greece	+	-	-
Denmark	-	+	-
Estonia	-	-	+
Ireland	-	+	-
Spain	+	-	-
Italy	+	-	-
Cyprus	-	-	+
Latvia	+	-	-
Lithuania	+	-	-
Luxembourg	-	+	-
Malta	-	-	+
Netherlands	+	-	-
Germany	+	-	-
Poland	-	-	+
Portugal	+	-	-
Slovakia	+	-	+
Hungary	+	-	-
Ukraine	+	-	-
Finland	-	+	-
France	+	-	-
Czech Republic	+	-	-
Sweden	-	+	-

In the case of multicenter clinical trials, another example could be the procedure for obtaining a single ethical opinion for each of the participating countries. In some countries, there is a central ethics committee that reviews the data and information of multicenter trials, while in other countries it is allowed to choose an ethics committee from a list of specially accredited committees (Table 2).

Therefore, for example, in Czech Republic, the State Institute for Drug Control is the body responsible for examination of clinical trials documentation. In the country, there are two types of expert commissions, created by the management of the relevant medical and preventive or research institution: local ethics commissions of individual health care institutions and expert commissions for multicenter trials, which, in turn, must be recommended by the State Institute for Drug Control and approved by the Ministry of Health of Czech Republic. At the same time, a multicenter trial must first receive the approval of one expert committee for multicenter trials (currently the sponsor is given the right to choose it, but in the future the procedure

Table 2. Differences in the legislation of EU countries and Ukraine regarding obtaining the opinion of the ethics commission for multicenter trials.

Country	Procedure for consideration of data and information for clinical trials	
	in one of several ethics commissions to choose from (the number of ethics commissions in the country)	in the central ethics commission
Austria	+ (26)	-
Belgium	+ (35)	-
Greece	-	+
Denmark	+ (8)	-
Estonia	+ (2)	-
Ireland	+ (13)	-
Spain	+ (136)	-
Italy	+ (177)	-
Cyprus	-	+
Latvia	+ (5)	-
Lithuania	+ (2)	-
Malta	-	+
Netherlands	+ (34)	-
Germany	+ (53)	-
Poland	+ (54)	-
Portugal	-	+
Slovakia	+ (50)	-
Hungary	-	+
Ukraine	+ (each health care institution has a separate local ethics commission)	-
Finland	+ (25)	-
France	+ (40)	-
Czech Republic	+ (60)	-
Sweden	+ (7)	-

of "random" selection is considered), and then approval in the central committee. From a procedural point of view, it is important that in the process of reviewing initial CTA documents, interaction and exchange of information/opinions of the expert commission and the regulatory body during the parallel examination is not foreseen. The application is submitted by the researcher for a single-center study, and by the sponsor for a multicenter study (Patras 2008).

In Finland, 25 regional expert commissions have been established, which review the materials of medical research projects, epidemiological studies and other tests involving humans. Along with that, there is also the National Committee on Medical Research Ethics and the National Advisory Board on Social Welfare and Health Care Ethics for the examination of multicenter trials, although it can delegate the right of review to a regional expert commission (Medical Research Act No. 488/1999 2010).

In Poland, there are three types of expert commissions: bioethical committees of medical universities, bioethical committees of medical or scientific institutions (not universities), bioethical committees of regional boards of doctors (and dentists). The trial can be considered by any type of committee, depending on the place, where Principal Investigator work, and in the case of a multicenter study, the Coordinating Investigator (Publications Office of the European Union 2005).

In France, the review of initial CTA documents is handled by competent regional research expert commissions and Personal Protection Committees. France also has the

Bioethics Law (Loi bioéthique) of 2011 (amended in 2021). This law regulates issues related to bioethics and medical research, in particular, the conduct of genetic research. In the above-mentioned law, which establishes a series of requirements for the consideration of 4 types of biomedical research (reproductive technologies, prenatal and genetic diagnostics, the use of stem cells and transplantation), a key role is played by the recently created Agency of Biomedicine ("Agence de biomedicine") – a public organization working under the supervision of the Ministry of Health. In the case of multicenter trials, the sponsor selects a national coordinating investigator and submits an application to the competent research expert panel of the relevant region.

In Germany, ethics commissions can be established at medical associations or universities. Such commissions review the materials of all research projects, including those whose objects are biological materials obtained from humans and personal data (in contrast to France, where epidemiological studies are subject to the Database Law, but not clinical trials) (The German Ethics Council 2007). Therefore, the analysis shows that different levels of centralization for clinical trials documentation review by ethics commissions are presented in the EU countries.

In Ukraine, the existence of ethics commissions is regulated by the Law of Ukraine "On Medicinal Products" (1996), in Art. 7 of which it is noted that clinical trials are carried out after a mandatory assessment of the ethical, moral and legal aspects of the study by ethics commissions that are formed and operate in medical institutions, as well as by Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009 "On approval of the Procedure conducting clinical trials of medicinal products and examination of materials for clinical trials and the standard regulations on ethics commissions", which actually approved the relevant Regulations on ethics commissions. Ethics commissions are required to carry out clinical trials ethical examination, conducted in Ukraine in accordance with national and international standards.

In accordance with the Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009, institutions engaged in clinical trials are responsible for the examination of ethical aspects of research, including the approval of clinical trials by ethics commission. In the case of multicenter studies, each center should have its own ethics committee and ensure coordination with other committees. For effective performance, commissions should consist of representatives of various professions, including medical workers, pharmacists, representatives of public organizations and other interested parties. Applicants of clinical trials submit a specified list of documents to the ethics commission in health care institutions to obtain the assessment of clinical trial ethical aspects. This procedure ensures its compliance with the requirements of Directive 2001/20/EC and the Law of Ukraine "On Medicinal Products" (1996).

During their performance, ethics commissions take into account such principles as the principle of non-interference, voluntariness, informed consent and confidentiality. They also monitor adherence to trial protocols, track adverse effects, and assess risks to trial participants. Ethics commissions provide ethical control both at the planning stage and at the stage of clinical trial conduction, which allows to ensure a high level of ethical conduct of research in Ukraine.

Therefore, as of today the Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009 is the main document that describes from start to finish the procedure for clinical trials conduction, the process of examination of documents for clinical trial approval, as well as the procedure of clinical audit in Ukraine. After the implementation of this Order, such Orders of the Ministry of Health of Ukraine as "On the approval of the Procedure for conducting clinical trials of medicinal products and examination of materials for clinical trial and the Standard Regulations on Ethics Commissions" (No. 66 dated 13.02.2006), "On the approval of the Procedure for the determination of specialized medical and preventive institutions in which clinical trials of medicinal products can be conducted" (No. 245 dated 17.05.2007) and "On approval of the List of medical and preventive institutions in which clinical trials of medicinal products can be conducted" (No. 560 dated 11.08.2006), were cancelled, which, for its part, contributed to the significant simplification of the regulatory framework of Ukraine and the introduction of simple and clear rules, which also correlate with the requirements of Directives of the European Parliament and the Council 2001/20/EC dated 04.05.2001, 2001/83/EC from 06.11.2001, Resolution of the European Parliament and Council 1901/2006 dated 12.12.2006 and Regulation 1902/2006 dated 20.12.2006, Guidelines on GCP, International ethical principles of biomedical research with human involvement (Council for International Organizations of Medical Sciences (CIOMS) 2016) and the Doctor's Code of Ethics (Code of ethics of a doctor of Ukraine 2009).

On 16.02.2009, by Order of the Ministry of Health of Ukraine No. 95, CT-H of the Ministry of Health of Ukraine 42-7.0:2008 Good Clinical Practice was approved, which contributed to the harmonization of the requirements of the specified practice with international standards in this field, in particular with the requirements of EMA and ICH. In accordance with the changes introduced by the Order of the Ministry of Health of Ukraine No. 1023 dated 04.05.2020, an updated version of CT-H of the Ministry of Health 42-4.0:2020 Good Clinical Practice was put into effect. The GCP defines the requirements for the organization and conduct of clinical trials in the field of medicine, in particular with regard to ethics, research quality, safety and confidentiality of patient data. It should be noted that today, the requirements for conducting clinical trials in Ukraine meet international standards, which allows clinical trials to be conducted in Ukraine within the framework of international research programs.

Analysis of the requirements of Regulation No. 536/2014 and the subsequent process of harmonization of Ukrainian legislation together with EU requirements is important for the development of clinical trials in Ukraine and contributes to its integration into the international community of scientists and specialists in the field of medicine.

Discussion

The obtained results of the conducted study demonstrate a significant improvement of the process of clinical trials, which has become necessary in connection with the development of medical and pharmaceutical science and practice. This is emphasized in the scientific works of researchers from the EU, which were published both before and after the entry into force of the new version of Regulation No. 536/2014. Thus, as early as 2017, Stahl E. described the state of preparation of EU member states for the introduction of amendments to Regulation No. 536/2014, in particular outlined issues related to the implementation of clinical trials in accordance with EU norms and requirements, as well as planning approaches to providing information and cooperation with EU regulatory authorities. The paper of Giannuzzi et al. (2016) highlighted the changes expected in the European system of submitting applications for clinical trials with the adoption of the new Regulation, discussed key changes to the submission of applications, the coordination mechanism between EU member states and interactions between different ethics committees, which will have implications for the pharmaceutical industry and patients. The above experience is also relevant for Ukraine, as understanding the ways of development of regulatory requirements and implementation in practice will contribute to ensuring the quality and safety of clinical trials in Ukraine, which also participates in international multicenter clinical trials.

According to Atzor et al. (2013), the new provisions of the Regulation will contribute to the harmonization and optimization of the procedures for conducting clinical trials in the EU countries, which allows to accelerate the introduction of new drugs to the market, as well as increase the attractiveness of the EU for conducting clinical trials. The results of these studies are also relevant for Ukraine, because the process of integration into the European pharmaceutical space is currently ongoing.

Special mention should be made of the work of Scavone et al. (2019), which discusses the changes and challenges related to Regulation No 536/2014, in particular the new application procedure for clinical trials to simplify and harmonize the process of approval of tests in the EU. Particular attention is paid to issues related to safety data and ethics in clinical trials, as well as the need for cooperation between different competent authorities in the EU. The example of such coordination can be followed by Ukrainian regulatory authorities, which, in turn, will simplify the process of interaction with regulatory authorities of EU countries during multicenter international clinical trials.

The results of the research carried out in the context of cooperation between Ukraine and the EU indicate specific advantages and prospects of harmonizing the legislation of the Ukrainian pharmaceutical sector with EU requirements. Attracting foreign investments is one of these advantages, because the implementation of international standards will contribute to the arrival of a greater number of foreign pharmaceutical companies and sponsors to Ukraine, which will open up new opportunities for the development of the industry and the use of advanced technologies.

Strengthening the scientific research base is another advantage of such cooperation, because it will allow the exchange of scientific knowledge, advanced research methods and technologies, which will contribute to the development of the national scientific research base and the adoption of scientifically based decisions in the field of examination of clinical trials documentation. Cooperation with EU countries will help to improve the process of clinical trials documentation, to ensure a high-quality assessment of the efficacy and safety of pharmaceuticals, as well as to reduce risks for patients.

It is important to develop innovations and introduce new technologies. Cooperation with EU countries will facilitate the exchange of information on the latest approaches and innovations in the field of examination of clinical trials documentation.

Therefore, the above will contribute to the development of the pharmaceutical industry, the improvement of medical and pharmaceutical care, the strengthening of Ukraine's position on the international arena, and the introduction of advanced standards in the field of clinical trials.

Practical importance

An important aspect of the practical significance of this research is the development of approaches to optimizing the conduct of clinical trials to ensure the safety and efficacy of new drugs introduced into the pharmaceutical market as a result of the harmonization of the legislation of the Ukrainian pharmaceutical sector with EU requirements. At the moment, Ukraine is actively working on adapting its legislation to EU standards and requirements, the analysis of which, compared to Ukrainian legislation helps to identify gaps and common points, which will provide the basis for further strengthening of cooperation in the field of regulatory control of clinical trials.

Limitations of the study

Given that all regulatory and normative documents, as well as relevant information from regulatory bodies of both the EU and Ukraine are freely available, this study had no limitations that could affect the results obtained.

Prospects for further study

Based on the analysis of the EU countries regulatory requirements regarding clinical trials, it is planned to carry out a further assessment of approaches to regulation in the EU countries and to develop ways to improve the organization of clinical trials in Ukraine.

Conclusion

Based on the results of the study, the main development trends and the most important, both distinct and similar, normative and legal aspects of the organization of examination of materials for clinical trials in different EU countries, taking into account the updated Regulation No. 536/2014, which entered into force on 31.01.2023, have been revealed, that:

- the requirements for safety reports have been simplified;
- the efficiency of regulatory bodies performance was increased by involving artificial intelligence for the examination of materials in order to obtain a permit for their implementation;
- a single portal for submission of materials for clinical trials was introduced;
- the operation of a database for submitting and considering applications for conducting clinical trials, as well as obtaining authorization within the EU was introduced in order to simplify the interaction of the clinical trial applicant with regulatory authorities.

Based on the results of the analysis of the Ukrainian legislation, the simplicity of the procedure for obtaining the opinion of the Central Executive Authority of Ukraine and the assessment of the ethical aspects of the clinical trial by the relevant local ethical commissions, the clearly prescribed requirements for researchers and the place of the study, and the detailed description of the process of examination of the materials for clinical trials should be highlighted.

However, in order to improve the efficiency and speed of clinical trials materials examination, it is worth paying attention to modern technologies. Currently, the Central Executive Authority of Ukraine does not use electronic document flow with applicants, while processing documents in paper form. The introduction of a single portal, which would provide the possibility of submitting a single package of documents, exchanging data (providing additional materials, responding to experts' comments, etc.), as well as receiving the opinion of the Central Executive Authority of Ukraine and evaluating the ethical aspects of clinical trial by the relevant local ethical commissions, can significantly simplify and speed up the process of clinical trials approval. In addition, such portal will provide an opportunity to monitor the status of consideration of a package of documents, that will reduce the time of their consideration, decrease the risk of delays and increase the efficiency of the process.

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