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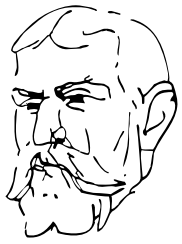

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ORIGINAL ARTICLE

THE INFLUENCE OF THE REGULATORY SYSTEM ON THE STUDY DESIGN AND DATA MANAGEMENT PRACTICES IN CLINICAL TRIALS

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ABSTRACT

The aim: To review real-life regulatory-dependent study design and data management practices of post marketing multicenter studies of medical devices conducted in 2021 in Ukraine and Poland.

Materials and methods: This article presents the case study of 4 post marketing multicenter studies of medical devices conducted in 2021 in Ukraine and European Union.

Results: The case study presented effective cross-border cooperation between Ukrainian and European actors. Despite the gaps in Ukrainian legislative framework on medical devices, complex solutions on employment of the most stringent regulatory provisions led to appropriate study design. Usage of the highly compliant electronic data capture led to fast-track study start-up and solid clinical data collection.

Conclusions: Publications on real-life regulatory-dependent clinical trials conduct might be essential to innovate the regulatory system in Ukraine. The cross-border cooperation might assist the advancement of clinical trials industry in Ukraine. Gaps in medical devices regulations in Ukraine impede the context-specific clinical trials solutions for biotech industry in Ukraine. The regulatory framework and practice in Ukraine may be perceived as externally driven due to gaps in medical devices regulations, lack of capacities of domestic notified bodies and business interests of Sponsors.

KEY WORDS: Clinical trials design, medical devices, clinical trials regulation, clinical data management

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INTRODUCTION

The literature on the clinical trials' management in Ukraine is scarce. Hence, most scientific, and legal sources on clinical trials in Ukraine from 2012 to 2020 are part of the scientific discussion on the legal aspects of clinical trials regulation. Therefore, a review of these sources might be incomplete without mentioning the primary sources – regulatory documents.

Kornatsky V. at al. discussed in 2012 that since independence Ukraine has made significant progress in the industry of clinical trials of drugs since the first study in 1996. The period of the industry from 1996 to 2012, according to the article, can be characterized by the introduction of new regulations and harmonization of existing regulatory acts with the Declaration of Helsinki, Good Clinical Practice, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 (international regulatory acts) [1].

In several reviewed articles the global regulations, such as the World Medical Association's Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [2], the International Covenant on Civil and Political Rights, and Article 7. [3], Article 4 of the Convention for the Protection of Human Rights and Dignity of the Human Being regarding the Application of Biology and Medicine were highlighted [4].

Particular attention is also paid to Article 28 of the Constitution of Ukraine, which pinpoints the right to respect for one's dignity and the prohibition of medical, scientific, and other research on humans without their voluntary consent, and Article 32, which explicitly prohibits the collection, storage, use and dissemination of confidential information. a person without their consent [5].

These legal principles are elaborated in the regulation, that establishes the rules and basic requirements for clinical trials of medicines in Ukraine is the Order of the Ministry of Health of Ukraine dated 23.09.2009 № 690 and designates the main notified body with an expert function – the State Expert Centre of the Ministry of Health of Ukraine. It is a state enterprise designated by the Ministry of Health. Almost all sources focusing on clinical trials in Ukraine are devoted to the analysis of this order and the activities of the state enterprise State Expert Centre of the Ministry of Health of Ukraine [6-12]. However, as clinical trials of medical devices are not regulated with Order #690 of MoH of Ukraine [13], and Order #616 [14] lost its force on March 28, 2017, it presents the gap in current regulation in Ukraine and current practices follow the regulatory

framework of the country(ies), in which the investigated medical device is to be marketed.

For the European regulations on clinical trials, Scavone et al. [15] mention regulatory aspects (implementation of Directive 2001/20/EC), which together with the economic crisis has led to a slowdown in the number of clinical trials in the European Union along with increasing the attractiveness of non-European countries. Directive 2001/20/EC, despite the aim of optimizing clinical trials in the European Union, this regulation has negatively affected the attractiveness of European countries for the clinical trial industry, increased requirements for sponsors, insurance, administrative costs.

The article by Markus K. Labude and Tsung-Ling Lee [16] it was stated that the Council Regulation (EC) following Directive 2001/20/EC 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC needed to reduce administrative pressure on Sponsors by unifying the submission and evaluation of research applications together with short and expected review times. At the same time, this regulation does not allow extending the deadlines for reviewing the application for a clinical trial by ethics commissions, which may interfere with adequate ethical evaluation of the study.

Concerning regulations on medical devices, in the comparative study of such regulations in the United States and the European Union [17] authors state that prior to the changes in regulatory process in European Union, US FDA employed more restrictive regulatory approach. Even though it led to faster progress in clinical development in Europe, it entailed the device failures to present efficacy and safety on market. These facts provoked European regulators to adjust the approach to more stringent.

Another comparative study of medical device regulations in European Union, USA, and Japan [18] concluded that there are substantial international differences between medical device frameworks. These differences have a tendency to be abated by voluntary global harmonization. However, the author pinpoints the implementation of harmonized norms is influenced by the national and supranational regulatory rules, practices, and politics.

The aforementioned harmonization is embodied in the modified medical device regulation of the CE marking applications of the medical device in European Union. These regulations imply that clinical investigation requirements will be obligatory to produce solid clinical data on the clinical benefits of the device [19].

However, there are currently no modern comprehensive studies on the influence of the regulatory system, primarily Medical Device Regulation [20-23], on the state-of-the-art management of clinical trials conducted in Ukraine and in European Union. Lack of publications on good study design and data management practice leaves a number of issues unresolved and controversial.

Thus, the urgency of the problem, its lack of development in the theory and practice of management the need to solve urgent problems related to improving the process of study design and data management practices, the need to update the testing of modern pharmaceutical innovations led to the choice of dissertation research topic.

THE AIM

To review real-life regulatory-dependent study design and data management practices of post marketing multicenter studies of medical devices conducted in 2021 in Ukraine and Poland.

MATERIALS AND METHODS

STUDY STRUCTURE

The study consisted of three subsequent stages. Firstly, the selection of study objects. For the purposes of this research the following criteria were applied to determine the sample: 1. The author took part in the clinical trial design and data management procedures. 2. The study was post marketing and multicenter study of medical device for Medical Device Regulation procedures. 3. The study was conducted in Ukraine and in European Union. These criteria were chosen predominantly to obtain real-world state-of-the-art knowledge on regulatory-dependent study design and data management practices of post marketing multicenter studies of medical devices. Secondly, available materials of eligible studies were cleared of any information confidential information comprising commercial secret of all parties involved. Thirdly, the methods listed below were applied in order to achieve the study aim.

METHODS

This article presents the case study of 4 post marketing multicenter studies of medical devices conducted in 2021 in Ukraine and European Union. Synthesis, abstraction, generalization, systematic analysis, and comparative method were used to identify Ukrainian and European regulatory practices for clinical trial management, to specify key issues of clinical trial management through the prism of the regulatory system, to highlight the potential of the regulatory system in clinical trial management.

Applying the analytical method, the key trends in the regulatory system of Ukraine for the organization and conduct of clinical trials were considered.

The dialectical and synergetic methods were used to prove the need to innovate the regulatory system in Ukraine.

RESULTS

In all 4 studies, the Sponsor employed 3 contractors: CRO for clinical operations in Poland, CRO for clinical operations in Ukraine, CRO for study design (medical writing and statistics) and data management provider.

The CROs were clearly divided in responsibilities and areas of coverage, whereas the Sponsor carried out coordination. Thus, either duplication of efforts or gaps in service provision were avoided.

The author was the technical employee of the CRO for study design (medical writing and statistics) and data management provider.

The study design should have satisfied the following points to be accepted by Sponsor:

- Writing and statistics must be compliant with both European Union and Ukrainian regulations.
- The study documents must be accepted by both European Union and Ukrainian notified bodies.
- The study design and data collection planning must address both safety and efficacy claims of investigated medical devices manufacturer.
- The data collection planning must not be dependent on local language.

If final versions of study documents had been amended due to the comments from local notified bodies, documents would have been resubmitted to all notified bodies. This outcome should have been avoided whenever possible because of tight project budget and short time frame for the study conduct.

For little was known about best practices for study design in this type of studies, the accessible guidance was taken literally. Taking into account previous experience of submissions to notified bodies of all parties involved, the documents should have present maximum possible compliance given the study aims, manufacturer claims, clinical development stage and risk-benefit ratio.

At the study documents drafting stage, the Ukrainian notified bodies decision on that the study is out of current regulatory scope could not be obtained.

Therefore, the study design followed primarily the ICH E6: Good Clinical Practice: Consolidated Guideline [24]. The study documents were drafted in line with Medical Device regulation [20-23], and order #690 [13] concurrently following the guidance and structure of the ISO 14155:2020 International Standard [25]. Whenever the regulation presented stricter limitation, this regulation was applied and referenced in the document. Consequently, development of the specific regulation on medical devices in Ukraine or adoption of the European regulation, would have led to more clear document flow and contributed to realistic planning of this type of studies in Ukraine.

Considering the post marketing stage of clinical development, the statistics section aimed to present low-risk statistical models in order to corroborated acceptable efficacy of the investigated medical devices. The good practice to apply in statistical section was strict compliance with ICH E9: Statistical Principles for Clinical Trials [26]. Consequently, the minimal sample size was reached through thorough justification of the outcome measures and anticipated effect sizes. As well, the wording of study hypotheses was aligned with the anticipated clinical benefits and manufacturer's claims.

The study documents were developed in English and therefore translated into local languages for domestic notified bodies whenever required.

To avoid delay in study data collection, processing, and analysis and to ensure the appropriate level of compliance, the electronic data capture with electronic case report forms was used for all studies. The case report form was developed and deployed in English, translations into local languages were done for the Investigator's ease of reference (not regulatory-driven decision).

Given that electronic data capture used for these studies was compliant to 21 CFR Part 11, Computerized Systems Used in Clinical Investigations [27], and General data protection regulation [28], only general compliance with the corresponding European Union regulations was checked. As the data management procedures and software followed stricter regulations, no additional measures to ensure regulatory compliance were introduced. This fact laid behind the relatively short electronic data capture start-up (2-3 weeks).

Electronic data capture start-up usually was carried out in parallel with the data processing and analysis planning. Development of statistical analysis plans, plans for data exports and statistical reports shells development at this stage is utmost beneficial for the study results reporting. However, it was not a case for neither of these studies as the data collection was planned to be launched as soon as regulatory approval was obtained.

DISCUSSION

Despite the fact that regulations are published in open access sources, practices of their implementation in real life are not usually published in peer-reviewed literature [1-9]. Details of study design and data management practices of post marketing multicenter studies of medical devices are not published independently of study results. Therefore, we found it difficult to retrieve any solid data on real-life regulatory-dependent clinical trials conduct in Ukraine and European Union.

CONCLUSIONS

The case study lets us draw only several conclusions on common features of study design and data management practices of post marketing multicenter studies of medical devices in Ukraine and in European Union.

- Regulatory framework and practice in Ukraine may be perceived as externally driven due to gaps in medical devices regulations, lack of capacities of domestic notified bodies and business interests of Sponsors (registration of medical device under Medical Device Regulation procedure).
- Gaps in medical devices regulations in Ukraine impede imposition of the context-specific clinical trials managerial and technical solutions for biotech industry in Ukraine.
- The cross-border cooperation might assist the advancement of clinical trials industry in Ukraine.
- Publications on real-life regulatory-dependent clinical trials conduct might be essential to innovate the regulatory system in Ukraine.

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The Authors declare no conflict of interest.

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