MODIFICARI DETERMINATE DE REGULAMENTUL EUROPEEAN PRIVIND STUDIILE CLINICE
CHANGES DETERMINED BY THE EUROPEAN CLINICAL TRIALS REGULATION

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ABSTRACT: *Doctors should do what is best for their patients, should not do any harm, and allow individuals to manage their own healthcare choices. These principles apply to medical research in tandem with clinical practice. How do we know the best treatment for a particular condition? How do we know that a new treatment (medicine) does not cause any harm? We could guess, "try and see what's going on," or we could design a clinical trial with defined endpoints, a statistical analysis, and monitoring adverse events to gain proof of benefit. Clinical studies provide some knowledge to practice medicine in an ethical manner.*
Are there regulations on clinical trials of medicinal products? What is the framework for authorization of clinical trials in the EU? The Regulation UE establishes a uniform framework for the authorization of clinical trials in all Member States through a single evaluation of the results, facilitating international cooperation in clinical trials, in the development of special treatments. Also, simplified experimentation rules are introduced which provide authorized medicines or used medicinal products based on scientific evidence published. A challenge for stakeholders is the complex processing procedures and shorter implementation times in comparison to the previously regulations, for the development of innovative medicines.

KEYWORDS: *Clinical trias; new regulation, data protection, clinical trials. K32*
JEL CODE: K31+

1. INTRODUCTION

According to *"Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency"* [1], the number of applications for authorization to clinical trials in the EU decreased by about 25% between 2007-2011, while the clinical costs of performing this clinical trials increased and the average waiting times for these studies increased by 90%.

Starting on 17 July 2012, the European Commission has proposed a regulation on clinical trials for medicines, an opportunity for economic development and access to

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innovative medicines, ensuring maximum protection for patients as regards the principles of ethics and protection of individual rights. The regulation was adopted in April 2014, published on 27 May 2014 in the Official Journal and applied since 2017 [2]. This regulation seeks to harmonize of the approval process for international clinical trials rather than the choice of a Directive to lay down the rules on clinical trials in the various U countries, for minimize regulatory autonomy at national level. This ensures obtaining accurate scientific data for patient safety [3].

The first application of the regulation was scheduled for *second semester of 2019* [2], running parallel to Directive 2001/20 EC for 3 years, thus there was a transition period between old and new procedures. The harmonization involves an authorization dossier, a single portal managed by the European Commission, a request for authorization to conduct a clinical trial linked to a European database, a rapid evaluation procedure with the involvement of the Member States, where the process is to be conduct trial and the limits precise time.

2. CLINICAL PRACTICES AND COMPLIANCE WITH REGULATION 536/2014

According to *art. 3 of Regulation UE*, a clinical trial may be conducted only if:

(a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and

(b) it is designed to generate reliable and robust data.

The European Medicines Agency publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). [4].

"Good clinical practice" (pg.9) is the set of detailed ethical and technical-scientific quality requirements in EU current legislation designed to translate the ICH guidelines into binding rules.

The rules in vigor (Directive 2001/20) refer to good clinical practice, but the title of the Regulation does not refer to them. According to art. 47, *"Respecting the Protocol and Good Clinical Practice" can be read. ,,The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and principles of good clinical practice. . ",* leads us to the fact that it is limited to the principles of good clinical practice (rights, safety and good health status).

The current rules require mandatory to comply not only the principles of good clinical practice, but also all their requirements, be observed; but also of the clinical study's behavioral requirements such as design, recording and communication of results (D.2001/20, art.1, (2)).

In the new Regulation, there is a requirement for tacit consent after deadlines, but is not properly to the requirement in D2001 / 20, where the Ethics Committee is required to be consulted in the good clinical practice principles.. This Regulation sets high standards of quality and safety for medicinal products by ensuring that data generated in clinical trials are reliable and robust, thus ensuring that treatments and medicines which are intended to be an improvement of a treatment of patients build on reliable and robust data. Moreover, this Regulation sets high standards of quality and safety of medicinal

products used in the context of a clinical trial, thus ensuring the safety of subjects in a clinical trial [2].

According to section M, paragraph 65, it is obligatory for investigators to have evidence of good clinical practice at the workplace with clinical trials.

Regarding the adequacy of the structures, the specific and detailed requirements are listed in Section N, paragraph 67. *"A duly justified written statement on the suitability of the clinical trial sites adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise, issued by the head of the clinic/institution at the clinical trial site or by some other responsible person, according to the system in the Member State concerned, shall be submitted." (all. 1, section N, paragraph 67.)"*

Regarding the quality control by the Regulatory Authority, it is done according to art. 78 (1) and 79, by monitoring compliance with the Regulation and the relevant quality requirements, but not by checking of good clinical practice compliance. This control is carried out on three different levels: 1. national, 2. EU and 3. non-EU, in line with the principles of the subjects` rights, safety, reliability, and robustness of data.

In an analysis of the regulation, the main issue is to at least observe the ICH principles of good clinical practice, but with some inconsistencies, such as the possibility of initiating a clinical trial by tacit consent after authorization times deadlines, which is inconsistent with the ***Helsinki Declaration*** [5], which says that ***a clinical*** *trial cannot be conducted without a favorable opinion from the competent Ethics Committee.*

3. STEPS NEEDED FOR A CLINICAL TRIAL

The Steps to a clinical trial are not concrete and vary depending on the system, planning can be simplified by key questions that are formulated and involvement of stakeholders.

According to [6], a clinical trial involves one or more *human subjects***,** assigned to interventions prospectively, and he effect of the intervention being a biomedical or behavioral outcome, expected in relation to the health of the subjects. Clinical trials cover a wide range of topics, answers to questions, using several methods such as mechanistic, exploratory, developmental, interventional or behavioral.

The first step in this process is to formulate the question want to answer. Part of the questioning process is to conduct a comprehensive literature review and search for clinical trials so far. Importantly, the question should serve as the basis for the clinical trial being conducted. This should motivate not only the investigator, but also those interviewed to support this concept. If the question answers, why the clinical trial is of importance then. the details of how the study will be done and what is measured will be followed.

If the concept of the clinical trial has been formulated, it follows the definition of other questions for identifying opinions and the confirmation that the approach is in-line with the stakeholders' vision. The participation of a mentor who has developed and supervised clinical trials over the years is important in defining the primary objective of the study and for modifying the trial if necessary.

There must be a rationale and feasible (technically and monetarily) the clinical trial. If a similar clinical trial has been successful, it can help determine the feasibility of the

new study, but if previous studies in the same population have failed, the deficiencies of the previous study can be used to improve the design of the new study.

From a technical point of view, *the feasibility* depends on the environment, the necessary equipment and other facilities available, such as access to a core facility, where the study samples will be stored, some aspects to be answered when designing the clinical trial.

Is it equally important to know if the clinical trial is economically feasible? The answer is yes, given that a preliminary budget must be estimated for the funding needed to complete the study. If funds such as own funds, donations, subsidies, endowments have been reserved, it is necessary to have rules for their use, including indirect costs and those of specialized personnel, from the beginning of the clinical trial.

From *the ethical point of view*, the following questions are asked, such as whether the study will contribute to the significant change in the clinical practice, will it be beneficial to the patient and if his life will be endangered if the treatment applied is not effective?

All the personnel involved must have the necessary training carried out by their own institution and the regulatory bodies. If necessary, an ethicist may be involved in the planning phase of the study.

When *planning a clinical trial*, the following aspects can be analyzed:

- Is there a protocol for data collection?
- How will data be collected, entered and secured in the system?
- Who will monitor the adverse reactions?
- Is there a Monitoring and Data Safety Committee in the clinical trial?
- Is the clinical trial a multicenter study?
- How will the grants and contracts be administered?
- What are the technological challenges?
- Is there an own data management system in the study or is there an electronic health record-EHR?
- If there is new research for the application of a new drug, who / what group can contribute to the process?

Here are some of the issues analyzed to help plan a successful clinical trial. Experience can generate collaborations and relationships that can lead to feasible and sustainable research in clinical trials.

4. DATA PROTECTION REGULATION AND CLINICAL RESEARCH

Clinical research is confronted with contradictory requirements. On the one hand, the application of the principle of transparency and data sharing, the reuse of data on healthcare or research data, and on the other hand, the application of the requirements of the „*General Data Protection Regulation"* (acronim *GDPR).*

The clinical research is in the midst of a digital revolution due to massive data access and the possibility of reusing digital data. The digitization of clinical research data and health data or data on the health system allows reuse of data for research for a secondary (information to the patient) purpose, either for clinical studies or for observational studies. Information from hospital data banks can be used to select locations for a clinical trial, select patients, optimize the study design, or collect data for a clinical trial or a "real-world" study [7].

Taking into account the reuse of clinical search data in accordance with the FAIR (Findable, Accessible, Interoperable, Reusable) principle, focus is put on the methods applied in data protection, access and exchange of data, how to obtain consent [8].

In France (2018, Giens- France) discussed aspects of promoting clinical research and a new regulatory framework, ensuring a high level of patient protection, with implications for information to patients, consent and withdrawal of consent. It also, has been approached the impact of clinical research on public and private institutions, the role of data protection officer, technical aspects of data security and confidentiality, medical data storage conditions, reuse of research data for clinical research, access conditions and secondary analysis.

„Regulation (EU) 2016/679 of the European Parliament" and of the Council of 27 April 2016 on the protection of individuals entered into force on 25 May 2018 [9] with the role of harmonizing data protection rules in Europe, facilitating the movement data and reponsible for those involved. The data processing principles aim at a specific, explicit and legitimate purpose, respect for human rights, security obligation, relevant, up-to-date, non-excessive data and a limited retention period.

„Règlement (UE) 2016/679 du Parlement européen et du Conseil du 27 avril 2016, (2018)", a new regulation was adopted in May 2017 to harmonize the conditions for the approval and conduct of clinical investigations concerning medical devices and access to the market [10].

And in the case of secondary (information to the pacient) use of data outside the clinical trial protocol, it must comply with data protection legislation, including GDPR and the national legislation, but in Art. 28 of Regulation 2014/536 provides that the sponsor to ask participants when they give their consent to participate in the clinical trials on medicines, to accept data re-use outside the *„clinical protocol exclusively for scientific purposes" [*10].

Another aspect to consider is *minimizing data*. Since the GDPR applies to personal data, regardless of whether the person is identified or identifiable, the European framework favors the processing of only the data strictly necessary to avoid the need to re-identify the person, with all costs, related technologies and time required for processing.

Personal and anonymous data oppose each other, ultimately allowing researchers to avoid GDPR provisions, such as informing participants, maintaining a level of security. The concept of anonymity must be reasonable over time, and health research data is considered non-anonymous, until otherwise proven.

In Romania, the National Authority for Personal Data Processing Supervision (ANSPDCP), the Center for Statistics and Informatics in Public Health (CNSISP) and the National Institute of Public Health (INSP) function with 4 national centers and 6 regional public health centers.

How it is applied the legislation in the field of processing and protection of personal data on health ? Is there a data administrator for this? At organizational level, are there procedures in this regard? Who validates and approves the provision of individual information to the data subjects?

In Romania, health data is that personal data related to the physical or mental health of a natural person, including the provision of healthcare services, which reveals information about its state of health, according to *"Law 363 / 28.12.2018 on the protection of the data of individuals regarding the processing of personal data"* [11]. According to „*Law no. 677/2001 for the protection of persons regarding the processing of personal data and the free movement of such data"* [12], processing of health data can only be done by or under the supervision of a healthcare professional, provided that professional secrecy is respected, unless the data subject has written and unequivocally given his consent for so long as long as such consent has not been withdrawn, and unless the processing is necessary to prevent imminent danger, to prevent the commission of a criminal act, to prevent the occurrence of such an act or to remove its harmful consequences. Healthcare professionals, health institutions and their healthcare staff may process personal data relating to health without the authorization of the supervisory authority only if the processing is necessary to protect the life, physical integrity or health of the data subject. Where the stated purposes relate to other persons or to the general public and the data subject has not given its written and unambiguous consent, the authorization of the supervisory authority must be sought and obtained in advance. The processing of personal data outside the limits set out in the authorization is forbidden.

The aim is to apply the GDPR, achieving *three essential scientific values:* I. Openness; II. Transparency and III. Reproducibility of clinical trial data, even if there is an apparent conflict between the need to protect personal data and the sharing of healthcare data; or research to improve knowledge.

According to paper *"Sharing clinical trial data: a proposal from the International committee of medical journal editors"* [13], the International Committee of Medical Journal Editors (ICMJE) expects, in January 2019, that those who pass the clinical outcomes will detail the intentions about the de-identified data, a timely sharing plan of these data before the start of the clinical trial, registered in a dedicated registry, but GDPR could complicate compliance with the requirement of transparency.

How will *the conflict between the protection of personal data and the transparency of research data and information exchange to managed*?

Some GDPR provisions on patient information and consent on secondary use of data could slow progress in research and improve knowledge. Therefore, recommendations are needed to exercise the rights of individuals with regard to their data. Thus, there is a need for a model form with patient information and information to give to patients.Also, *can come into conflict the right of removal and to opposition with the requirement to conduct exhaustive analysis of the data for gross use or re-use of data.* Where missing data, the validity of the treatment effect estimated in randomized controlled trials is undermined, and it is advisable to carry out an analysis with the intention of treating patients in order to eliminate from the outset the biases of the lack of data.

When patients change their place of care, the portability of data is ensured in GDPR, based on their consent to data and the continuity of health care, but an exception to this right should be made when study data are not useful for care.Reuse of data is the possibility of secondary use, informing the patient when planning a study, anticipating future use, or reusing a database subsequently created. Who can access the data, what data and how (controlled or anonymous? What database will be used?

It's important:

- Promoting patient representatives to database management for secondary use of data;
- Promoting incentives for data sharing.

Recommendations for the elaboration of the procedures:

- Elaboation a procedural framework defining the public interest for data processing for research purposes;
- Developing software tools to support data management and training for data managers to anonymize data [14].
- Classification of anonymous or pseudonymized data;
- Elaboration of technical files in support of researchers for accessing data banks;
- Registration of studies in the World Health Organization (WHO) registries, mandatory for publication and by law, with the inclusion of at least 20 items, in accordance with [15].
- Evaluating national legislation and data protection requirements for medical research, for harmonization throughout Europe of health research regulations and procedures.
- Separate personal data databases containing personal data when reimbursing some costs generated by clinical trials;
- Involving stakeholders in developing a code of conduct on multinational processing of clinical trial data, in accordance with [16].
- Developing interoperability conditions for clinical trial data.

5. CONCLUSIONS

It is necessary to clarify:

- which data can be declared anonymous (not covered by GDPR) and pseudonym (GDPR target);
- what is considered to be of public interest ?;
- under what conditions does the right of withdrawal apply to the secondary use of data?
- the way to access various databases with specific infrastructure

Any small pilot clinical study can be a way to develop a research career, and the experience can generate collaborations and relationships that can make subsequent efforts much more feasible. Access to health data, such as data on health insurance and data from activities within medical institutions, should be opened, thus facilitating the conduct of research and studies in the field of health, care and social assistance.

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