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Sustainability of Clinical Trials after the Historical Experience of COVID-19

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Abstract. *Clinical trials are unknown to most people in Romania. Associated most of the time with innovative and advanced medicines for patients. Research of every new and innovative methods and drugs in medicine have a great impact economically, socially and medically. The Covid 19 pandemic, which has hit every part of the globe hard, has also meant for Romania and people to rediscover new words: RNA vaccine, study stages, vaccine efficiency, adverse effects. But all this was ideologically covered up with a lot of prejudices and preconceived ideas. Difficult to combat, every misconception found its place in the patient's mind and succeeded, in addition to the resistance to getting vaccinated. Mass-media become a "specialist" in everything that modern medicine means and applied for the common good. The methodology of this research is based on the qualitative evaluation of the specialist literature and the analysis of existing data series in clinical trial management. The results show that clinical trials contribute to global sustainability and the bottlenecks developed by certain pandemic periods. Through this article we have tried to penetrate beyond prejudices and unfounded opinions most of the time.*

Keywords: Sustainability, clinical trials, Covid-19, Management, investment, pandemic.

Introduction

In a dominant concern for sustainability both nationally and internationally, clinical trials are strengthening their importance for increasing society's health by offering a marketing mix

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appropriate to patients' needs (Pislaru et al., 2010, 2011). In short, we must imagine that the clinical trial is the one that establishes the "leaflet" of the drug.

The pandemic period represented a major limitation of the studies by limiting patient travel and their participation in study visits. The logistical management of medication and equipment was made more difficult by the restrictive measures imposed.

The information that each of us reads, or not, when we buy drug or medical equipment: the effective administration schedule, the recommended doses, the age from which it can be administered, the duration, nature and frequency of the side effects it can cause, etc. It must be said that clinical trials are a mandatory component of the authorization procedure of any drug that is launched on the market.

Clinical trials validate new, innovative treatments (Sun et al., 2022). The entire clinical trial process is extremely well regulated at global (FDA), European (EMEA) and National Agency for Medicines and Medical Devices with strict compliance with the criteria of ethics and integrity towards the patient (Eleskina et al., 2023c).

The paper is structured in two parts. The first part presents the concepts and stages of clinical trial management. The second part presents a qualitative assessment of the importance of trials for society by evaluating some costs and studies conducted. Research conducted in this area of clinical trial management is very limited, therefore there are limitations of information for the present research. The research answers the questions:

"Are clinical trials important for sustainable development?"

"What is the current situation of clinical trial management?"

"How impact COVID-19 period for clinical trial world-wide?"

"What are the investment costs for clinical trial in general?"

The answers to these questions are given through the qualitative and quantitative methods used in the present research. At the Romanian level, management studies regarding the development of a clinical trial center are scarce and even non-existent in many aspects. This paper aims to identify the general framework for identifying the variables that matter for a sustainable center.

Literature review

There are a number of definitions in the literature. Through a qualitative assessment of the specialist literature and using empirical experience, the definitions of this field are evaluated. A systematization of them is presented below. We have analyzed the definitions in the literature and selected a few definitions that we consider relevant for clinical trials, Figure 1.

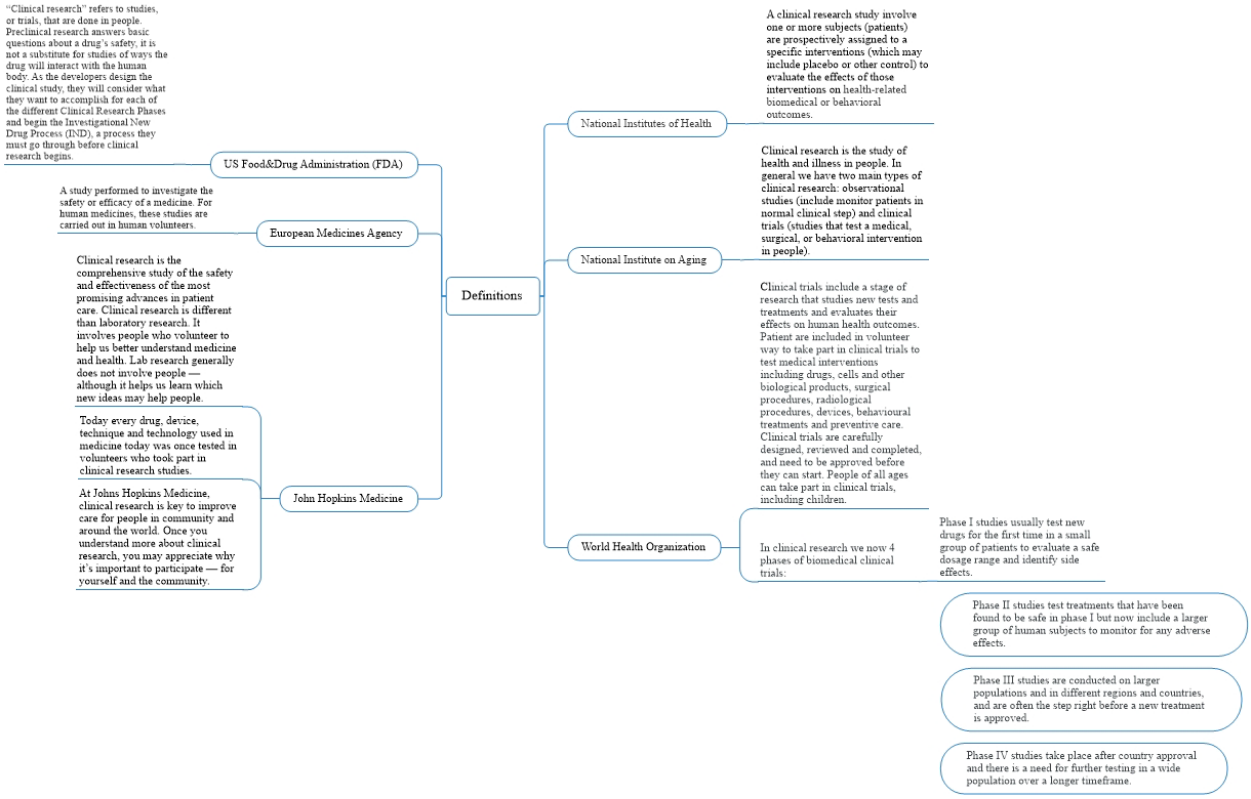


Figure 1. Concepts and implications

Source: Authors' own development.

Investments in clinical trials contribute to supporting the health of the population and economic efficiency. Based on technology, a clinical trial contributes to obtaining the best results for the development of medicines expected by the population and helps treat diseases. Efficient studies bring improved financial results for manufacturers and affordable prices for buyers (Eleskina et al., 2023c; Sathian et al., 2020). Using innovative technologies, adequate marketing mixes can be developed and accepted by consumers. Investments in clinical trials can be direct financial investments, Figure 2, investments associated with clinical trials, investments in infrastructure and technology, Figure 3, and investments in patient recruitment and study management, Figure 4. The knowledge maps for these types of investments are presented below.

Figure 2. Direct financial investments

Source: Authors' own development.

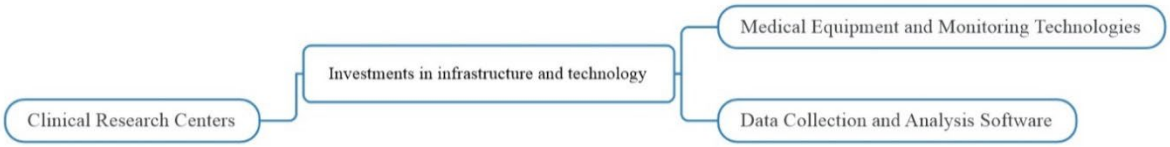


Figure 3. Investments in infrastructure and technology

Source: Authors' own development.

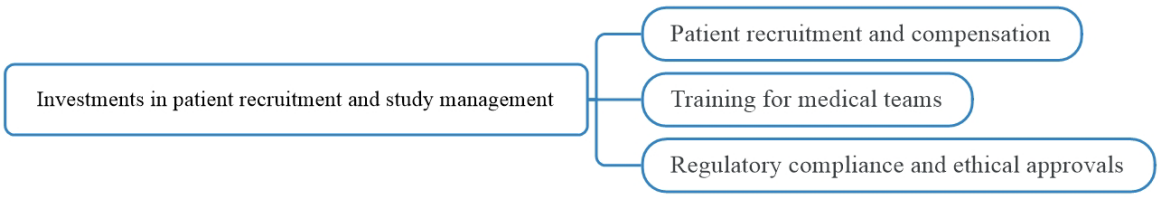


Figure 4. Investments in patient recruitment and study management

Source: Authors' own development.

Investments and the phases of the clinical trials are presented in the following paragraphs (Akacha et al., 2020; Chen et al., 2021; Eleskina et al., 2023c, 2023a; Lasch et al., 2022a).

- Phase 1 – Initial patient safety testing. In phase 1 of the study, the effects of the molecule (the chemical compound that will be the basis of the future drug) are tested for the first time on a small group (indicatively we are thinking of 40-99 people), who voluntarily agree to participate in the study. It is the beginning of a long road, the first step (Lasch et al., 2022b), sometimes of several years, 10-15 years, and which analyzes pharmacological effects (metabolism in the human body) and pharmacodynamic effects (beneficial effects and side effects). This stage takes place only in medical centers authorized for Phase 1 and involves hospitalization of the patient and supervision by a multi-specialized medical team (laboratory, internal, cardiology, hematology, neurology, etc.).
- Phase 2 – In this phase, the patient efficacy of the newly tested drug is evaluated in 99 – 499 volunteer patients.
- Phase 3 – Phase III studies are the most important for the statistics of studies (data base) related to patient safety (most important criterion). Phase III trials can enroll between 999 and 4999 patients or even more.
- Phase 4 – The last phase is basically a "fine-tuning" of the positive and adverse effects of the drug. Most of the time the drug is already on the pharmaceutical market, has a trade name and is available in pharmacies.
- The five phases reflect the step plan of clinical trials. Developing a management plan is a key for effective trial management. It is essential that project management includes details of the arrangements for developing and monitoring all aspects of a trial.

If the return on these investments is evaluated, a series of variables should be taken into account: the total revenue generated by a successfully developed drug, the risk being high, a 10% success rate can be recorded in the preclinical phase, technological advances contribute to streamlining the process, and artificial intelligence (AI) or computer modeling technologies help reduce costs and increase efficiency.

In all these studies, management principles are very important (Ivascu, 2018; Ivascu et al., 2021). Each stage of the process implies a particular importance for clinical trials. All projects include a series of processes, a set of actions to bring about results. The five basic process stages are presented in Figure 2.

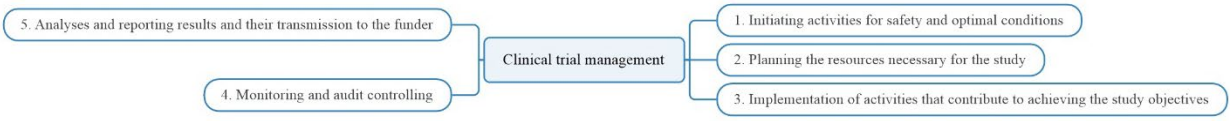


Figure 2. The five basic process stages

Source: Authors' own development.

Management of clinical trial shares many features with other type of business project as defined in the field of project management. These features include the following:

- Clear objective aimed to bring about change
- Requiring a good team with experience in clinical trial
- A set time planning
- Clear resources to achieve objectives

This qualitative inventory of the specialized literature provides answers to the questions "Are clinical trials important for sustainable development?", "What is the current situation of clinical trial management?" and "What are the investment costs for clinical trials in general?".

Methodology

This research uses the qualitative evaluation of the data series found on the website of the National Institute of Statistics, the data presented by the World Health Organization, articles that analyzed the impact of the COVID 19 pandemic and that present strategic directions of action for the next period.

The quantitative methodology tracked statistical data from the period 2000-2024 and the values of the amounts allocated to medical research from 1990-2024. As part of this research, we wanted to know what the situation was of clinical trials before the COVID 19 pandemic and what changes occurred after this period.

Results and discussions

We analyzed the data with the amounts that each major economic area was allocated for pharmaceutical research and development. Starting from 1990 to 2020, the upward trend for China and the USA can be observed, a constant, but modest growth of the European Union, Table 1.

Tabel 1. Amounts allocated for each major economy in million EURO

Area	1990	2000	2010	2019	2024
Europe	7766	17849	27920	37880	39656
USA	6803	21364	40688	64357	72412
Japan	5161	7462	12760	13392	13216
China	-	1925	12263	60956	78460

Source: Authors' own development.

The post-Covid-19 pandemic period marked a historic shift in the way we are challenged as humanity to cope with various global medical events. In a globally connected open-space generation, we have lived unique experiences: restricting some rights, controlling the movement of people, blocking some medical services, speeding up clinical trials on the pandemic, fear of an unseen enemy.

Addition to the legislative and organizational changes, we have seen a shift of the population's trust pillar regarding doctors and the medical act to a dangerous area, of mistrust, suspicion. An apocalyptic movie-type scenario, in which the idea of population control and chip implantation have been more validated as "Truth" than the conclusions of scientists. A modern war on modern concepts, science versus "public opinion".

In the parallel world of research involved in clinical trials, there was a completely different reality. The best trained minds in the field of research were assigned to work against the clock with what seemed to change our entire human existence.

Each stage of research was expedited and not skipped. Each step has been approved by the FDA and approved. It is true that any drug has adverse effects. We are struggling to discover these in studies: what is their nature, what is the impact in the sample of patients, how serious are they, are they related to other related diseases? Research is first and foremost about questions, the openness to look at something from several possible angles. But if the response to the new medication is clearly above the negative effect of the disease, it is definitely a success. Exceptional times, exceptional measures (Eleskina et al., 2023c).

"The existing system of clinical trial protocol creation is dependable and adequate. It allows reacting flexibly to unexpected challenges, like COVID-19, fully complying with the prescribed procedures and carefully observing participants' safety and well-being. That is why the current pandemic did not affect the number of protocol amendments" (Eleskina et al., 2023c)

The pandemic has passed. The year 2020 is somewhere far in the past. However, the collective mentality of patients has undergone changes that in the short term are irreversible and difficult to overcome. Distrust, suspicion, the orientation towards "old people's cures" have sprouted strongly. Establishment of virtual meetings by Skype/Zoom/MS Teams study training sessions and for sharing information become a natural change to face-to-face metting.

Today, conducting clinical trials in Romania is a challenge. Convincing a patient that he has access to innovative, future-oriented treatment, chances for the disease to be controlled and his life to be better. Imagine a COPD patient who can barely breathe when he enters the office, going up a floor is an ordeal. His life is strongly affected by restrictions and non-fulfillment of the simple activities of life, dressing, washing, shopping, taking part in social events. He is enrolled in a study, research program, is monitored daily through electronic journals, monthly functional explorations, analyzes at the best laboratories in the world and is under a new medication. After 6 months he is a completely different person.

"The impact that COVID-19 had on different procedures of the trial was believed to have several cascading effects on the scientific validity of the trial, both in terms of external and internal validity" (Massazza et al., 2023)

We have cases in practical clinical experience that after a period of 6-12 months, patients who needed help to get dressed end up climbing two floors, working in the household, their life is radically changed for the better. Science is for a better life, regained health, the strongest argument for clinical trials is to see lives changed for the better.

"Image" by John Lennon is a world of our children's children in which cancer or HIV no longer exists in the vocabulary and has long since been solved. Belief in what is good precedes the first step into the unknown or impossible.

"The coronavirus disease 2019 (COVID-19) pandemic has a major impact not only on public health and daily living, but also on clinical trials worldwide." (Lasch et al., 2022).

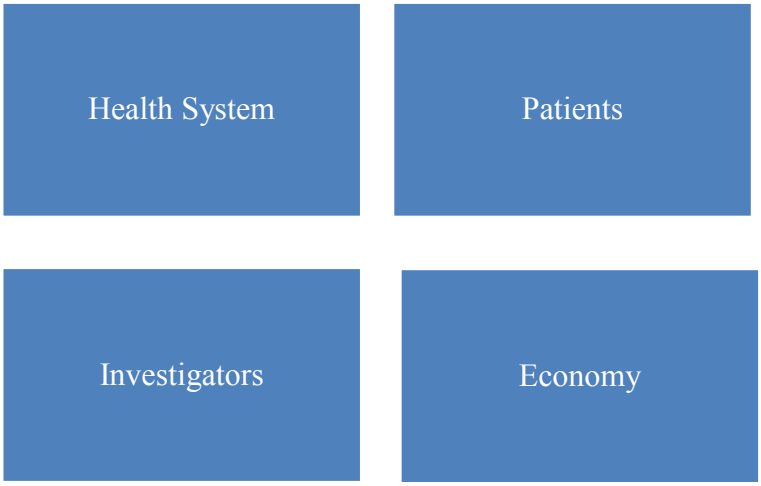
Following discussions with representatives of clinical trial sponsors, the clinical research community faced many challenges, many clinical trials were suspended or even postponed, patients' access to new treatment was almost totally limited. The recruitment of new patients has been stopped, and the sending of medication to patients has been delayed by transport problems during the pandemic.

"While there was a massive decline in overall trial recruitment, some research activity continued such as in oncology where research represents part of cancer care and is reflected in our results." (Chlan et al., 2023)

The clinical trial can only be carried out in centers authorized by the National Medicines Agency. The novelty forecast for 2024-2025 is that the clinical trial centers will operate under a

simplified authorization, the legislative framework is not yet finalized and at this time we cannot present more details. In Romania, for the time being, this research activity can be carried out both in university centers, university hospitals, and in private clinics or state-funded hospitals. It is a temporary feature only in Eastern Europe if we look only at the European Union area. In highly developed countries, especially Germany or Italy, these studies are carried out only in university centers. We can consider it a normal development trend, so in Romania too we predict that at some point studies will be concentrated only around a university center.

The main advantages in economic terms of conducting clinical trials for a country's economy are schematically presented in the following chart:



We analyzed the values of the services reimbursed through the Health Framework Contract applied in Romania in 2024. The value of the point is 12 RON and is based on the second semester of 2023. We have considered some examples of investigations that are usually carried out in the specialized outpatient clinic, Table 2.

Tabel 2. Investigations costs

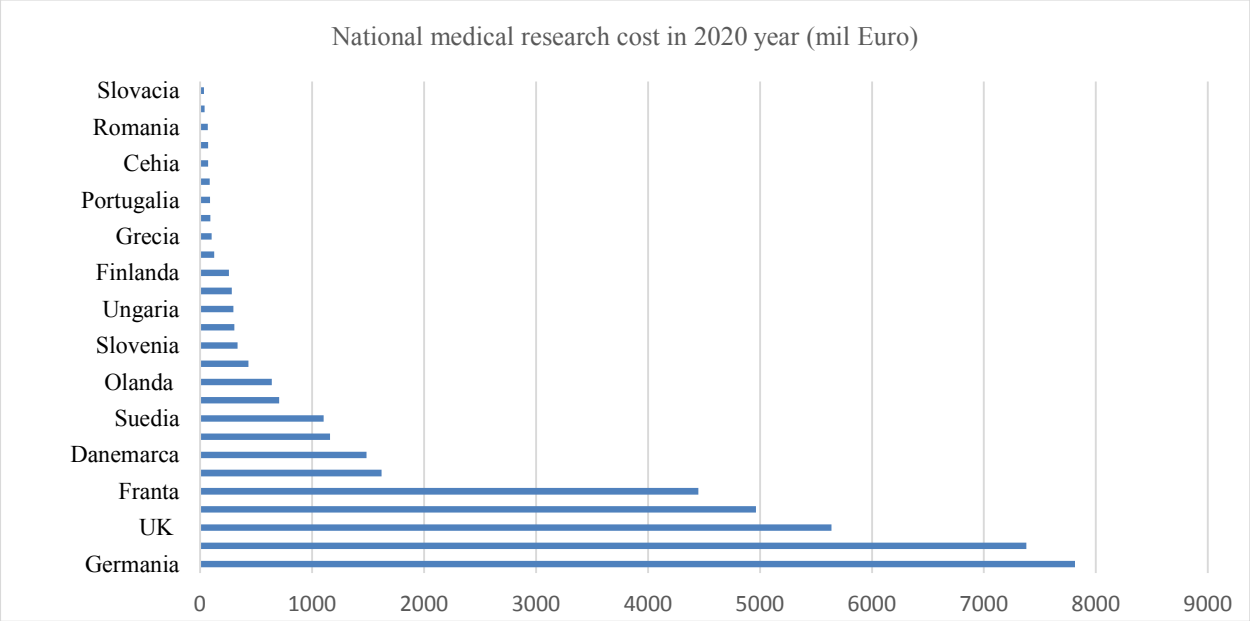
Investigation	Average cost	Patients enrolled in clinical trial	Reduction to the national health budget
X-Rays	52 EURO	10.000	520.000 EURO
EKG	48 EURO	10.000	480.000 EURO
Spirometry	24 EURO	10.000	240.000 EURO
Blood pressure and holter control	48 EURO	10.000	480.000 EURO

Source: Authors' own development.

From the example above, only from 4 investigations carried out on a regular basis, a saving of 1,720,000 EURO can be made to the central health budget. Also, during the participation of patients in clinical trials, they benefit from additional medication for background therapy and concomitant medication supported by the Sponsor. In the context of an underfunded medical system, this process allows access to new medicines that are not yet available in Romania. It's a verry simple concept to have a big picture of costs savings if number of investigations is more.

Conclusion

We have analyzed the national budgets allocated for research and for Romania it is a challenge to allocate financial resources for innovative procedures.



Source: Authors' own development.

In the following graph we have the value in millions of EUR for several countries. Clinical trial management is an "on-going" activity with many restrictions and challenges that are known. The emergence of a crisis, pandemic, adds new factors and complexity increases. The success is given by the professional quality of the clinical trial management staff, their flexibility and adaptation to the new conditions.

This study is based on the experiences of clinical staff involved in clinica trial. Who have adapted to managing trial activities during the COVID-19 in a clinical research facility. Further research is necessary to analyze the workload of clinical trial managers, to understand their role and its critical interface with clinical trial participants, sponsors, medical staff, national authorities.

A role in information and data management will be possible faster with the help of Artificial Intelligence. How much human activity will be taken over by artificial intelligence (AI) we do not know. Today we have clinical trials in which the interpretation of spirometry is analyzed by AI.

An answer that 1 year ago was at the level of 2-3 days, today it is instant. AI will play a role in the selection of possible study participants through access to health databases. Change challenges us for all generations (Boom, X, Y, Z), it depends on us how generation A (AI) will be.

This research includes a series of limitations mentioned from the beginning of the research. These include the confidentiality of clinical trials, the few research carried out in the management of clinical trials, the non-existence of a sustainable clinical trial center in Romania, the few experiences that can be learned from other researchers. Therefore, the research is built with small steps based on management experience, business risk and medical experience. The research is carried out by medical experts and management experts.

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