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Review

REVIEW OF CLINICAL TRIALS DURING THE COVID-19 PANDEMIC

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ABSTRACT

Objective: The systematic data on clinical trials during the COVID-19 pandemic are scarce. We aimed to review the dynamics of clinical trials in the new reality. **Materials and methods**: We collected data for all 112 clinical trials completed or prematurely ended in 2019-2021. The main data sources are the Register of Authorized Clinical Trials, the Bulgarian Drug Agency, and the European Union Clinical Trials Register of the European Union Drug Regulating Authorities Clinical Trials Databases. **Results**: General information of clinical trials is aligned with international trends, while the population of trial subjects is in line with the demographic situation in Bulgaria. The adaptability of trial sites to conduct multi-regional trials is the newest factor for clinical trials dynamics. **Conclusions**: The size of country's population is not a factor in the dynamics of clinical trials. A therapeutic area of clinical trials in line with local trends and the adaptability of trial sites to the international trends of most common diseases are attractive factor for conducting clinical trials in Bulgaria.

Key words: trial register, trial protocol, Bulgaria

INTRODUCTION

The COVID-19 pandemic created a huge demand for rapidly available, trusted scientific advice (1). Despite the numerous information sources about the pandemic, data for the clinical trials and the population of trial subjects remain scarce. The rationale for our review is to manipulate the available data from public registers for academic processing.

A process of adaptation related to a shift of societal attitudes towards clinical trials has been observed in Bulgaria. Modern healthcare budgets and access to innovative forms of treatment have focused public attention on the benefits of clinical trials. Our claim is based on the participation in clinical trials primarily of patients, in contrast to international practice which involves healthy volunteers.

The purpose of the article is to review the dynamics of clinical trials in Bulgaria. We created a unique database of clinical trials in the new reality – the pandemic of COVID-19 (2019-2021). Our vision for a clinical trial is a controlled process of artificially modelling future treatment effects. Unlike launched drugs, where treatment effects are already modelled by historically accrued statistical data, future treatment effects of tested drugs are modelled through conducting clinical trials in compliance with launched statistical models.

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MATERIAL AND METHODS

Publicly available clinical trial data are provided in registries that allow analysis of only one trial. Another source of data are articles based on surveys of investigators for personal observations of conducting clinical trials. Our review is innovative – we have transformed public registries into a unique database that provides great opportunities for analyses by various criteria.

Data collection

In the process of reviewing the dynamics of clinical trials, we have used data from the Register of Authorized Clinical Trials, Bulgarian Drug Agency, and the European Union Clinical Trials

Register of the European Union Drug Regulating Authorities Clinical Trials Databases (http://www.clinicaltrialsregister.eu/). In four cases, we collected data from the sponsor's site, the contact person's site, the database of private and publicly funded clinical trials (ClinicalTrials.gov), and the National Library of Medicine (http://www.nlm.nih.gov).

Our review includes collection and comparison of data for clinical trials in 2019-2021. Data were collected from trial protocols (planned data for clinical trials) and trial results (reported data for clinical trials).
The inclusion criteria in the database are:
1. Status of completed or prematurely ended clinical trials from the register of Bulgarian Drug Agency for 2019-2021,
2. Available data for the trials in the European Union Clinical Trials Register,
3. Published results for trial subjects from Bulgaria.

Data analysis
We have created a unique database based on both national and EU registries for clinical trials. The structure of the review follows the structure of the European Union Clinical Trials Register and therefore is suitable for comparative analysis both on an annual basis and among countries.

RESULTS
The dynamics of clinical trials is influenced by indirect factors (medical condition or disease being investigated, scope, type, phase, and design of clinical trials) and direct factors (age, gender, and health status of clinical trials subjects).

Local sites for conducting clinical trials
Innovative forms of treatments and free movement of know-how have increased the number of multi-regional clinical trials in a disproportionately small number of trial sites (2). In addition to international trends, in Bulgaria there is a decrease in the number of clinical trials for cardiovascular diseases, in which a large number of trial subjects participate (3).

The Register of Authorized Clinical Trials of the Bulgarian Drug Agency contains 112 completed or prematurely ended clinical trials with participants in Bulgaria in 2019-2021. The clinical trials were conducted on 707 trial sites **(Table 1).**

Table 1. *General data of clinical trials (number of)*

	2019	**2020**	**2021**
clinical trials	64	39	9
trial sites	441	221	45
completed trials	47	26	7
prematurely ended trials	17	13	2
planned duration of clinical trials (days)	56 910	35 069	4 508
reported duration of clinical trials (days)	37 728	18 326	2 040
sponsors of clinical trials	43	29	9
sponsors' countries	15	11	6
countries for conducting clinical trials, incl. in Bulgaria	73	72	68
clinical trials conducted in Bulgaria only	4		1
planned trial subjects to be included	4 271	1 802	451
reported trial subjects enrolled	3 259	1 062	153
clinical trials with female subjects	64	36	9
clinical trials with male subjects	61	36	9
substantial protocol amendments	156	69	18
changes requested by competent authorities	9	8	1

Sources: Register of Authorized Clinical Trials, Bulgarian Drug Agency and European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

The success of clinical trials depends on trial sites because of the practical problem of failure to enrol subjects. Some of the risks of the trial are endemic to trial sites, for example the moral dimension of the clinical trial. Appropriate trial sites are needed when deciding the risks and benefits of a clinical trial. A trial site's capability to enrol subjects in a reasonable time, with planned disease, age- and gender-specific populations, are major cost concerns for clinical trials, especially for insurance.

The largest decline in the number of clinical trials is in 2020. The number of clinical trials is declining faster than the number of trial sites. We explain the growing number of trial sites with the shifts made in the Bulgarian legislation for the separation of skin centres and oncology centres as autonomous entities with independent management and budget. The dynamics is to reduce the number of trial sites from an average of seven trial sites per clinical trial (2019) to six and five trial sites (in 2020 and 2021, respectively).

Status of clinical trials

Sponsors regularly notify the competent authorities of the trial status and the competent authorities inform stakeholders of the trial's dynamics, incl. for adverse drug reactions (4). According to sponsors' reports to Bulgarian Drug Agency, the number of completed clinical trials has decreased due to the COVID-19 pandemic (an additional factor for the decrease in the number of clinical trials is the process of exiting the United Kingdom from the European Union, 2020). The pandemic caused interruption of five trials due to a reduction in the number of subjects, and in six cases – for substantial changes in trial protocols. Another effect of the pandemic is the increase in the relative share of prematurely ended clinical trials, compared to the share of completed ones. The data reported the largest decline in completed trials in 2021, while 2020 reported the largest share of prematurely ended trials **(Table 1).** The European Commission has encouraged Member States to apply the harmonized guidelines to the maximum extent possible to mitigate and delay the disruption of clinical trials in Europe during the COVID-19 pandemic (5).

The planned duration of a clinical trial has decreased from an average of 889 days (2019) to 501 days (2021). Reported trial duration saw the largest drop from the planned duration of 589 days (2019) to 227 days (2021). The trend in planned and reported duration of clinical trials is similar to the trend in planned and reported number of subjects in clinical trials.

Clinical trial sponsors

Sponsors of clinical trials propose variations of in-sites and out-sites visits (6). All clinical trial sponsors in the database are drug manufacturers or their R&D affiliations **(Figure 1).** The number of sponsors decreased similarly to the dynamics of the number of clinical trials – from 1.5 trials per sponsor to one trial **(Table 1).**

Figure 1. Top 10 sponsors of clinical trials in Bulgaria (http://www.wordclouds.com)
Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

The status of all sponsors is commercial except for one trial. In nine cases, the sponsors were financially or materially supported by their affiliates in the United States to conduct the clinical trial.

Our database contains 68-73 sponsors' countries **(Table 1).** Sponsors from four countries conducted the largest share of clinical trials in Bulgaria: United States (36%), Belgium (10%), Switzerland (10%), and Germany (9%). The smallest drop is in the number of sponsors' countries – 40 %, compared to sponsors. The number of sponsors and countries decreased from an average of 2.9 sponsors per country (2019) to 1.5 sponsors (2021).

Countries for conducting clinical trials

With the increasing globalization of drug development, it has become important for regulatory authorities to be able to accept data from multiregional clinical trials (7). These trials are planned primarily for therapeutic area of skin and connective, as well as for digestive system diseases.

The average number of countries per clinical trial has halved in 2021. In five trials, subjects were only from Bulgaria (adult age group, approximately 200 subjects in clinical trials, for a period of less than a year). The trials planned for conduction only in Bulgaria were for therapeutic exploratory purposes (Phase II).

In one case, the clinical trial had been planned to take place in 48 countries. Its duration was more than 2 000 days, and it was designed to study chronic spontaneous urticaria (skin and connective tissue diseases), with a wide scope (safety, efficacy and pharmacokinetics). The type of this trial was a therapeutic confirmation (Phase III) with a complex design (controlled, randomized, double-blind) covering three age groups (adolescents, adults, and elderly). The trial results are available on the sponsor's website.

Clinical trials subjects

The health culture of the population influences the enrolment of an appropriate number of suitable subjects in an unbiased manner (8). A basic principle in drug development is that subjects entering clinical trials are reasonably representative of the population that will later be treated with the tested drug. The investigator determines the number both of subjects according to their health status and the trial sites according to their capability to conduct a clinical trial. The number of subjects was an important factor in the planned course of the trial – in 14 cases the trials were terminated due to a small number of subjects, and in 28 cases the number of subjects was the reason for substantial trial protocol amendments.

The number of clinical trials subjects marked the biggest drop. The decline in enrolled subjects was greatest in 2021, when just one-third of the planned number of subjects participated in the conduction of clinical trials. When presenting the clinical trial subjects, we noted that due to the insufficient number of subjects in other countries, Bulgaria had been additionally included to the planned countries in one trial (33 subjects were enrolled).

Gender of clinical trials subjects

Gender dynamics of clinical trials subjects depends on the nature of the trial – the medical condition or disease being investigated and the composition of a specific vulnerable population group. In three cases the clinical trials subjects were male only and in six cases – female only (2019).

The therapeutic area of clinical trials was the most important factor in gender dynamics. For example, clinical trials for the therapeutic area of musculoskeletal diseases included predominantly male subjects.

Therapeutic area of clinical trials

New scientific approaches for drug discovery are expanding the scope of therapeutic areas. The modern therapeutic area is a function of the nature of the disease and the safety of therapeutic interventions. The complexity of the therapeutic area determines its leading importance in planning the cost of the trial, including the number of trial subjects. For example, the complexity of the clinical trials reviewed was systematized into 25 therapeutic areas **(Figure 2**), describing the medical conditions investigated in 659 words and the medical condition in easily understood language in 971 words.

Agency

Sponsors and their commercial status determine the implementation of international trends in the therapeutic area at a national level. The data includes systematized medical conditions that have been investigated. The large number of planned trials in the therapeutic area of skin and connective tissue diseases did not correspond to the most common diseases in Bulgaria, but to

the international trends for priorities of clinical trials (9). The COVID-19 treatment with launched drugs was a therapeutic area for 18 clinical trials in Bulgaria (971 enrolled subjects).

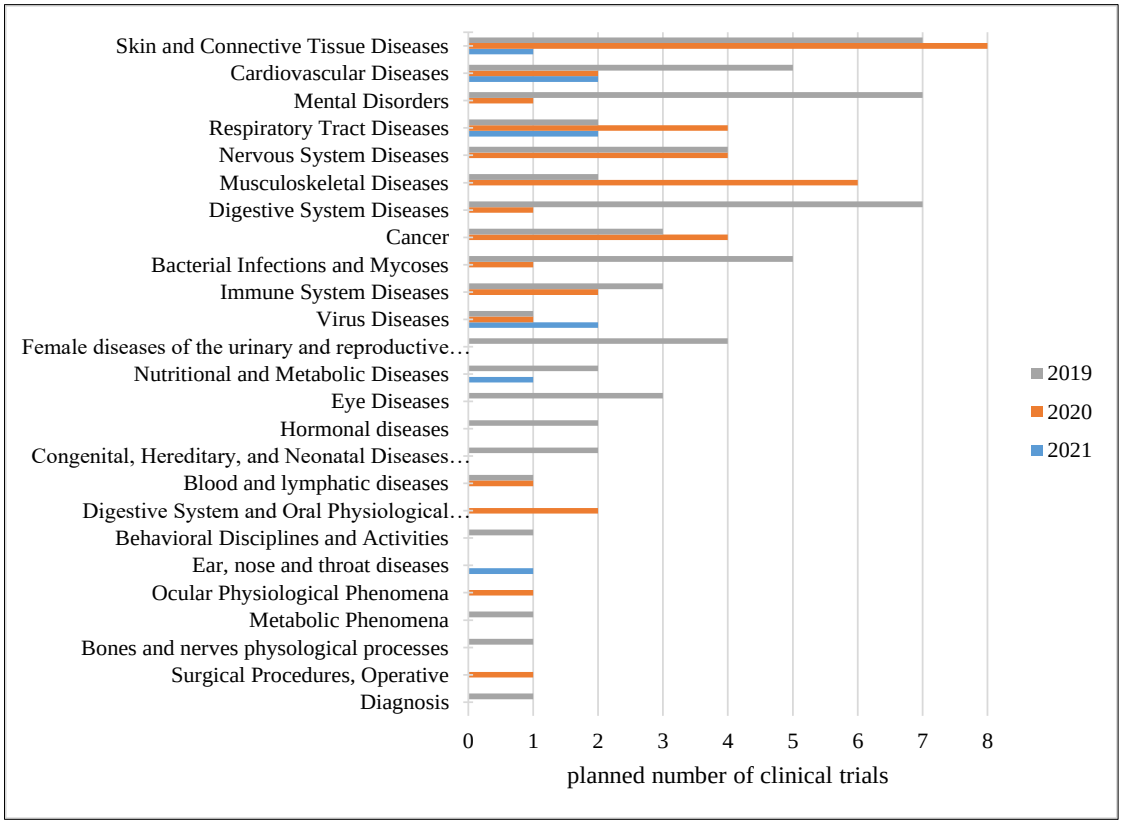

Figure 2. Therapeutic area of clinical trials
Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines

Scope of clinical trials

Data from the database identified 11 clinical trial scopes **(Figure 3).** The leading positions in terms of safety and efficacy as a scope of clinical trials in Bulgaria confirmed the application of modern trends thanks to the participation in multi-regional trials. Other trial scopes included tolerability (11 clinical trials), biomarkers (7 clinical trials), immunogenicity (7 clinical trials), and the subject's quality of life (6 clinical trials).

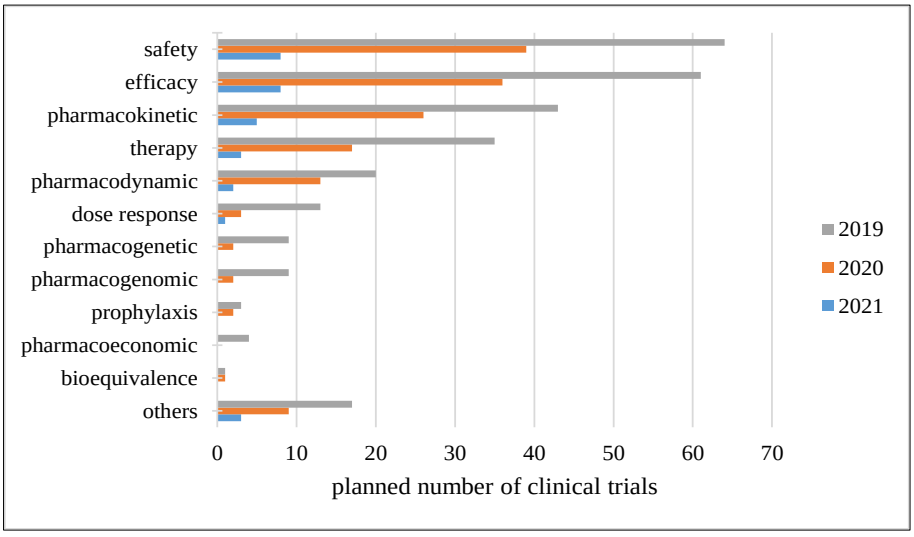

Figure 3. Scope of clinical trials
Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

The scope of the clinical trials explained the subject groups from Bulgaria – mostly patients and to a lesser extent – healthy volunteers. Trial scope and subject groups determined subject recruitment and insurance costs.

Trial type and phase

Clinical trials for therapeutic confirmatory (Phase III) were the most numerous **(Figure 4)**. There was only one trial combining Phase I, Phase II, and Phase III in which the medical condition being investigated was COVID-19. There was another trial combining Phase II and Phase III in which subjects were incapable of giving consent.

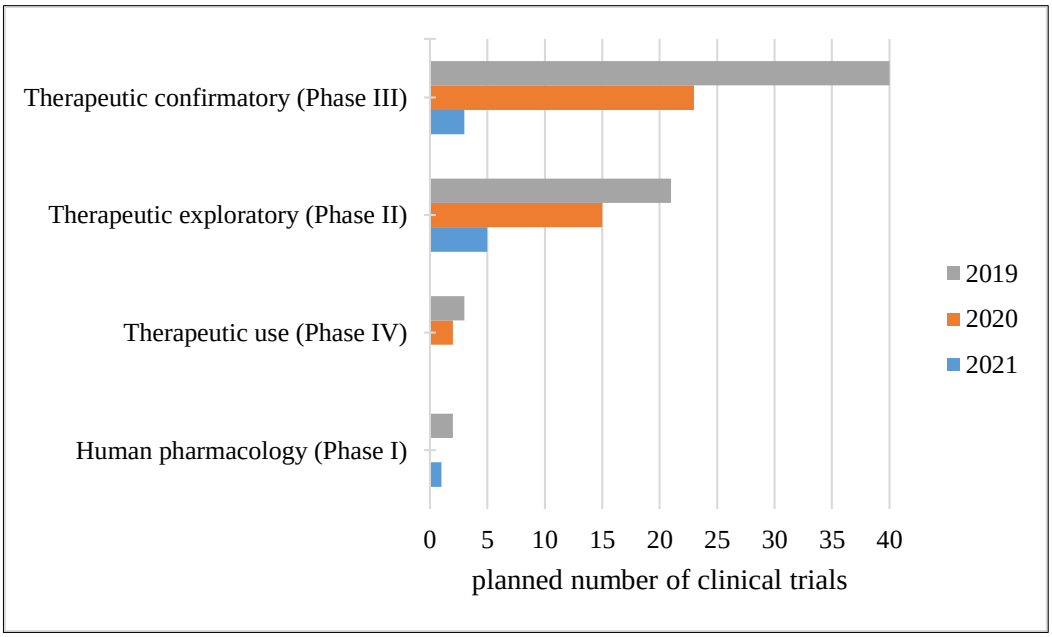

Figure 4. Type and phase of clinical trials
Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

In the database, the type and phase influenced the dynamics of clinical trials:

- Phase I clinical trials were planned for a specific group of trial subjects because the trials were related to new vaccines and with the smallest number of countries involved in conducting the clinical trials.
- Phase II clinical trials had the most significant protocol changes at the request of the competent authorities for changes to the enrolled trial subjects.
- Phase III clinical trials had the largest number of trial subjects enrolled because of the included experimental and control groups to detect a clinically significant difference. The choice of a control group is always a critical decision in designing of a clinical trial because this choice affects the inferences that can be drawn from the trial (9).
- Phase IV clinical trials were planned for specific age groups: 18-64 years and ≥ 65 years.

Design of clinical trials

The scope and type of a clinical trial mainly determined its design. The large number of randomized clinical trials corresponded to the scope of the safety trial and the type of therapeutic confirmatory trial **(Figure 5).** The randomized design of the trials included a parallel group and the number of subjects enrolled increased to more than 90% of the planned trial subjects. Uncontrolled clinical trials were used for trials whose scope was to determine the pharmacokinetic effects (Phase IV). The small sample size of trial subjects from Bulgaria necessitated the application of a cross-over design for the clinical trials.

Clinical trials with a double-blind design had the largest difference between the reported and planned number of trial subjects (300%). Uncontrolled clinical trials were planned for trial subjects from Bulgaria only. Open clinical trials had the broadest in scope and therefore included a large number of trial subjects.

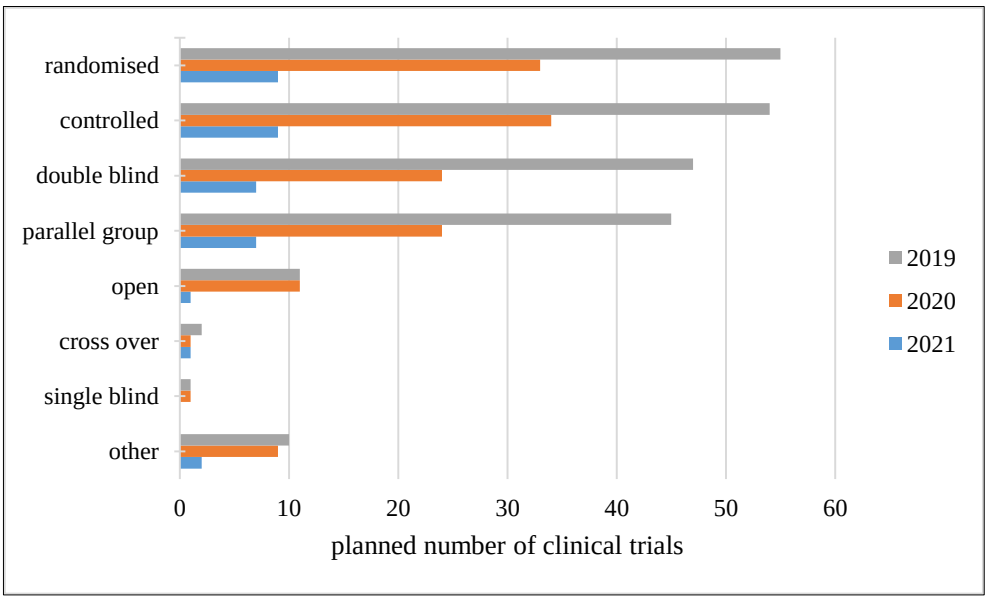

Figure 5. Design of clinical trials
Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

Age range of clinical trials subjects

The planned age groups of the clinical trials subjects corresponded to the demographic situation in Bulgaria (11). The adult age group formed 71% of all clinical trials subjects **(Figure 6).** In 2019, all age groups were clinical trials subjects, in 2020 – children, adolescents and adults, and in 2021 – adults only. As patients aged, insurance costs increased (12).

The number of clinical trials subjects was declining due to a decrease in the adult and elderly age groups. As the age of the trial subjects increased, the number of countries participating in the trial decreased, with young subjects participating in a trial in approximately 30 countries and adults in Bulgaria and approximately in four other countries. As the age of the trial subjects decreased, the duration of the trials decreased – clinical trials for subjects in the elderly group had the duration of 530 planned days, and for the young age group – approximately 450 days.

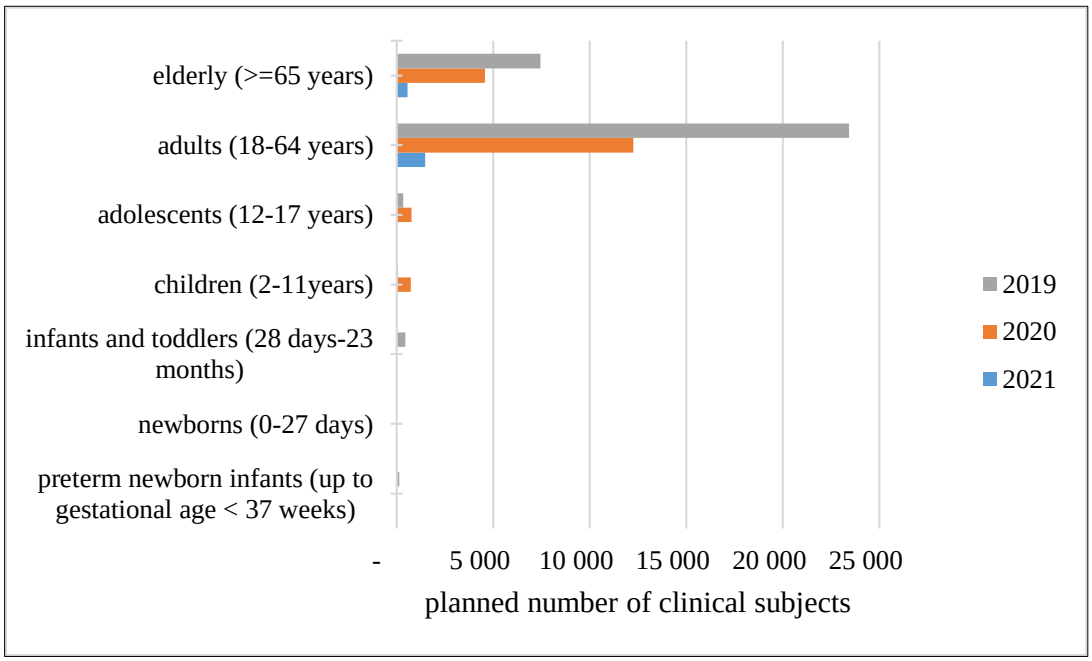

Figure 6. Age range of subjects to be included in clinical trials
Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

The therapeutic area of the clinical trial largely determined the age groups, for example, cancer and endocrinology were for adult age group. Another example, the new-born age group, were clinical trial subjects with a therapeutic area of eye diseases, the adult group – of cardiovascular disease investigations, the elderly group – of mental disorders. Another factor in determining the age group was the scope of the clinical trial – the adult group and the elderly group were subjects of dose-response clinical trials.

Health status of clinical trials subjects

Patients were subjects in 110 clinical trials, of which in 100 trials the subjects were specific vulnerable populations **(Figure 7)**. Healthy volunteers were subjects in two trials, for therapeutic use (Phase IV) with a parallel group. There were no cases involving pregnant women as clinical trial subjects.

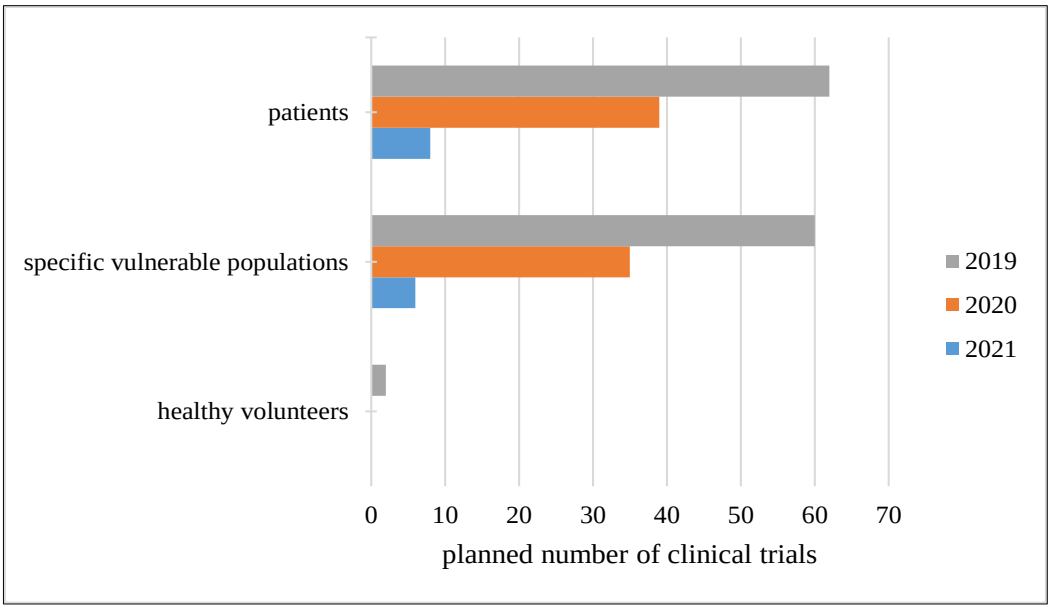

Figure 7. Groups of clinical trials subjects

Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

In 11 cases, the clinical trials subjects were unable to give consent in person – paediatric patients, subjects with mental illness, and subjects that used a court-appointed legal representative. Women of childbearing potential using contraception were subjects in 96 clinical trials, and women of childbearing potential not using contraception – in two clinical trials.

DISCUSSION

The dynamics of clinical trials is a consequence of two factors: global trends for launching new drugs in certain therapeutic areas and the capacity of trial sites to conduct clinical trials. The clinical trials reviewed (2019-2021) were a consequence of the decisions taken in the last decade by leading pharmaceutical companies and international organizations to launch new drugs (pipeline drugs).

Shifts in national legislation for registration of autonomous trial sites were a leading factor for adapting to the international environment. The planned therapeutic areas of reviewed clinical trials did not correspond to the most common diseases in Bulgaria, while the planned age groups were in line with the local demographic trend.

The main advantage of the selected registers was the ability to systematize the factors for the dynamics of clinical trials. On the other hand, the structure of the registers was a disadvantage for in-depth study of the dynamics. For example, there was no opportunity to review the contribution of clinical trials to Bulgarian healthcare, apart from benefits to the participating trial sites, subjects and physicians. Population size of a country was not a factor in the dynamics of clinical trials. For example, Bulgaria (seven million inhabitants) had more clinical trials subjects than China and India, whose population is respectively 1 411 million inhabitants and 1 425 million inhabitants **(Table 2).**

Table 2. *Number of subjects in multi-regional clinical trials conducted in Bulgaria and in countries with large populations*

Clinical trial №	Bulgaria	China	India
2016-004086-87	53	3	
2017-002144-33	1		1
2018-002930-19	36		83
2018-003985-15	12		20
2019-003431-33	177	81	
2020-001083-29	24	16	

Sources: European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency

Modern clinical trials are conducted in multiple regions due to the need to enrol an appropriate number of suitable trial subjects in a reasonable time as well as to create a market for the test drug after its approval by the competent authority.

CONCLUSIONS

The article reviews the dynamics of clinical trials in Bulgaria (2019-2021). The results show that it is influenced by international drug launch trends and the ability of trial sites to conduct clinical trials. The COVID-19 pandemic is a factor in the high number of prematurely ended trials. Population of the country is not a factor in the dynamics of clinical trials subjects.

The results have a multiplier effect on the remaining stages of the value-added chain for new drugs and it is challenging to assess their contribution to clinical trials worldwide.

REFERENCES

1. World Health Organization. *A healthy return: Investment case for a sustainably financed WHO*. Geneva, 2022.
2. Paquettea M, Kelecevicc J, Schwartza L, Nieuwlaata R. Ethical issues in competing clinical trials. *Contemporary Clinical Trials Communications,* 14:1-4, 2019.
3. KPMG Bulgaria. *Clinical trials in Bulgaria*. Main challenges. Sofia, 2015.
4. Kirilov B, Antonov L, Grigorov E. Dynamics and sources of adverse drug reaction reports related to COVID-19 vaccines in Bulgaria. *Social Medicine*, 30(1):13-16, 2022.
5. European Commission. *Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic*. Brussels, 2022.
6. Gergova V, Serbezova A, Sidjimova D. Analysis on decentralized clinical trials in some European countries. *Archives of the Balkan Medical Union*, 56(4):394-401, 2021.
7. Committee for Medicinal Products for Human Use. *ICH guideline E17 on general principles for planning and design of multi-regional clinical trials*. EMA/CHMP/ICH/453276/2016. London, 2017.
8. Zaykova K, Nikolova S, Pancheva R, Serbezova A. A survey of knowledge, attitudes and practice of antibiotics among Bulgarian population. *Biotechnology & Biotechnological equipment*, 36(1):933–941, 2022.
9. World Health Organization. *World health statistics 2022*. Geneva, 2022.
10. European Medicines Agency. *Choice of control group in clinical trials*. CPMP/ICH/364/96. London, 2006.
11. OECD/European Observatory on Health Systems and Policies. *Bulgaria: country health profile 2021, state of health in the EU*. OECD Publishing, Paris/European Observatory on Health Systems and Policies. Brussels, 2021.
12. Savova A, Manova M, Tachkov K, Petrova G. The role of insurance policies in the drug pricing landscape. *Expert Review of Pharmacoeconomics & Outcomes Research*, 24(3):1-14, 2024.