Trakia Journal of Sciences, No 2, pp 118-129, 2025
Available online at:
https://trakia-uni.bg

ISSN 1313-3551 (online) doi:10.15547/tjs.2025.02.007

Original Contribution

THE ADDED VALUE OF STATE-OWNED HOSPITALS IN CONDUCTING CLINICAL TRIALS

M. Nedelchev[1*], Y. Nedelcheva[2]

[1]Ministry of Education and Science, Sofia, Bulgaria
[2]University of Chemical Technology and Metallurgy, Sofia, Bulgaria

ABSTRACT

Objective: The object of the article is to review the clinical trials conducted in Bulgarian state-owned hospitals during the COVID-19 pandemic (2019-2022). **Material and methods**: We have created a unique database of clinical trials from public registers of competent authorities. Our review is based on the content of the protocols of 550 clinical trials conducted in all 62 state-owned hospitals. **Results**: The number of clinical trials is decreasing, as is the number of trial centres in state-owned hospitals. The clinical trial sector will not go back to pre-pandemic levels, as we predict for the year after the pandemic (2023). In the new reality, reduced budget and declined state funding, the attitudes of state-owned hospitals and patients are shifting towards the benefits of clinical trials. The primary motive for state-owned hospitals to conduct clinical trials is not revenues, but rather access to new drugs and treatment methods. **Conclusions**: We explain the decline in the number of clinical trials with the national measures addressed to the challenges of the COVID-19 pandemic. The therapeutic area of clinical trials is tailored to the local demographic trend and is not aligned to the most common diseases in Bulgaria. Therefore, Bulgaria is more of a market for the launching tested drugs than a market for testing new drugs.

Key words: COVID-19 pandemic, trial protocol, Bulgaria

INTRODUCTION

Modern society has challenged established perceptions and attitudes towards institutions with a traditional influence on society development, such as hospitals. In the new reality, state-owned hospitals reach two opposing goals – a social goal and a fiscal goal. In achieving the social goal, treating patients and maintaining the good health of citizens, state-owned hospitals should also achieve their fiscal goal – keeping certain financial indicators at macro level. In this regard, our object is to present the value added of state-owned hospitals to the healthcare sector in conducting clinical trials.

In Bulgaria the health spending has grown since 2000 and at the beginning of the COVID-19 pandemic their level is 7.1% as a share of gross domestic product (1). The biggest contribution to the economy belongs to state-owned hospitals – their revenues are 3 billion leva and have served over 900,000 patients (2). Despite the measures taken by the competent authorities the out-of-pocket payments, primarily for pharmaceuticals and direct payments for services not in the benefits package, remain the highest in the EU (3). As a result of the high costs of health care and the low capability for health payments by residents, a hospital-centric healthcare delivery model has been imposed in Bulgaria (4).

Over the last decade the Bulgarian healthcare sector has established itself as a world destination for clinical trials – it ranks as the 20th country in market share worldwide (5) and 6th for the number of clinical trial centres (6). A new point of view is beginning to emerge stating that clinical trials are not only an important source of prestige for many hospitals (7), but a decision to develop new drugs and treatment methods.

The complicated epidemic situation caused by the spread of COVID-19 poses serious challenges to the entire healthcare sector. State-owned hospitals find themselves in the most

***Correspondence to:** *Miroslav Nedelchev, PhD, PhD, Ministry of Education and Science, Sofia, Bulgaria, m.nedelchev@mon.bg*

difficult situation (8). Sponsors proposed variations of decentralized elements and hybrid approaches of conducting clinical trials activities and procedures (9). The pandemic has another impact on the healthcare system – an increase in the number of clinical trials to find a vaccine for COVID-19 (10). The introduced rules strengthened the leading principle of conducting clinical trials based on benefit-risk considerations and prevailing of trial subject safety (11).

Our analysis covers the added value of state-owned hospitals in conducting clinical trials due to their excessive requirements for accountability and disclosure under OECD guidelines for efficient use of public resources (12). We draw attention to the resources provided by sponsors and investigators. The time range causes a main difficulty in our analysis, as annual inflation and other macroeconomic indicators differ significantly given the dynamics in the economy caused by the COVID-19 pandemic. For example, the oldest trial (EudraCT Number 2011-004154-25) started in 2013 (planned duration of seven years), when annual inflation in Bulgaria was 0.9%, and in 2019 – 3.1%.

MATERIAL AND METHODS

We use quantitative data to achieve our review object. To generate appropriate conclusions, we have selected reliable information sources. To address our curiosity about clinical trials conducted in state-owned hospitals, we introduced the following inclusion and exclusion criteria:

Principal inclusion criteria. We selected sources that were publicly available and updated regularly. First, we formed a set of clinical trials that were authorized for implementation in Bulgaria by the competent authority, the Bulgarian Drug Agency (13). Second, we extracted the protocol details for each clinical trial following the structure of the European Union Clinical Trials Register (14).

Principal exclusion criteria. Due to the processing of secondary data, we studied those clinical trials that had a complete dataset. Another criterion was the availability of data on clinical trial revenues of state-owned hospitals. Based on these criteria, we created a database of clinical trial protocols conducted in state-owned hospitals – 550 clinical trials in all 62 state-owned hospitals. The database is unique, universal and pioneering. The collected information is systemised for sponsors and investigators, competent authorities and entities in the development of a competitive strategy at the micro and macro level. Our data are suitable for studying the future trend of clinical trials as well as for comparative analysis for other countries.

RESULTS

Medical centres for a specific disease in Bulgaria have had the right to conduct clinical trials since the country became an EU member-state in 2007. The increased number of medical sites and modern legislation have attracted interest in conducting clinical trials. Bulgaria has reported a meteoric rise in the number of clinical trials – an increase of 431% per year (15). As the number of clinical trials increases and the number of sites expands, researchers pay little attention to the added value of hospitals in testing new drugs and treatments. We noted this new paradox, which we called the ‘phenomenon of inertia’: as the number of clinical trials is increasing, the attention of academic researchers to clinical trials has been decreasing.

The trend towards increasing the number of clinical trials is shifting. Since 2022, there is a decrease in both the number of clinical trials and the number of sites in state-owned hospitals for conducting clinical trials (**Figure 1**). Our explanation for the observed shift is the COVID-19 pandemic, which limited doctor-patient contacts, as well as greater commitments of state-owned hospitals under the national pandemic policy.

After 2022, a declining trend in clinical trials started, with the lowest reported number of sites in state-owned hospitals. The COVID-19 pandemic had another impact on the health care system – shifting clinical trials from multi-profile state-owned hospitals to specialized state-owned hospitals, as well as from state-owned hospitals to autonomous medical centres for specific diseases.

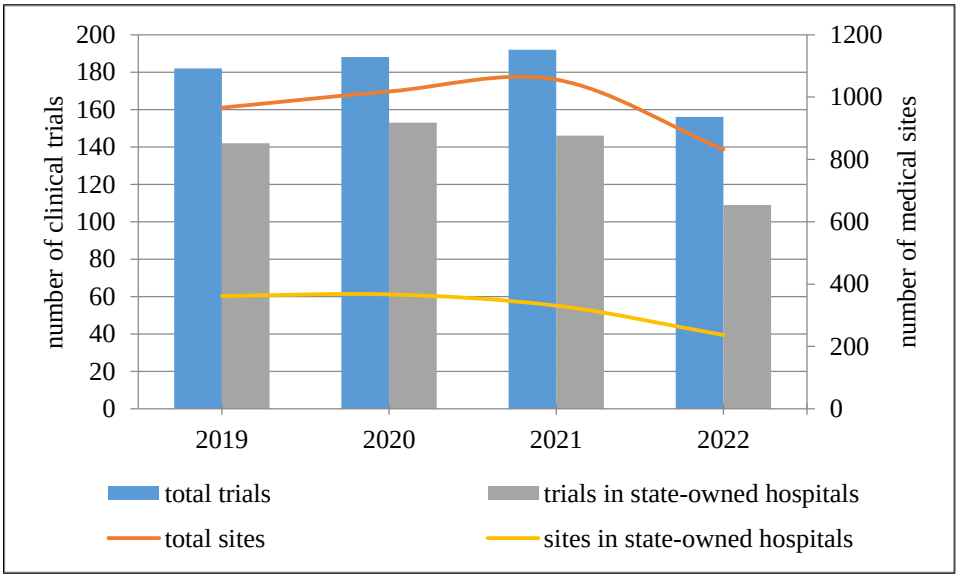

Figure 1. Number of clinical trials and clinical trial sites
Source: Register of Authorised Clinical Trials, Bulgarian Drug Agency

The decline in clinical trials found in 2022 had an additional dimension – a decrease in completed or prematurely ended clinical trials (**Figure 2**). Clinical trials authorised in previous years were reported with the status of prematurely ended, temporarily halted or restarted in accordance with the pandemic reality. Clinical trials with a completed or prematurely ended status do not always mean that the purpose of the trial has been achieved, as in most cases the sponsor has decided to close the files due to the COVID-19 pandemic. In some cases, the clinical trial is restarted as a new trial in the register, further increasing the number of clinical trials.

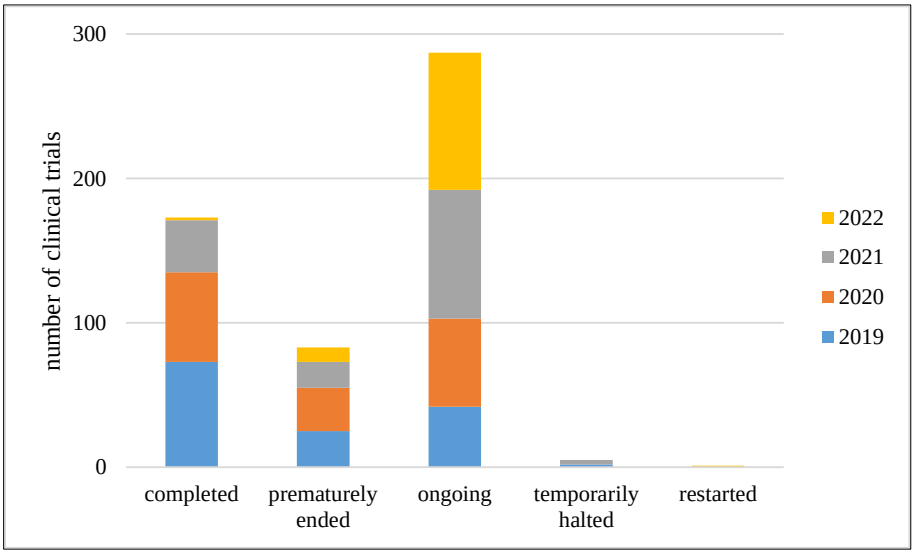

Figure 2. Status of clinical trials
Source: European Union Clinical Trials Register, European Medicines Agency

Clinical trials with on-going status account for half of all cases planned for conducting on site in state-owned hospitals. These trials are initiated by a small number of sponsors in therapeutic areas in line with international health trends – cancer, diseases of the immune system, diseases of the nervous system and diseases of the digestive system. The on-going trials are planned to include a large number of subjects in Bulgaria (over 15 500 persons) due to control groups in the trial design. Their duration reflects the type and scope of the clinical trial: a total of 817 years for all 550 clinical trials analysed.

Sponsors. Bulgaria began to attract the attention of sponsors as part of the EU market since 2007. The clinical trials sector is developing through

inorganic growth – acquisitions of local investigating companies by the R&D units of leading sponsors from pharmaceutical countries. Resources are concentrated and the local market is transforming towards completing multi-regional clinical trials. Interest in Bulgaria is constant from a narrow circle of sponsors – the drop in the number of sponsors is greater than the drop in the number of clinical trials (**Figure 3**).

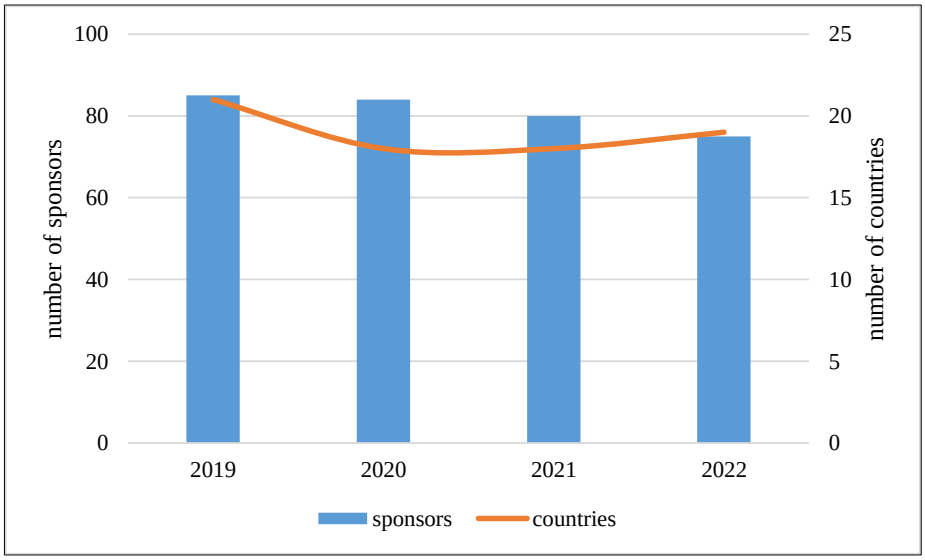

Figure 3. Sponsors and sponsor countries
Source: European Union Clinical Trials Register, European Medicines Agency

Over 200 sponsors have conducted clinical trials in Bulgarian state-owned hospitals. The widest circle of sponsors is reported in 2019, the narrowest – in 2022. The status of all sponsors is commercial, except one case (EudraCT № 2018-003671-35). In 29 cases, clinical trials were supported financially or materially by organisations from the United States. There is only one case (2020) of a sponsor from Bulgaria – Huvepharma, a human and animal drug manufacturer.

Data in 2021 formed the top 10 sponsors by number of clinical trials (**Figure 4**). They conducted 24% of the total number of clinical trials in state-owned hospitals.

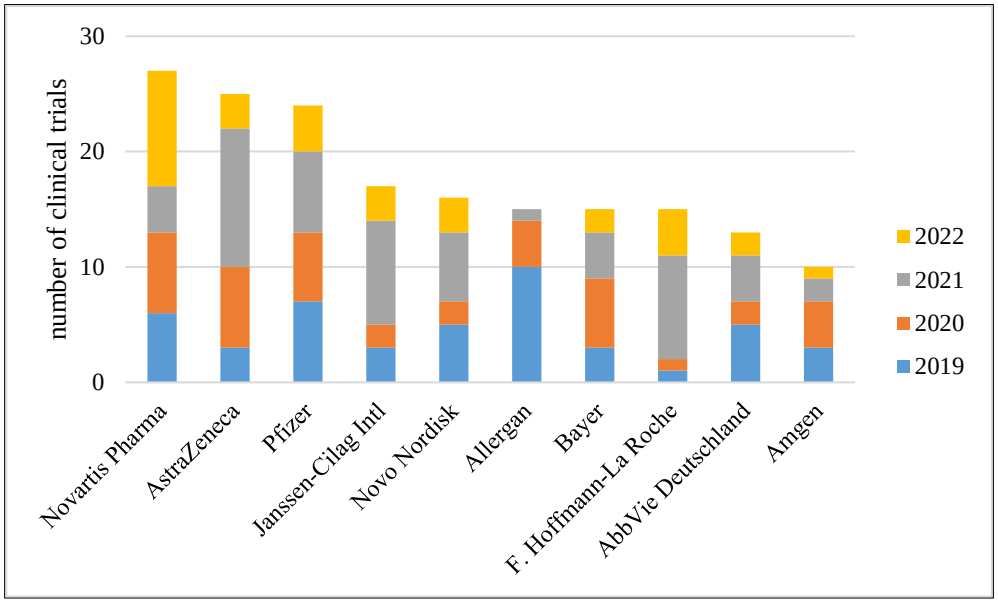

Figure 4. Top 10 sponsors
Source: European Union Clinical Trials Register, European Medicines Agency

The number of clinical trials of three sponsors is decreasing (Amgen, AbbVie Deutschland, and Allergan). Due to this trend, the number of clinical trials in state-owned hospitals, in certain therapeutic areas (diseases of the digestive system and mental disorders) is reduced, as well as for trials with a completed status.

The number of clinical trials of two sponsors is increasing (F. Hoffmann-La Roche and AstraZeneca). As a result, there is a rise in the number of on-going status clinical trials for therapeutic areas (cancer and cardiovascular diseases), the number of sites in state-owned hospitals (multi-centre clinical trials), the conduct of trials in several countries (multi-regional clinical trials), and the number of subjects due to the presence of a parallel group in the design of clinical trials. The dynamics of these sponsors reduce the age of subjects in clinical trials.

Country of the sponsor. Country data reflect sponsor dynamics. For example, the sponsors mentioned above reduce the shares of the United Kingdom and Germany, and increase the shares of Switzerland and Sweden (**Figure 5**).

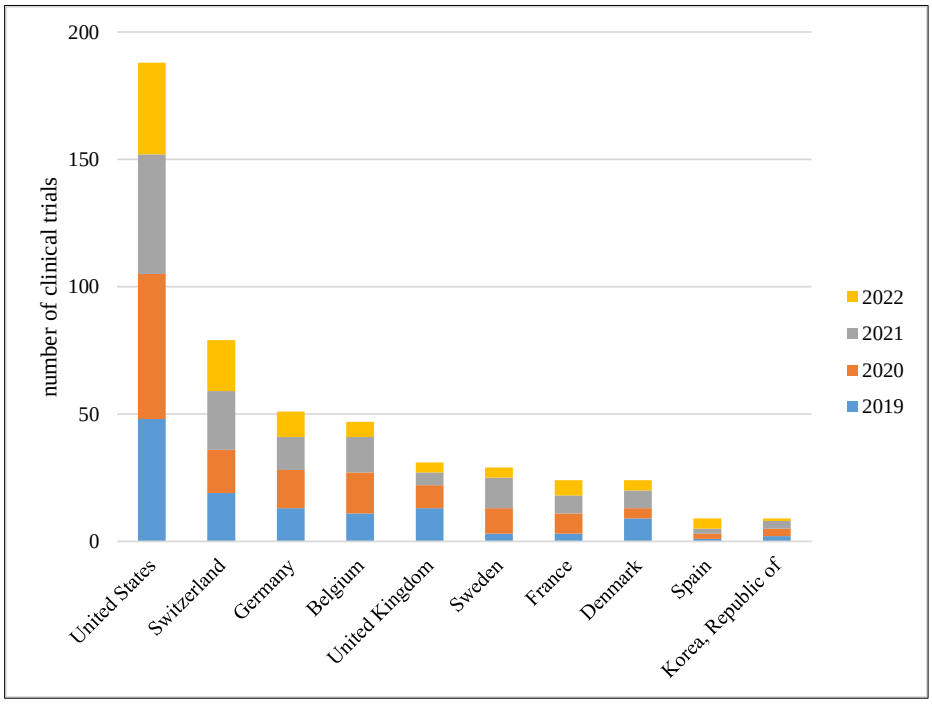

Figure 5. Top 10 sponsor countries
Source: European Union Clinical Trials Register, European Medicines Agency

When reviewing sponsor countries, we take into account the withdrawal of the United Kingdom from the European Union in 2020 (Brexit). Half of the clinical trials have sponsors outside the European Union. In 23 cases, the sponsors are subsidiaries of US companies.

Therapeutic areas. The main therapeutic areas of clinical trials are chronic and hereditary diseases which are not the most common diseases in Bulgaria (16). In a small number of cases, clinical trials are related to infectious diseases (**Figure 6**). There is no evidence of an increase in the number of clinical trials with therapeutic areas for the COVID-19 pandemic, but there is evidence of trials of similar diseases, or rather of the effects of the virus, that were known at the beginning of the pandemic.

We can point to the differentiation of clinical trials by their therapeutic areas and the specialisation of state-owned hospitals and their sites. In most cases, clinical trials are on diseases and body processes, and to a lesser extent, on analytical, diagnostic and therapeutic techniques and equipment. ‘Not possible to specify’ is the therapeutic area for two trials (2019 and 2020).

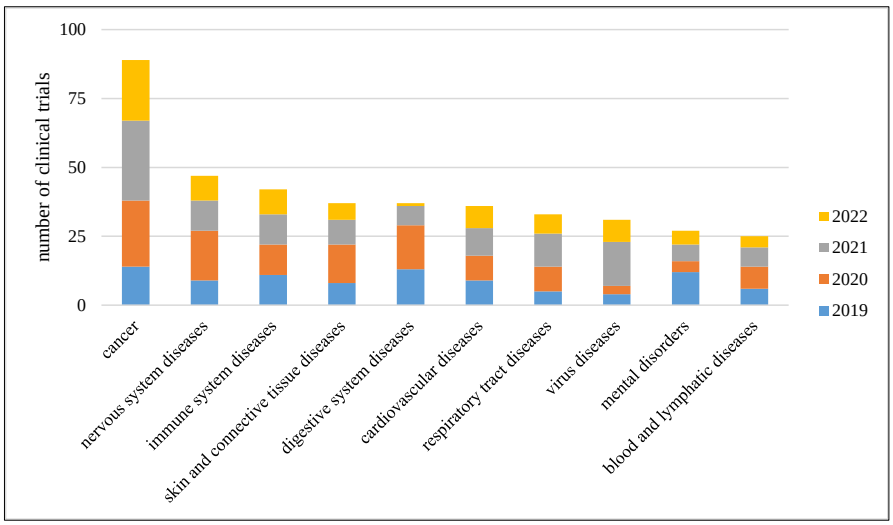

Figure 6. Top 10 therapeutic areas of clinical trials
Source: European Union Clinical Trials Register, European Medicines Agency

Scopes of the trials. The therapeutic area and a site's ability to conduct a clinical trial determine the scope of the trial. There is a lot of inertia and resistance as decisions for new drugs are implemented 5-8 years in advance and the only option for the sponsor is to change clinical trial sites or trial host countries. Depending on the life cycle of drugs in production line and the aim of the sponsors, a decline in the main scopes of clinical trials (safety and efficacy) has been reported (**Figure 7**).

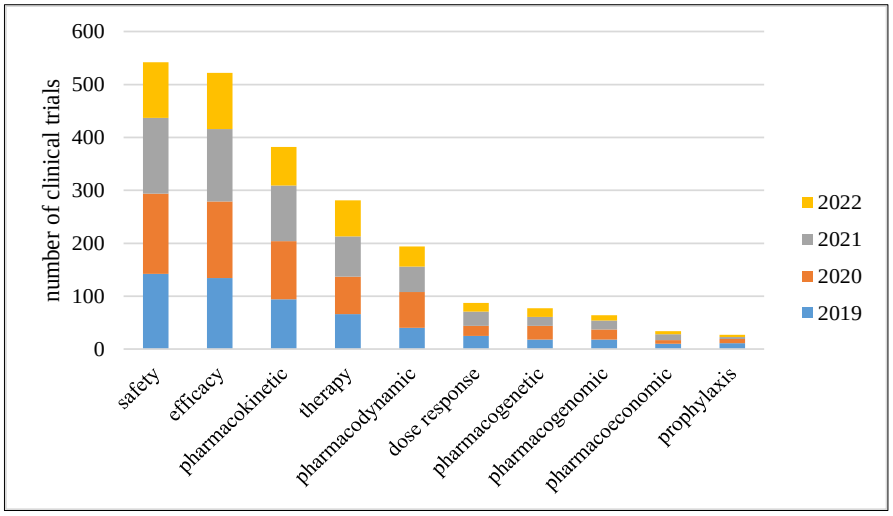

Figure 7. Top 10 scopes of clinical trials
Source: European Union Clinical Trials Register, European Medicines Agency

The data establishes a link between the scope of the clinical trial and the specific state-owned hospital. For example, clinical trials for pharmacodynamics are decreasing due to an increase in the commitments of state-owned hospitals with patients with the COVID-19 virus, as well as a decrease in clinical trials with subjects under the age of 18 (subjects who are not able to give consent in person).

7% of the clinical trials are reported as 'other' including 'tolerability', 'immunogenicity', 'biomarkers', and 'quality of life'. We recommend further research into the 'other' scopes and updating the structure of the registers.

Trial type and phase. The added value of Bulgarian state-owned hospitals as sites for clinical trial largely determines the type and phase of the trials. While phase I clinical trials are conducted in a country that retains the patent and owns other forms of intellectual property on the tested drug, phase II and phase III require large numbers of subjects worldwide with varying health status. For this reason, state-owned hospitals in Bulgaria mainly conduct clinical trials phase II and phase III (**Figure 8**).

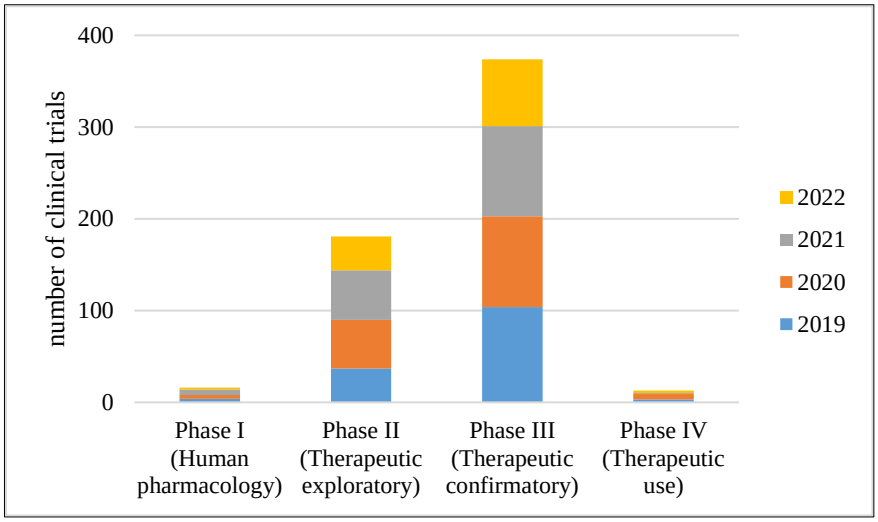

Figure 8. Type and phase of clinical trials
Source: European Union Clinical Trials Register, European Medicines Agency

Phase I clinical trials are planned for conducting primarily in specialized state-owned hospitals. Their scope is pharmacodynamic, with an expected duration of three years, for small number of patients and with a gender difference (predominantly male). There are eight trials for first administration to humans (two cases in 2019, two cases in 2020, three cases in 2021, and one case in 2022) and two trials for bioequivalence study (one case in 2019 and one case in 2021).

Phase II clinical trials are planned in a wide range of sites, including multi-profile state-owned hospitals. The number of these clinical trials reflects the health status of the local population: a narrow circle of a therapeutic area with a large number of patients (cancer, diseases of the digestive system and diseases of the nervous system). Their main scope is pharmacokinetic.

Phase III clinical trials have a large number of sources of financial or material support for clinical trials. These trials are planned in a large number of countries, which is a challenge given the requirements of national competent authorities (for example, there is one case in 2020 planned for simultaneous conduction of the trial in 48 countries). They report a good ratio of enrolled to planned subjects for completed trials (more than 50% of planned subjects are enrolled).

Phase IV clinical trials are primarily for adults (18-64 years) and elderly patients (>=65 years), with a short trial completion period (more than one year). They are conducted in a small number of sites, mostly in state-owned hospitals, with the goal of drug substitution, and report for 50% of enrolled/planned subjects in clinical trials.

Registry data reported a small number of clinical trials as a combination of the individual phases (**Table 1**). These trials are conducted in a large number of countries and sites, incl. outside state-owned hospitals.

Clinical trials combining the separate phases are planned for a small number of therapeutic areas – cardiovascular diseases, cancer and congenital, hereditary, and neonatal diseases and abnormalities. These cases have a wide scope, for example one of the trials covered 12 therapeutic areas (prophylaxis, therapy, safety, efficacy, pharmacokinetic, pharmacodynamic, bioequivalence, dose response, pharmacogenetic, pharmacogenomic, pharmacoeconomic, others).

Table 1. *Number of clinical trials planned for more than one phase*

	2019	2020	2021	2022
Phase I + Phase II	1	3	4	1
Phase I + Phase III	1	1	2	
Phase II + Phase III	2	5	7	4
Phase I + Phase II + Phase III	1			

Source: European Union Clinical Trials Register, European Medicines Agency

***Design of the trials*.** The dynamics of the design followed the dynamics of the clinical trials except for the parallel-group and double-blind cases (**Figure 9**). These trials are mostly conducted in multi-profile state-owned hospitals.

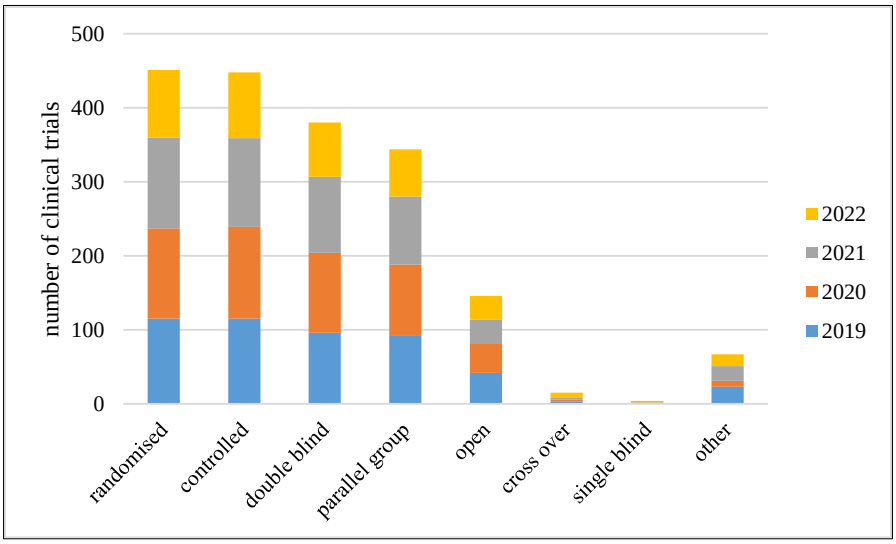

Figure 9. Designs of clinical trials
Source: European Union Clinical Trials Register, European Medicines Agency

The scope and type of the trial determine the trial design. For example, in the case of therapeutic exploratory (phase II) and dose response, the designs are randomised and parallel groups, while in the case of confirmatory (phase III) and therapy, they are randomised and double-blind. For 67 clinical trials, the design is 'other trial design description' and in most cases included a double dummy and dose ranging.

***Age range of subjects in clinical trials*.** As the age of subjects increases, the number of clinical trials in state-owned hospitals increases. Two age groups (elderly and adults) follow the dynamics of the number of clinical trials (**Figure 10**). The remaining age groups follow the dynamics of the remaining elements of clinical trials – scope, type and design. Clinical trials for subjects under 18 are planned for conducting mostly in state-owned hospitals compared to private hospitals.

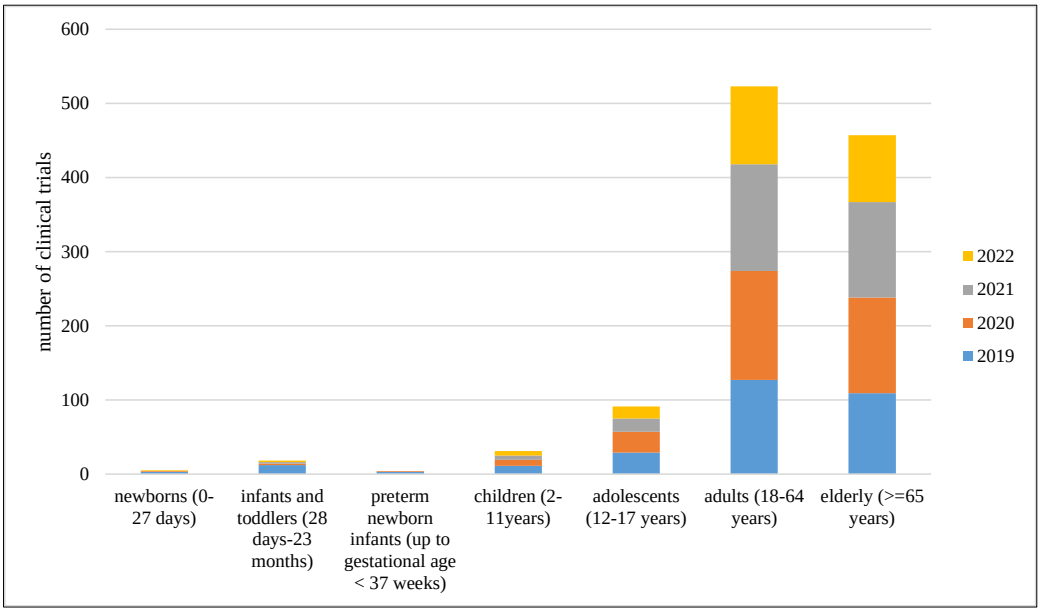

Figure 10. Age range of clinical trial subjects
Source: European Union Clinical Trials Register, European Medicines Agency

Groups of subjects under 18 years of age have safety as the scope of clinical trials. These groups have cases of only two types – therapeutic exploratory (phase II) and therapeutic confirmatory (phase III). Trials are planned for an average duration of 1.3 years. Reports reveal 84% of enrolled/planned subjects for the completed trials. There were

four cases where the clinical trial subjects were healthy volunteers (therapeutic areas – virus diseases and congenital, hereditary, and neonatal diseases and abnormalities; type – therapeutic confirmatory; design – parallel group).

***Gender of subjects*.** The gender dynamics of subjects follows the dynamics of clinical trials. A determinant of subject gender is the therapeutic area of the clinical trial. In a small number of cases, differences in subject gender have been reported.

Most cases with gender differences in subjects were conducted in state-owned hospitals. In 25 cases the trial subjects were only female (10 cases in 2019, six cases in 2020, five cases in 2021, and four cases in 2022), and in 17 cases – only male (seven cases in 2019, six cases in 2020, three cases in 2021, and one case in 2022). In a small number of completed female-only trials, the number of subjects enrolled was greater than the planned number of subjects.

For female-only clinical trials, therapeutic areas were for body processes (circulatory and respiratory physiological phenomena), while for male-only they are for diseases (congenital, hereditary, and neonatal diseases and abnormalities). The male-only type of clinical trials was mostly for therapeutic confirmatory (phase III).

***Group of trial subjects*.** Clinical trials in Bulgaria are mostly conducted in hospitals – in 97% of cases the subjects are patients. In 91% of cases, patients are specific vulnerable populations, and the duration of clinical trials is five years or more.

In nine trials, the subjects were healthy volunteers (four cases in 2019, two cases in 2020, two cases in 2021, and one case in 2022), conducted mostly in state-owned hospitals. The main difference between patients and healthy volunteers is in the therapeutic area of the clinical trial.

There were six cases whose subjects were pregnant women (three cases in 2019, one case in 2021, and two cases in 2022), one case of a breastfeeding woman (2019), and 32 cases of subjects who could not give consent in person (16 cases in 2019, six cases in 2020, one case in 2021, and nine cases in 2022). The last group included minors, illiterate or blind patients. Informed consent on their behalf was provided by a parent(s) or legally authorized representative appointed by the court.

DISCUSSION

The peak in the number of clinical trials was in 2020 – 28% of the total number of clinical trials authorized to be conducted in Bulgaria. Multi-profile state-owned hospitals have a higher number of clinical trials compared to specialized state-owned hospitals. In our review for added value of state-owned hospitals we point out 13 hospitals which did not conduct clinical trials – mostly specialized rehabilitation hospitals (**Figure 11**).

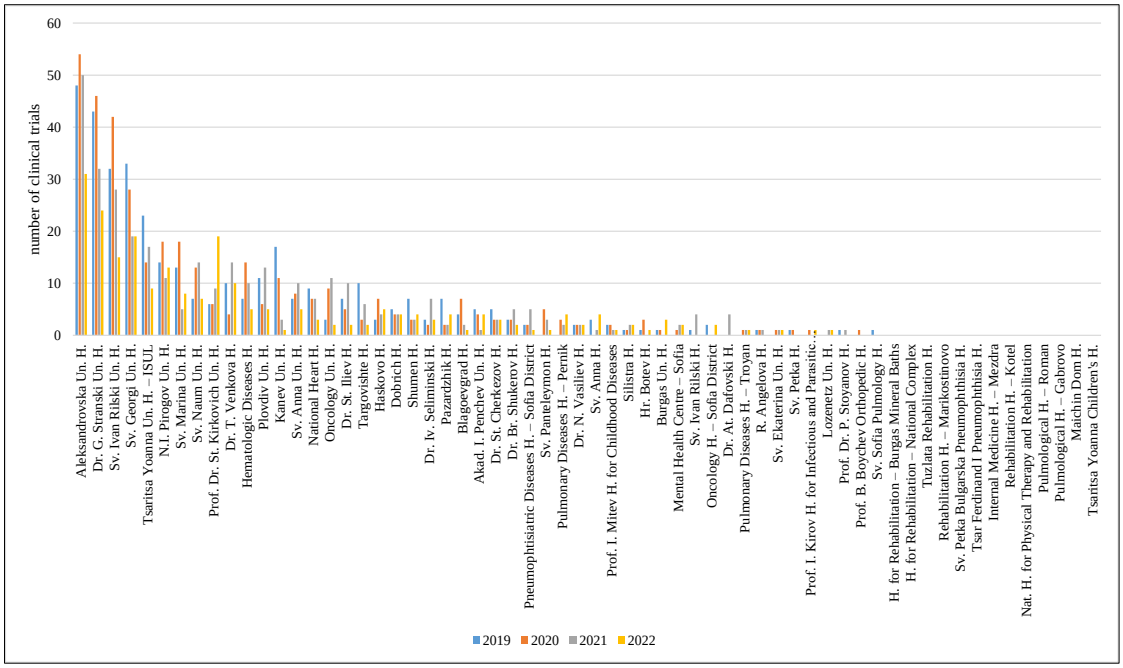

Figure 11. State-owned hospitals conducting clinical trials during the COVID-19 pandemic
Source: European Union Clinical Trials Register, European Medicines Agency

Revenues from clinical trials account for less than 3% of all revenues of state-owned hospitals (**Figure 12)**. The annual reports reveal higher revenues from clinical trials for specialized state-owned hospitals compared to multi-profile state-owned hospitals. It is necessary to conclude that state-owned hospitals were not motivated by financial reasons to conduct clinical trials. It is recommended to conduct additional research on the motives and goals of state-owned hospitals for conducting clinical trials, for example, access to new drugs and treatment methods, balancing the healthcare budget, social responsibility good practices.

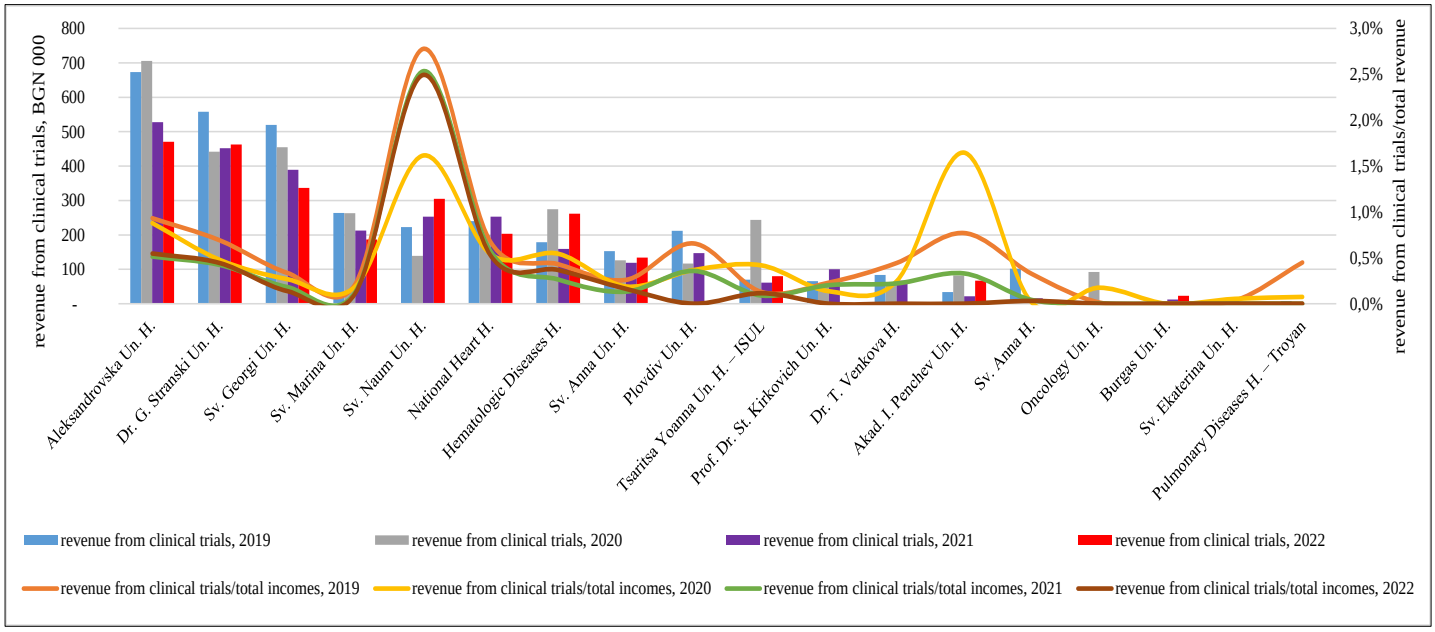

Figure 12. Revenue for state-owned hospitals
Source: Ministry of Health, Public Enterprises and Control Agency

Recruiting subjects is one of the challenges of conducting clinical trials. Best subject utilisation was reported in 2019, when more than 50% of planned patients were enrolled (**Figure 13**). In subsequent years, the percentage was reduced to 39%, 29%, and 0%, respectively, given the fact that a significant proportion of the planned number of trials were completed or prematurely ended (70% in 2019, 60% in 2020, 37% in 2021, and 11% in 2022).

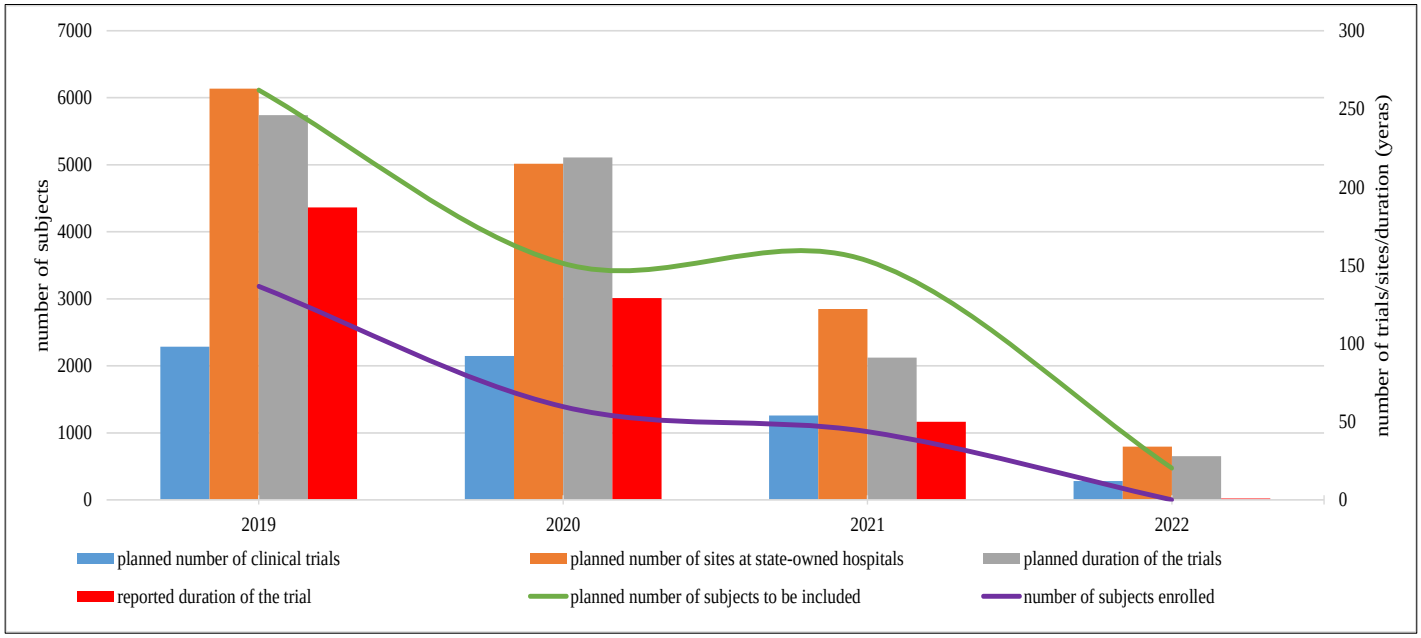

Figure 13. Completed or prematurely ended clinical trials
Source: European Union Clinical Trials Register, European Medicines Agency

Another resource, clinical trial time, is better utilised. The reported duration was 76% of the planned time in 2019 and we can argue that the 'time' resource was optimised. Assuming clinical trials number was constant in 2019-2022, our study reveals a time optimization. A possible explanation is better time planning or better utilisation of planned clinical trial time. Optimizing time also affects other resources such as the number of subjects, financial costs, expert composition, additional tested drugs, shorter time for drug launching, etc.

On-going clinical trials support our findings. Most of the number and subjects of clinical trials, as well as the planned time, have not yet been utilised (**Figure 14**). A reason for such optimism is the utilisation of a third resource – the sites in state-owned hospitals. Despite the decline in the clinical trial number, we have seen an increase in the number of completed trials, as well as an increase in the number of subjects enrolled.

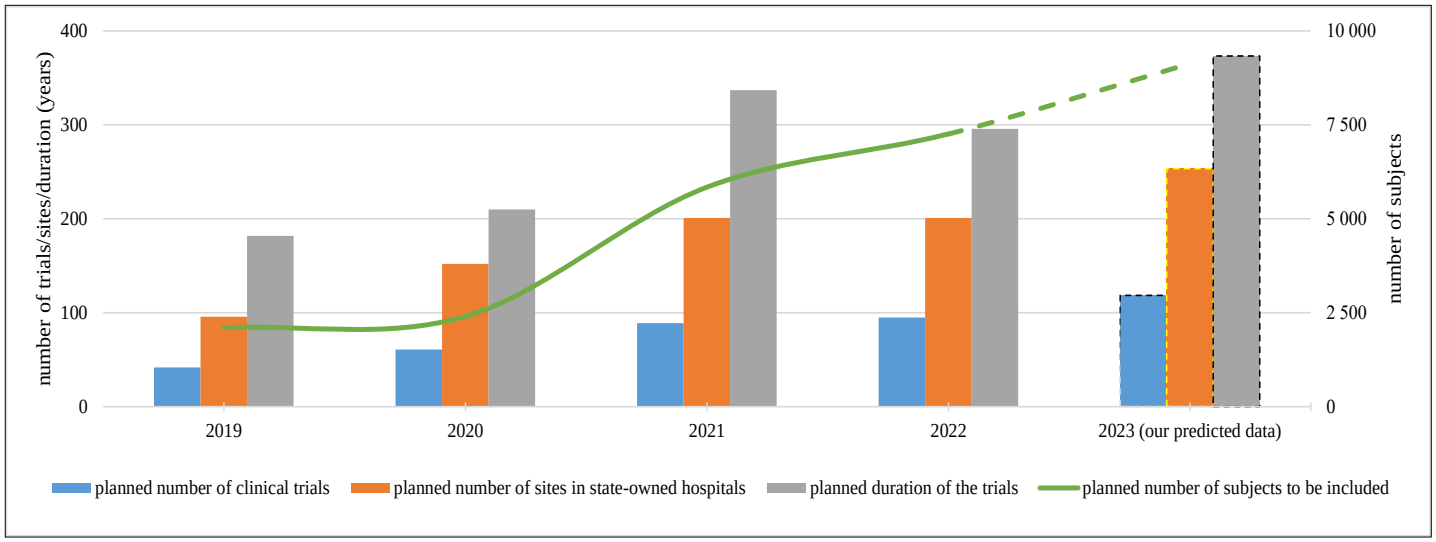

Figure 14. On-going clinical trials
Source: European Union Clinical Trials Register, European Medicines Agency

Resources in 2021 remain unattainable during the COVID-19 pandemic. There was a similar growth in the number of planned clinical trials, state-owned hospital sites, and trial duration, while the number of subjects showed the largest upward trend (peak in hospitalisation during the pandemic). The number of state-owned hospital sites increased more than the clinical trial number. The largest increase in resources was the planned duration of the trials, which we take as a benefactor for the successful conduct of the clinical trials and the achievement of the aims by the sponsors.

Based on our results in 2019-2022, as well as using engineering methods, we could predict clinical trial trends for the year after the COVID-19 pandemic – 2023 (**Figure 14**). In the near future, we expect an increase in the number of clinical trials to levels close to those before the pandemic. The number of clinical trials in state-owned hospital sites will increase given the end of the pandemic. The average duration of a trial will decrease by up to one year. The number of subjects in clinical trials will continue to grow, but at a slower pace. Our prediction reveals that the clinical trials sector will not go back to pre-pandemic levels.

CONCLUSIONS

Our study achieved its object – to review the clinical trials conducted in Bulgarian state-owned hospitals during the COVID-19 pandemic (2019-2022). Official registers, and more specifically their structure, are the main benefactors in achieving the object. We must also consider the impact of registers on our results: the structure of the registers determines the results achieved, incl. performing the study at a consolidated level due to the structural limitations of registers. We recommend updating the registers to provide greater opportunities to examine the features of each clinical trial. For example, the ability to enter data as 'other' is beneficial for sponsors and registry administrators, but at the same time red tape for researchers and stakeholders.

The COVID-19 pandemic has had a major impact on the dynamics of clinical trials. State policy during the pandemic reduced the share of state-owned hospitals in clinical trials

conducted. Multi-profile state-owned hospitals have a higher number of clinical trials than specialized hospitals. There is no evidence that revenues are the primary motive for state-owned hospitals to conduct clinical trials. The motive is rather intangible – access to innovative drugs and treatment methods in search of safety and efficacy (preferences to health, not wealth).

Through the objectives of clinical trials, we can gain insight into diseases and their treatment on the agenda of international organisations as well as in the national plans of home countries for the last 5-8 years, given the length of the clinical trial life cycles. Clinical trials are aligned to the aim of sponsors and do not respond in all aspects to trends in host countries. For example, data from clinical trials outline therapeutic areas that are not fit for the most common diseases in Bulgaria. The data also reveal a match in the demographic characteristics of clinical trial subjects and local demographic trends. Our findings identify host countries, including Bulgaria, more as a market for the tested drug rather than a market for testing a new drug.

The period of the analysed trials corresponded to the COVID-19 pandemic. Given the capabilities of registries for detailed analysis, we cannot draw conclusions about the impact of the pandemic on the dynamics of clinical trials. Our experience with registry data leads us to anticipate a shift in attention and resources to the pandemic and its health consequences, with clinical trials for diseases outside the scope of the pandemic being prematurely ended or temporarily halted. Our prediction would mean neglecting remaining diseases other than coronavirus, whose societal consequences are beyond the scope of a single article.

Our review is a contribution to informed decision-making and resource optimisation in conducting clinical trials.

REFERENCES

1. Dimova A, Rohova M, Koeva S, Atanasova E, Koeva-Dimitrova L, Kostadinova T, Spranger A, Polin K. Bulgaria: Health System Summary, 2022. WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies. Copenhagen, 2022.
2. Ministry of Health. Medical-statistical and financial information. Sofia, 2023.
3. OECD/European Observatory on Health Systems and Policies. Bulgaria: Country Health Profile 2023, State of Health in the EU. OECD Publishing, Paris/European Observatory on Health Systems and Policies. Brussels, 2023.
4. Mitkova Z, Doneva M, Gerasimov N, Tachkov K, Dimitrova M, Kamusheva M, Petrova G. Analysis of Healthcare Expenditures in Bulgaria. *Healthcare (Basel)*, 10(2):274, 2022.
5. German-Bulgarian Chamber of Industry and Commerce. *Pharmaceutical Industry in Bulgaria*. Sofia, 2021.
6. International Trade Administration. Bulgaria – Healthcare and Life Sciences. Washington, DC, 2024.
7. Advisen. Clinical Trial Research in Hospitals. New York, 2012.
8. Public Enterprises and Control Agency. *Annual summary report on state-owned public enterprises for 2021*. Sofia, 2022.
9. 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.
10. Georgiev K, Kirilov B, Georgieva M. Pharmacological features of drugs with potential activity against COVID-19. *Pulmonology Science*, 1: 11-18, 2020.
11. European Commission. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic. Brussel, 2022.
12. Organisation for Economic Co-operation and Development. *OECD Guidelines on Corporate Governance of State-Owned Enterprises*. Paris, 2015.
13. Bulgarian Drug Agency. *Register of Authorised Clinical Trials*. Sofia, 2025.
14. European Medicines Agency. *European Union Clinical Trials Register*. Amsterdam, 2025.
15. Bartoszkiewicz M, Kufel-Grabowska J, Litwiniuk M. Number of clinical trials of new therapeutic agents in the European Union countries of Central and Eastern Europe, 2000-2019. *Polish Annals of Medicine*, 29(1):26-30, 2022.
16. Dimova A, Rohova M, Polin K. Bulgaria: Health System Summary, *2024*. European Observatory on Health Systems and Policies. Copenhagen, 2024.