CLINICAL TRIALS FOR COVID-19 TREATMENT - VIEW ON A PERIOD 2020-2022

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ABSTRACT

The purpose of the article is to provide an overview of the dynamics of clinical trials for the COVID-19 treatment. We have therefore created a database from the Register of Authorized Clinical Trials, Bulgarian Drug Agency and from the European Union Drug Regulating Authorities Clinical Trials Databases, European Medicines Agency. We studied all 27 clinical trials authorized for conduction in Bulgaria in the search of a COVID-19 treatment during the pandemic (2020-2022).

The results of the article reveal the share and impact of the Bulgarian trial sites in the search for treatment of COVID-19. The pandemic has fundamentally changed clinical trials themselves and diverted attention from diseases other than COVID-19. Competent authority databases include clinical trials with therapeutic areas of impact close to the coronavirus, the results of which would be a benefactor for the accelerated launch of COVID-19 treatment, which motivated us to overview all clinical trials during the pandemic.

Keywords: trial protocols, COVID-19 pandemic, Bulgaria.

INTRODUCTION

Modern clinical trials in Bulgaria began with the transition to a market economy (since the early 1990s) and the adapted legislation for EU membership (at the beginning of 2007). Healthcare investments increase the interest of sponsors, investigators, manufacturers and competent authorities in the local market, incl. to the hospital sites, for conducting clinical trials. Bulgaria is establishing itself as a destination for clinical trials of several pharmaceutical and biopharmaceutical companies [1]. The increase in both the number of clinical trials and the interest of sponsors has not been sufficiently reflected in the academic research. Therefore, the purpose of this article is to provide an overview of the dynamics of clinical trials conducted.

The pandemic caused by COVID-19 has led to radical lifestyle changes worldwide, and was a factor for global changes in economics, politics, healthcare and daily life. Significant burden was imposed on population status and disease diagnostics, control, and treatment [2]. Resources were focused on one goal, the successful treatment of COVID-19 as an urgent matter for which it was essential to have data like our results. We tried to reach clinical trial data for therapeutic areas close to COVID-19 in search of opportunities to shorten treatment times for coronavirus. We will use an abductive approach as 'surprising facts' or 'puzzles' prevail [3]. To avoid any scepticism to our overview, no findings will be classified as 'rare observation' [4].

The COVID-19 pandemic has increased the burden on healthcare system. We will present the pandemic as both a threat and an opportunity to conduct clinical trials. Pandemic restrictions by the competent authorities have changed all aspects of society, including the conduct of clinical trials. The traditional approach required trial subjects to visit hospitals, but due to the risk of infection and declining subject enrolment, clinical trials were interrupted, as well as premature termination of a clinical trial by the sponsor due to drug shortages arising from the reality of the COVID-19 pandemic.

EXPERIMENTAL

We have created a unique database from the Register of Authorised Clinical Trials, the Bulgarian Drug Agency and the European Union Drug Regulating Authorities Clinical Trials Database, the European Medicines Agency. A total of 27 clinical trials for the treatment of COVID-19 are authorized to be conducted in Bulgaria in 2020-2022. We ad hoc consider COVID-19 and novel coronavirus as equivalent, even though in the trial protocols these concepts find different application - in the medical condition studied or in the medical condition in an easily understandable language.

RESULTS AND DISCUSSION

On March 11, 2020 the World Health Organization declared the COVID-19 pandemic. On April 27, 2020 the initial clinical trial was authorized by the Germany's competent authority - BfArM, and June 11, 2020 is its actual subject recruitment start date (EudraCT Number 2020-001264-28). Over 100 clinical trials are conducted in the world to test SARS-CoV-2 medicines, but so far there is no approved drug by the European Medicines Agency and the US Food and Drug Administration [5].

The conduct of clinical trials has been adapted to the new reality due to limited access to public places, incl. hospital visits [6]. The situation is developing rapidly, and the measures differ from country to country - governmental authorities have introduced restrictive measures, for example closing borders and shops, self-isolation of people (EudraCT Number 2017-000846-23). Modern approach creates new coordination for data sharing between sponsors, physicians, competent authorities and trial stakeholders worldwide [7]. Competent authorities required a collaboration between sponsors and principal investigators to decide which trial visits can be done remotely and which can be delayed or cancelled, applying a risk-based approach (including a trial amendment) when necessary [8]. Sponsors of clinical trials propose variations of home visits and virtual contact points with the patients instead of visits at the clinical sites, as well as other digital and remote solutions [9].

We synthesized a share of the effects to minimize the impact of COVID-19 on trials and incorporate changes in trial processing required by health authorities:

- temporary halt to recruitment following the declaration of the COVID-19 pandemic by the World Health Organization (EudraCT Number 2019-001996-35);

- extraordinary measures to reduce the burden on patients participating in the trial and to provide clarification and guidance to sites in response to restrictions that may be put in place due to COVID-19 (EudraCT Number 2019-003756-37);

- updating the study design for the implementation of the Decentralized Platform in response to the COVID-19 pandemic (EudraCT Number 2019-002425-30);

- permitting (optional) home health visits during the COVID-19 pandemic, describe home nursing visit procedures, and acknowledge that COVID-19 measures only apply if they are in accordance with current, locally-applicable recommendations/regulations (EudraCT Number 2020-003494-22);

- stop onsite monitoring visits (EudraCT Number 2017-000846-23);

- harmonisation of all local protocols for inclusion of COVID-19 risk measures in case of multiregional trials (EudraCT Number 2019-004509-29).

On March 8, 2020, the first proven case of the disease COVID-19 is reported in Bulgaria, and on 13 May 2020, the first clinical trial for the treatment of COVID-19 is authorized by the competent authority - the Bulgarian Drug Agency (EudraCT Number 2020-002091-12). The first report of an adverse drug reaction with a suspected connection to a vaccine against COVID-19 was received in the national competent authority on 27.12.2020, i.e. on the first day of the start of the vaccination process in Bulgaria and the EU. The data revealed a reduced number of clinical trials due to restrictions on hospital visits and direct physicians-patient contacts (Table 1). The subject of clinical trials for potential activity against the COVID-19 are preparations that have already been approved or undergoing approval with other indications but are being used experimentally for COVID-19 treatment [5].

On the other hand, the pandemic has caused a boom in trials in attempts to treat COVID-19 worldwide. Over time, the number of clinical trial regions is increasing, with more than 2,000 trial subjects planned in 2021 and the planned duration of clinical trials being less than 5,000 days. Clinical trials have been reported in a small number despite the increase in the number of hospitalized patients with COVID-19 symptoms. The data show a decline in the number of subjects enrolled

Table 1. Data on clinical trials authorised to be conducted in Bulgaria [10, 11].

	2020	2021	2022
Authorised clinical trials	199	200	170
Authorised clinical trials for COVID-19 treatment	2	16	9
state-owned hospitals	8	18	13
trial sites	10	41	21
sponsors	2	13	7
planned time, days	210	4 940	3 090
reported time, days	420	3 842	694
subjects to be included	210	2 358	706
subjects enrolled	71	778	114

Table 2. Number of clinical trials for the treatment of COVID-19 authorized to be conducted in Bulgaria [10, 11].

	2020	2021	2022
completed trial*s*	2	10	3
prematurely ended trial*s*	-	5	3
ongoing trials	-	1	3

and trial sites. Another clinical trial resource, time, is better used in response to greater number of completed trials (Table 2). National medical standards predict a shorter length of stay in clinical pathways than the time of conducting a clinical trial - the average hospital stay is 5.3 days for 2020 [12], 6.0 days for 2021 [13] and 5.1 days for 2022 [14]. The longest stay is reported by the Pulmonary Hospital, Pernik - 10.2 days in 2021 [15].

Completed trials were planned for less than ten months and reported high rates of subject enrolment (less than 70 % of planned subjects reported as enrolled). Prematurely ended trials have the primary objective of evaluating the efficacy of the treatment (Phase II). Ongoing trials have tolerability as the scope and Phase IIb as the phase of the trials.

The state's policy to deal with the COVID-19 pandemic is primarily implemented through state-owned hospitals, which is reflected in their share of clinical trials. Only 23 state-owned hospitals (63 entities in total) conducted clinical trials for the treatment of COVID-19 in 2020-2022 (Fig. 1). No trials have been conducted in state-owned pulmonary rehabilitation hospitals (15 entities).

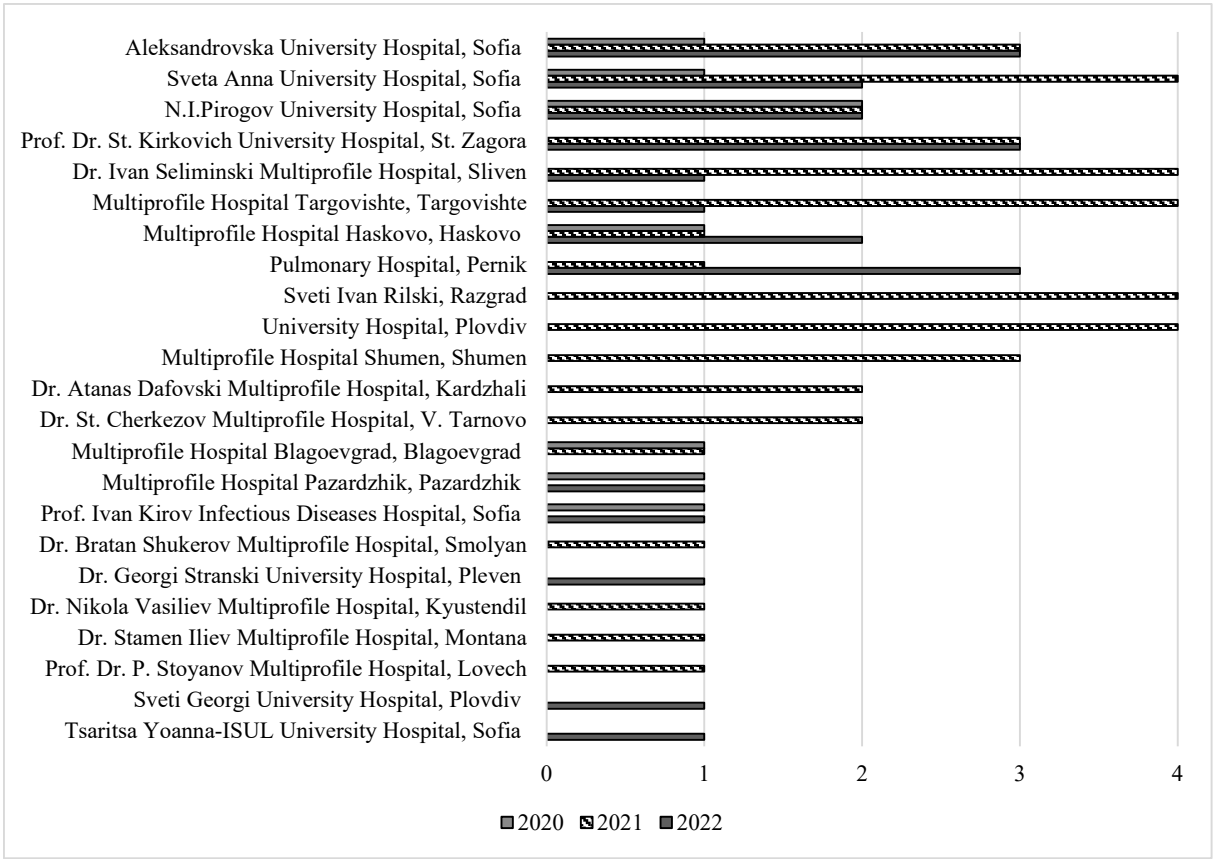

Fig. 1. Number of clinical trials for the COVID-19 treatment in state-owned hospitals.

In 2020, two new trial sites were included in addition to the planned number (Prof. Ivan Kirov Infectious Diseases Hospital, Sofia, EudraCT Number 2020-001264-28, and Sveta Anna University Hospital, Sofia, EudraCT Number 2020-001264-28), and in 2021 - one new site (Multiprofile Hospital Blagoevgrad, Blagoevgrad, EudraCT Number 2021-000344-2110). In 2021, one site was denied conducting a clinical trial (Dr. Tota Venkova Multiprofile Hospital, Gabrovo, EudraCT Number 2020-005366-34). In another case, a clinical trial is not allowed to be conducted in 2021, as there is no order for the restructuring of the medical facility for the treatment of COVID-19 (Multiprofile Hospital Blagoevgrad, Blagoevgrad, EudraCT Number 2021-000344-216). In 2022, one site was closed at the planned trial time (Tsaritsa Yoanna-ISUL University Hospital, Sofia, EudraCT Number 2021-000748-24).

Therapeutic area

Clinical trials in Bulgaria in 2020 - 2022 cover a total of 23 therapeutic areas (analytical, diagnostic and therapeutic techniques and equipment, body processes, diseases, and psychiatry and psychology). Most cases are clinical trials for cancer and digestive system diseases in accordance with international trends and not in accordance with national common diseases, the conclusions of which reflect the role of sponsors and pipeline drugs in determining the therapeutic area, region and method of clinical trials. Clinical trials for the COVID-19 treatment cover two therapeutic areas: respiratory tract diseases or virus diseases (Fig 2).

In conducting clinical trials for the treatment of COVID-19, sponsors have used a variety of approaches to:

- evaluate the effects of oral treatment on COVID-19 development (EudraCT Number 2020-005849-16);
- manage moderate COVID-19 infection (EudraCT Number 2020-005951-19);
- prevent of COVID-19 (EudraCT Number 2021-000904-39);
- prophylaxis study of an individual with symptomatic COVID-19 (EudraCT Number 2021-002894-24);
- treatment of coronavirus disease 2019 (EudraCT Number 2020-002091-12).

A total of 23 clinical trials have been authorised for the treatment of COVID-19, i.e., trial subjects were patients with symptoms of coronavirus (two clinical trials in 2020, 14 trials in 2021, seven trials in 2022). At the end of 2021, the medical conditions under investigation are shifting from treatment of patients with COVID-19 to prophylaxis or prevention of the coronavirus: two trials in 2021 (EudraCT Number 2020-005598-28 and EudraCT Number 2021-002894-24), and two trials in 2022 (EudraCT Number 2021-000904-39 and EudraCT Number 2021-001938-19).

The number of clinical trials for the treatment of COVID-19 determines the number of subjects and the duration of the trials. The trials involve the same number of subjects to be enrolled in the trials and a shorter duration of the trials compared to other trials for respiratory tract diseases or virus diseases. The number

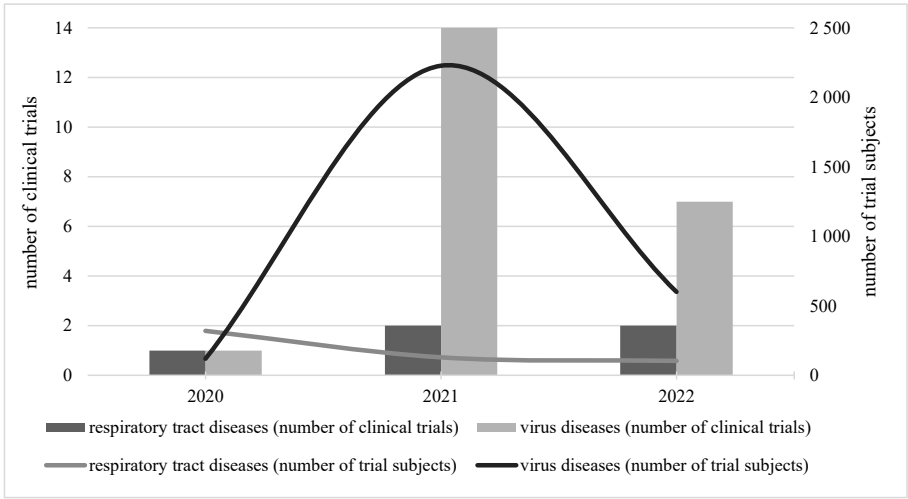

Fig. 2. Therapeutic areas of clinical trials for the COVID-19 treatment.

of subjects enrolled, and the duration reported refer only to clinical trials with completed or prematurely ended status.

The trials for respiratory diseases are therapeutically exploratory (Phase II), planned in a small number of regions and include two age groups - adults and elderly. The trials for virus diseases are for the prevention of COVID-19, with a double-blind trial design and include adolescents as an additional age group of subjects.

Subjects are a critical resource for any clinical trial and most importantly in the treatment of COVID-19. The recruitment of patients with symptoms of COVID-19 and the requirements of competent authorities to conduct clinical trials in the context of a pandemic determine the number of trials with preliminary ended status. The dynamics of clinical trials indicate optimization of time as a resource, both in planning and in its use. In a pandemic, both factors, subjects and time, interact and reinforce each other, for example in one case enrolment of subjects in trials was paused for two months due to the pandemic (EudraCT Number 2019-002668-28).

Sponsors

The pandemic has changed not only the clinical trials themselves, but also the practices of the sponsors. Sponsors testing the treatment of COVID-19 with launched drugs are targeting Bulgaria. The 27 clinical trials for the treatment of COVID-19 reviewed have 21 sponsors from nine countries, some of which are brand new to the host countries due to the growing demand for emergency treatment (Fig 3).

All sponsors are of commercial status. The predominant number of sponsors are R&D units of global pharmaceutical companies. The composition of the sponsors reflects COVID-19 treatment through multi-regional clinical trials.

While subjects have the opportunity to participate in a clinical trial abroad based on the EU principle of freedom of movement, sponsors select the countries according to the local legislation and the pool of subjects to conduct the trials [16]. Sponsors influence analysis data, for example the selection of regions for clinical trials, while investigators influence the number of sites (Fig. 4).

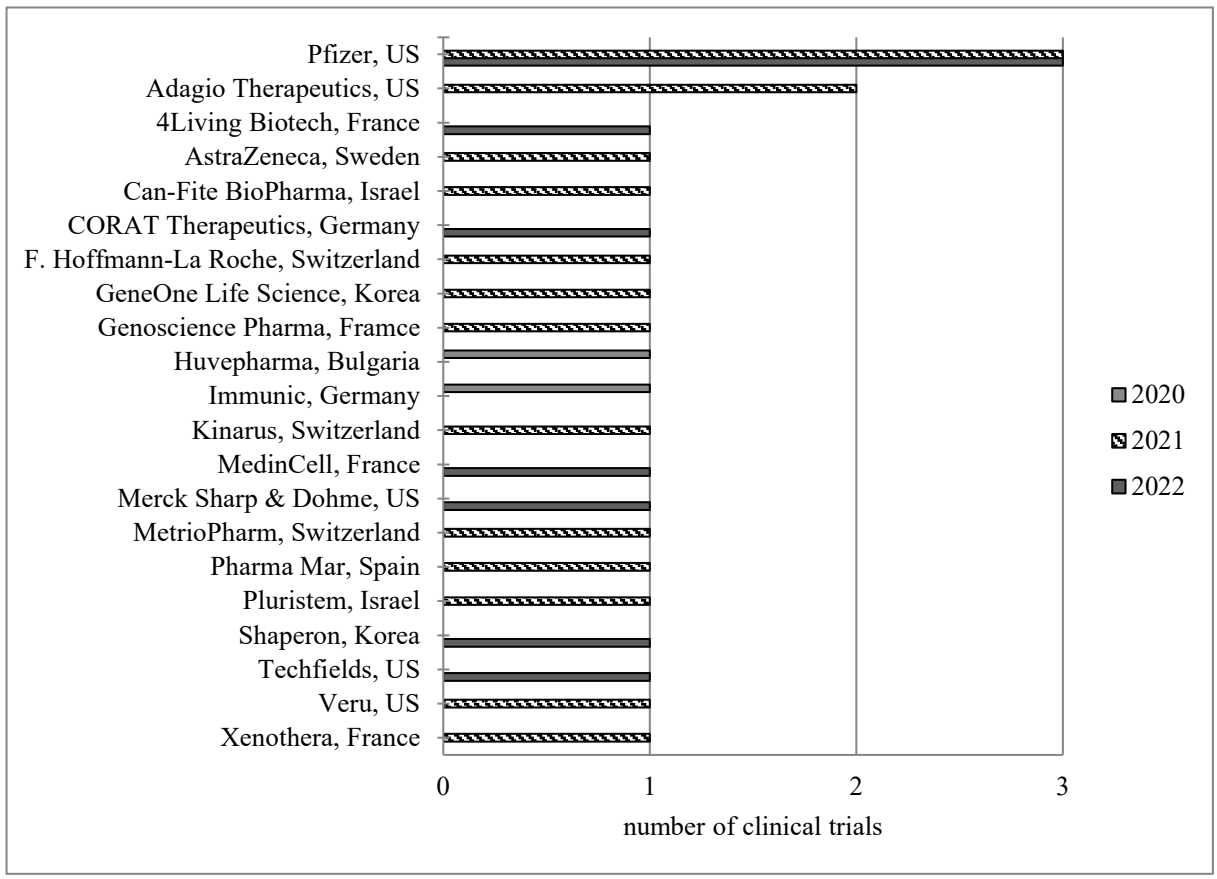

Fig. 3. Sponsors of clinical trials.

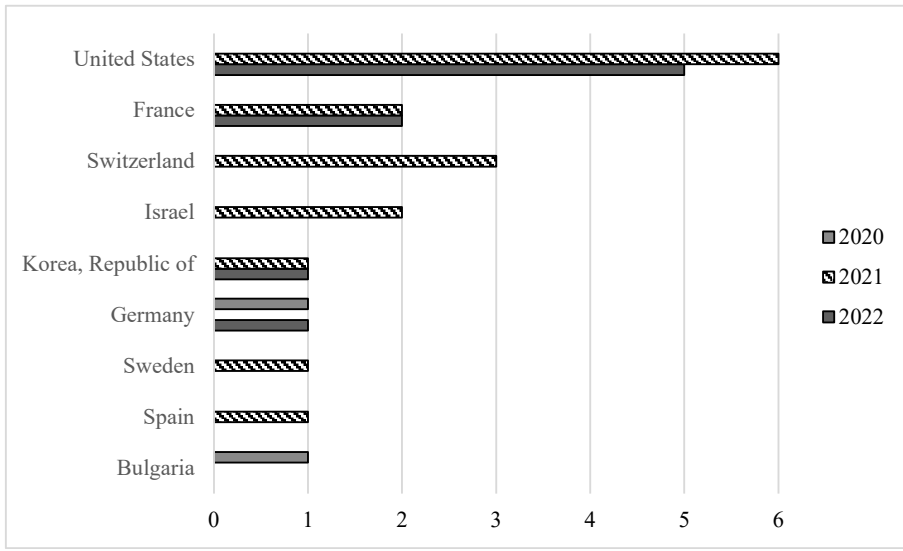

Fig. 4. Country of the sponsors.

In one case, the clinical trial is planned to be conducted in many trial sites - 72 (EudraCT number 2021-002857-28) and regions (26 countries), including Bulgaria, in compliance with the requirements for all national competent authorities. (EudraCT number 2021-002857-28). The longest term for conducting a clinical trial planned by the sponsor is two years (EudraCT Number 2020-005849-16).

Sponsors have adapted the conduct of clinical trials to the pandemic:

- termination prematurely the study due to operational challenges stemming from the coronavirus disease 2019, treatment limitations, rarity of the disease, and drug supply considerations (EudraCT Number 2019-001059-37);

- interpretation with caution the results due to early termination of the study and insufficient number of participants enrolled (EudraCT Number 2019-001996-35);

- update the exclusion criteria related to infections with information about COVID-19 (EudraCT Number 2019-002161-36);

- pause of new participant screening and enrolment due to the COVID-19 pandemic (EudraCT Number 2019-002579-33);

- reporting as adverse events COVID-19 related symptoms with clinically unusual worsening during the trial (EudraCT Number 2020-001264-28);

- change protocols to minimize the impact of COVID-19 on the trial and to reduce the burden on patients participating in the trial (EudraCT Number 2019-003756-37);

- remove the use of historical severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) test results for eligibility assessment and to clarify the timing of safety data required for dose-selection decision making (EudraCT Number 2020-005366-34).

Scopes of the trials

The main purpose of the trials is to reduce the risk of progression from moderate to severe COVID-19, and in a small number of cases, to prevent symptoms of the coronavirus. In most cases, conducting clinical trials consists of establishing the efficacy of a treatment for COVID-19 by giving new doses of a launch drug to trial subjects. There are no cases for testing a new drug or a vaccine, only testing a new therapy (new dose and new combination of launched drugs). In a pandemic situation, clinical efficacy trials take precedence over traditional scope of safety (Fig. 5).

There are no diagnostic or bioequivalence cases as the scope of the trials.

Trial type and phase

The topic of our overview determines the leading number of clinical trials for therapeutic confirmation as type and for Phase II (Fig. 6). There are no clinical trials for therapeutic use (Phase IV).

Our topic largely determines the presence of clinical trials that are planned to be conducted in more than one phase. The innovative nature of the pandemic and the urgency to find a treatment for COVID-19 are reflected in several cross-cases. In 14 cases, the trials span more than one phase, with the largest number (12 cases) being a combination of phase II and phase III.

The number and distribution of cross-phase cases largely follows the dynamics of clinical trials with a peak in 2021. These cases include clinical trials for the prevention of symptomatic coronavirus by evaluating the safety and tolerability of launched drugs compared to placebo. Cross-phase clinical trials cover more than two age groups and, in most cases, include adult trial subjects aged 18 years (and over) and adolescent aged 12-17 years.

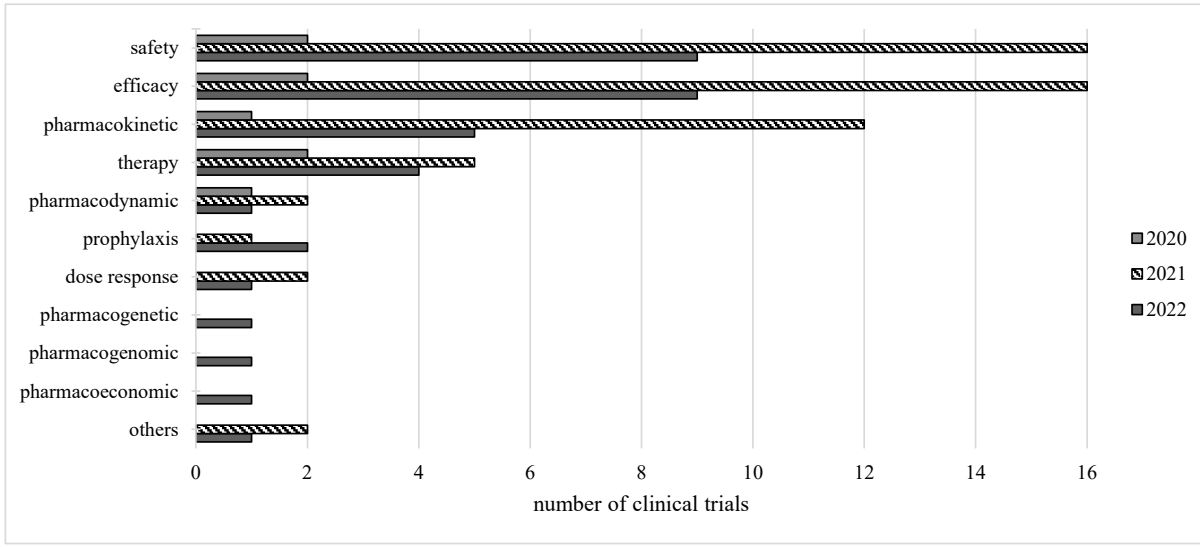

Fig. 5. Scopes of the trials.

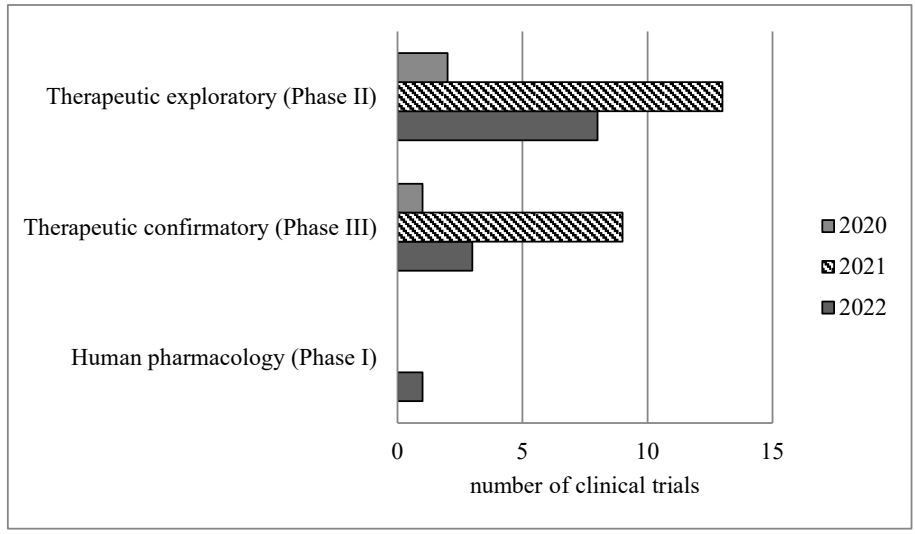

Fig. 6. Type and phase of clinical trials.

Design of the trials

The choice of topic for our overview is largely reflected in the design of the clinical trials. For example, each of the clinical trials overviewed was controlled and randomized. In this sense, the large number of parallel group cases due to comparison with placebo is not surprising (Fig. 7). The inclusion of subjects with symptoms of COVID-19 as well as the trial scope of the efficacy and tolerability trial of new doses of launched drugs is among the factors influencing the design of our overview.

There were no cases of single-blind and cross-over design of trials. In one case, the other trial design is a proof of concept (EudraCT Number 2021-000344-21).

Group of trial subjects

Recruitment of subjects has always been a critical factor in the conduct of any clinical trial. Subjects have an additional function in conducting clinical trials - they showed a higher activity in reporting adverse drug reactions. The unusual genesis of COVID-19 and the challenges of its diagnosis further complicate the enrolment of the planned number of subjects in the trials.

High percentage of trial subjects from Bulgaria can be reported compared to regions with a significantly larger number of inhabitants (Germany, the Russian Federation, Ukraine, and the United States) - subjects that should be included in Bulgaria is 66 % of all subjects to be included in the world for 2020, 12 % for 2021 and 17 % for 2022. In search of subjects, clinical trials are being conducted in sites where patients were hospitalized at the beginning of the pandemic (mid-2020). For example, have been reported clinical trials conducted in a gastroenterology clinic, a skin and venereal disease department, a rheumatology department, and an endocrinology office. At a later, the trials are conducted in COVID-19 sectors of the pulmonology or cardiology hospital departments. In all 27 clinical trials, the gender representation of clinical trial subjects was equal. The target group is patient that has a documented laboratory-confirmed SARS-CoV-2 infection (WHO Clinical Progression Scale scores > 1 and < 4) [17].

Sponsors responded to the pandemic by changing the criteria for conducting clinical trials. At the beginning of the pandemic, patients diagnosed with COVID-19 were withdrawn from the trial:

- participants diagnosed with COVID-19 must be permanently withdrawn from the study intervention (EudraCT Number 2019-003297-53);

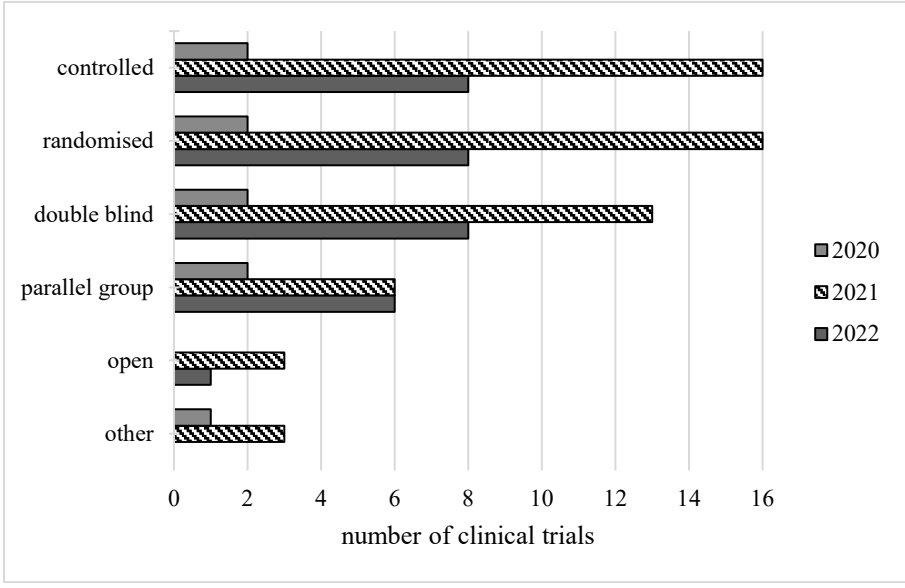

Fig. 7. Design of the trial.

- participants who tested positive for COVID-19 infection were discontinued from investigational medicinal product (EudraCT Number 2020-001927-15).

At a later, patients diagnosed with COVID-19 are the focus subject in the trials. The scope is shifted to the safety and prevention of trial subjects seeking treatment for COVID-19:

- patients with proven SARS-CoV-2 infection and manifested clinical symptoms (EudraCT Number 2020-002091-12);

- participant has a documented laboratory-confirmed SARS-CoV-2 infection (EudraCT Number 2020-005315-44);

- coronavirus disease 2019 with symptoms in adults and adolescents (EudraCT Number 2020-005598-28).

The trial subjects were described extensively, but we found that the overall difference was between patients and healthy volunteers (Fig 8). A third group of trial subjects, specific vulnerable populations, includes women of childbearing potential using contraception (two cases for 2020 and nine cases for 2021). There are no cases of women of childbearing potential not using contraception, as well as for pregnant women. Trial subjects, incapable to give consent in person, are three cases for 2021 and two cases for 2022. For example, subjects, incapable to give consent are intubated, mechanically ventilated, and the subjects are very likely to be sedated (EudraCT Number 2020-001857-31).

Trial subjects are patients with proven SARS-CoV-2 infection, documented by a PCR test performed in a certified laboratory, and manifested clinical symptoms. Hospitalization is for medical reasons or cannot be due to housing insecurity. The main objective of the trials is prevention of COVID-19 for adults residing with a person with COVID-19 in cases with healthy volunteers, and treatment of COVID-19 in other cases. For healthy volunteers, the trials are for the prevention of COVID-19 in adults residing with a person with COVID-19.

Cases of healthy volunteers have prevention of COVID-19 and prophylaxis of COVID-19 infection as medical conditions being investigated. In the first case, one of the principal inclusion criteria is the participant is a household contact of an index case, i.e., a person with documented COVID-19 (EudraCT Number 2021-000904-39). In the second case, the principal inclusion criteria are: close contact with a person who has a PCR-confirmed SARS-CoV-2 infection within 5 days before screening and will be enrolled only one member in the same household (EudraCT Number 2021-001938-19).

Specific examples of describing trial subjects are

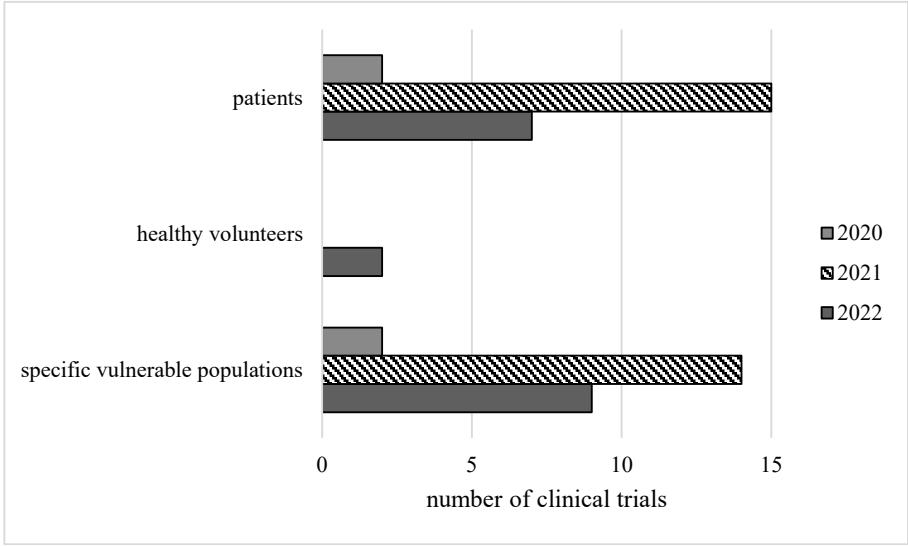

Fig. 8. Group of trial subjects.

divided into another approach - hospitalized and non-hospitalized subjects:

- patients requiring hospitalisation (EudraCT Number 2020-005951-19);
- ambulatory participants (EudraCT Number 2020-006082-11);
- non-hospitalized symptomatic participants (EudraCT Number 2021-002895-38);
- adult household contacts of an individual with symptomatic COVID-19 (EudraCT Number 2021-002894-24);
- non-hospitalized symptomatic participants with COVID-19 who are at risk of progression to severe diseases (EudraCT Number 2022-000075-39);
- adults residing with a person with COVID-19 (EudraCT Number 2021-000904-39);
- patients at high risk for acute respiratory distress syndrome (EudraCT Number 2021-001194-24).

Age range of subjects in clinical trials

Two age groups are the focus of clinical trials for the treatment of COVID-19 - the adults and the elderly (Fig. 9). The adolescent group has the largest planned time for conducting clinical trials. The small number of children-subjects in clinical trials may be explained by their proportion of hospitalizations due to SARS-CoV-2 compared to other respiratory viruses.

In 2022, the age limits for enrolment are extended to the group of new-borns as trial subjects. The new age groups include the same number of subjects as in the focus groups. There are no cases for the premature new-born age group.

The objective of trials to find an emergency treatment for COVID-19 is further complicated by the conduct of a clinical trial in several regions and trial sites. The diversity of policies and measures at national level has resulted in cases where the same clinical trial has a completed status in one country, while in another country the same clinical trial has a different status. For example, in one case, the trial protocols show the status “Prematurely Ended” in Germany and Poland, “Completed” in Czech Republic and Bulgaria, and “Ongoing” in Romania (EudraCT Number 2020-005598-28). In another case, the trial protocols contain a brand-new status - “Trial now transitioned” in Hungary, while in Bulgaria - “Temporarily Halted” (EudraCT Number 2022-000075-39).

We reported an improvement in the use of the time factor. In addition, we report for a time gap between the date of the ethics committee’s opinion and the date of the competent authority’s decision. While in 2020 it took an average of five days between both dates (2 % of the duration of all clinical trials), in 2021 the time gap increased to 31 days (10 %), and in 2022 to 18 days (12 %). There is one case where the time gap is 195 days between the two decisions, which is 46 % of

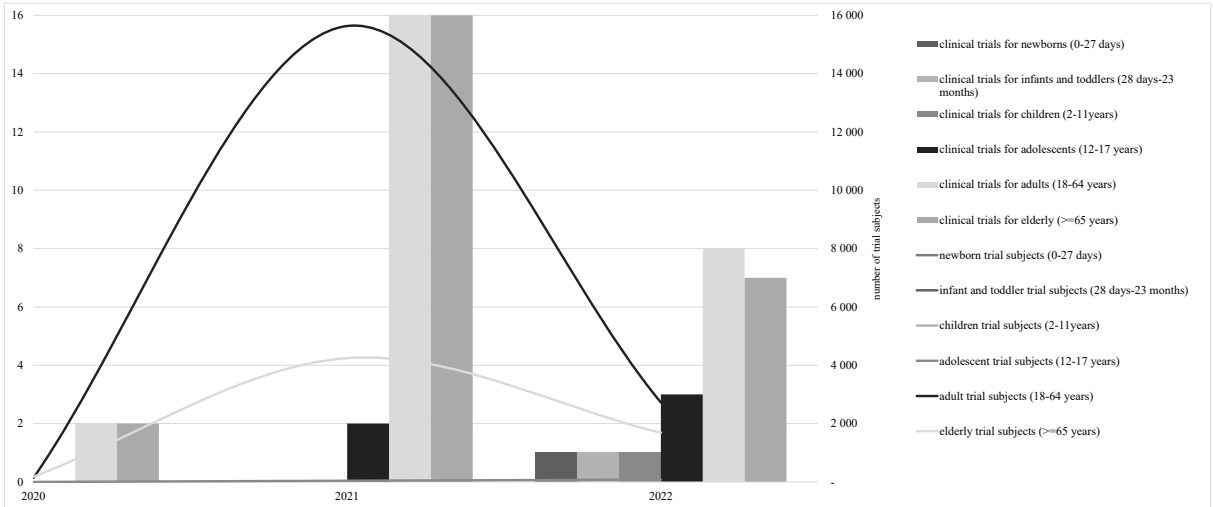

Fig. 9. Age groups of subjects in clinical trials.

the planned time to conduct the clinical trial (EudraCT Number 2020-005951-19):

- Date of Ethics Committee Opinion - 2021-05-25,
- Date of Competent Authority Decision - 2021-12-06,
- Date of the global end of the trial - 2023-01-31,
- End of Trial Status - Prematurely Ended,
- seven substantial protocol amendments,
- Limitations and caveats - Sponsor prematurely ended study on 31Jan23 due to decreased incidence of study population. Due to system restriction, EoT is entered as 01Mar23, primary completion date, despite Sponsor considering EoT the date of reporting early termination, 31Jan23.

In 2022, two clinical trials are reported, where the dates of the two decisions coincide (EudraCT Number 2021-000904-39 and EudraCT Number 2021-001938-19).

Cases with a completed clinical trial status do not mean that the case has achieved the main objective or even the secondary objectives of the trial and will contribute to the benefit of the sponsor. In most cases, completed status refers to clinical trials that have been terminated by sponsors because the results obtained did not meet the planned effects of the treatment. For example, a clinical trial was terminated before the planned time with comments in the protocol […the actual observed frequency was substantially lower, which prevented the primary endpoint from being evaluable…] and the recommendation - […warrant the further assessment…] (EudraCT Number 2020-001264-28). Cases with completed status and not meeting the objective of the trial are re-registered as a new clinical trial, which further complicates the conduct of overviews on the chosen topic.

At the end of 2020, over 100,000 cases of COVID-19 were registered in Bulgaria, with the peak at the beginning of 2022 - over 250,000 cases. The largest numbers of patients were hospitalized in the middle of 2021 - over 10,000. During the 2020-2022 period overviewed by us, clinical trials in the field of pulmonology and viral diseases were conducted in Bulgaria, outside of those included in our database, the resources from that would be helpful in finding a COVID-19 urgently treatment:

- in 2020, two other clinical trials are planned for over 60 subjects and over 400 days;
- in 2021, 15 other clinical trials for over 1,700 subjects and over 10,000 days;
- in 2022, 10 other clinical trials for over 1,500 subjects and over 6,000 days.

These data were the purpose of our overview - to present opportunities for optimizing resources in conducting clinical trials for COVID-19 treatment by monitoring other trials during the same period and similar objectives - treatment with new doses using launched drugs. Our recommendation is that clinical trial registries provide the abilities to retrieve data according to certain criteria and those competent authorities to direct attention to the resources of authorized clinical trials.

Since the global COVID-19 pandemic, vaccine development has become a global pharmaceutical priority [18]. The objectives of the clinical trials have changed, but the efforts and results of the clinical trials conducted remain, as well as the conclusions of our overview on the optimal use of resources through analysis and synthesis of other clinical trials, outside the scope of the treatment of COVID-19 using launched drugs.

Global pandemics pose unprecedented challenges to healthcare. The pandemic has created new opportunities to develop and implement innovative methods for clinical research and treatment. The progress of information and communication technologies in the COVID-19 pandemic created an unprecedented opportunity for medicine to adapt to new models of care. In case of a further pandemic is recommended to change the trial methodology to the decentralized clinical trials - a new approach in health technology research and development that take advantage of innovative digital technologies in data collection for clinical trial purposes through shorter participant recruitment periods, better adherence to assigned therapy, lower drop-out rates and shorter trial duration overall.

CONCLUSIONS

Our results lead to an expectation of a shift in attention and resources to clinical trials for the treatment of COVID-19. This means ignoring diseases, except for COVID-19, whose social and medical consequences are beyond the scope of our overview. The full impact of the pandemic and related clinical trials is expected over the next 10 years, given the approval period for pipeline drugs and the life cycle for launching a new drug.

Our data reveals substantial protocol amendments

for harmonize all local protocols due to the dynamic requirements of competent authorities. Inclusion and exclusion criteria are being modified to increase enrolment in trials involving subjects with COVID-19 infection. New physician-patient communications are noted, incl. when conducting clinical trials in accordance with local pandemic measures, remote medical devices, online diagnostics and electronic prescribing of drugs. In addition to the results of the clinical trials, the reports contain recommendations and requirements of the competent authorities and ethics committees to comply with the measures due to the pandemic.

Authors' contributions: *Data collecting and processing, Writing - Original draft and editing, Submission.*

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