Analysis of the COVID-19 cases

Phase 4

Abstract

Purpose The pace of the COVID-19 case development process is unprecedented and is challenging the traditional para-dig m of case science. The main pressure comes from the pandemic situation, but what makes it possible is a complex set of fact ors and innovative environments built along the times, which this manuscript aims to study.

Methods Through an exploratory study within the scope of innovation management, the present manuscript aims to identify and explore factors that are promoting this accelerated development scenario. The method comprises the monitoring of the strategies adopted by the developers and other stakeholders, as regulatory and humanitarian agencies, specific mechanisms from governments and non-governments bodies, and the background technology that has paved this pathway.

Results Technology-based and R&D strategy factors are the two main factors identified and explored herein. The break-through in the field of biotechnology and molecular biology is considered the main base-science that enables the rapid devel-opment of new vaccines. Additionally, new technological platforms can also be pointed out. Relating to R&D strategies, the parallelism of phases and adaptive clinical trials in consonance with regulatory agencies are the most relevant.

Conclusions The need to rapidly develop a cases against COVID-19 occurs at a time of great excitement in basic scientific u nderstanding, as well as strategies learned in the past by industry and optimization of regulatory pathways. It is expected t hat these factors, arising from the global emergency, may redirect the R&D processes for new drugs, especially in times of pandemic.

Keywords c a s e s · Product development process · COVID-19 · Innovation management

Introduction

The world has witnessed an unprecedented series of events triggered by the pandemic of COVID-19 (coronavirus disease), a disease caused by SARS-CoV-2, a new virus belonging to the Coronavideae family, of great impact on individual and collective health worldwide, and high impact implications for the global economy. On the other hand, it is possible to identify positive aspects in facing the pandemic, ranging from humanitarian solidarity aid actions to accelerating strategies for the development of vaccines, which assumes the position of main hope in solving this problem of global scope.

On December 31, 2019, the World Health Organization (WHO) was alerted of several cases of pneumonia in the city of Wuhan, Hubei Province, in the People's Republic of China. It was a new strain (type) of coronavirus not yet identified in humans. A week later, on January 7, 2020, Chinese authorities confirmed the identification of a new type of coronavirus, and a few days later, on January 11, 2020, the genetic sequence for SARS-CoV-2 was published, triggering intense global research and development (R&D) activity and the rush to develop a vaccine against the disease [1, 2].

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On January 30, 2020, WHO declared that the outbreak of the disease caused by the new coronavirus (COVID-19) constitutes a Public Health Emergency of International Importance—the Organization's highest level of alert, as established by the International Health Regulations. This was the sixth time in history that a Public Health Emergency of International Importance has been declared. The other five were the H1N1 pandemic (2009), international poliovirus spread (2014), Ebola outbreak in West Africa (2014), Zika virus and increased cases of microcephaly and other congenital malformations (2016), and Ebola outbreak in the Democratic Republic of Congo (2018). On March 11, 2020, COVID-19 was characterized as a pandemic by the WHO [3].

It is notable that the experience acquired over the years in confronting other epidemics of international importance brings greater experience and preparedness in fighting these global problems, as in the case of the current COVID-19 pandemic. The current scenario, as frightening as it may be, contrasts sharply with the lack of preparation, as well as lack of adequate and available tools and technologies, as in the case of the Spanish flu, which along 2 years, between 1918 and 1919, brought 3 waves of infection, plaguing a third of the world population at the time and approximately 100 million deaths [4].

In the process of preparing to face such threats, and in particular, invisible threats, such as those coming from microorganisms, the knowledge acquired in the last century is indisputable regarding the understanding of the scientific class on the best strategy to combat these pathogens, which is the provision of an effective and safe vaccine. In view of this, the advance in vaccine technologies together with the recent financing promises, medicine regulatory flexibility, and R&D strategies adopted by developers have contributed to the rapid COVID-19 vaccine licensing process bringing an important breath of hope for humanity.

According to continuous monitoring carried out by the WHO (up to December 8, 2020), the current COVID-19 vaccine development scenario (Fig. 1) has 214 candidates, 51 in the clinical stage, and 14 already in late-stage clinical development (phase III), with the expectation that others will soon enter this phase [5].

A great effort of research and global coordination, which has resulted in a rapid process of development of vaccines and other medical products considered strategic in the fight against COVID-19, is evident. Considering the initiatives for the rapid development of vaccines, the present manuscript aims at identifying the main factors and innovative environments that are promoting this phenomenon. It also seeks to understand the ways and processes that lead to the resolution of problems that plague our society, such as infectious diseases of global relevance, and, based on accumulated learning, to provide new perspectives of pathways and strategies that can be used for new vaccines within the scope of innovation management, specially in pandemic context.

This work is divided into 4 sections. The first is the introduction, which contextualizes and provides an overview of the theme to be studied; the second section presents the objectives and the methodology used. In the third section, the main factors that accelerate the R&D process in the context of the current pandemic will be discussed, and for the last section, a conclusion is presented with future perspectives of the positive legacy of this global crisis, focused on vaccine development process.

Objective and Methodology

The main objective of this work is to identify and explore the main factors that provide the rapid advance in the development of vaccines against COVID-19, classifying and

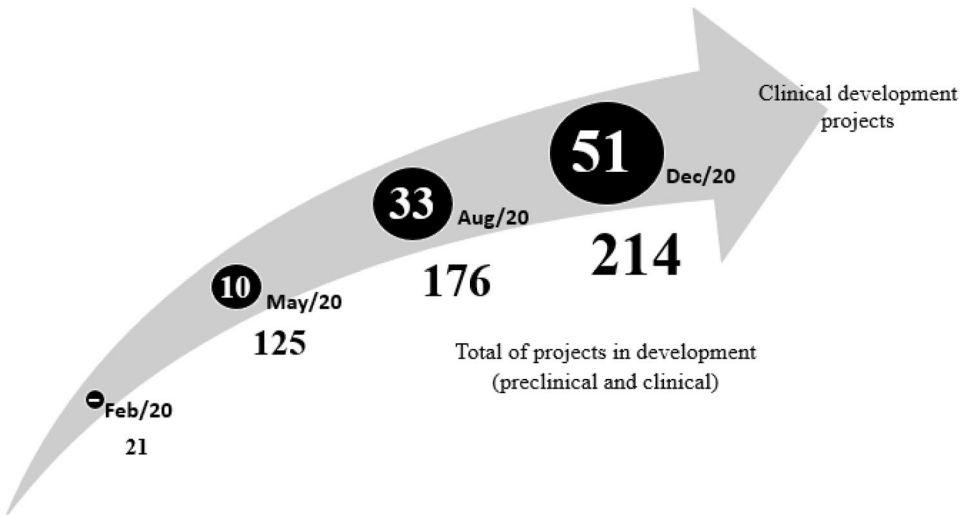

Fig. 1 Overview of vaccine development for COVID-19 in the last ten months (Note: data collection date related to the corresponding total number of vaccines under development and those in clinical development, respectively: 1. 02/18/2020 (21/0); 2. 05/27/2020 (125/10) 3. 08/31/2020 (176/33) and 12/08/2020 (214/51*). Figure based on documents found at the WHO website: DRAFT landscape of COVID-19 candidate vaccines [5]. *One candidate vaccine included in the WHO list was not considered in this study due the lack of information.)

characterizing them in different groups in order to facilitate the understanding and thus enabling an appropriate analysis of the complex innovation ecosystem, that contributes to the acceleration of R&D processes of COVID-19 candidate cases. The analysis period attempted to cover from the very beginning of the scientific effort focused on the development of COVID-19 cases (based on the first d ocument released by the WHO—DRAFT landscape of COVID-19 candidate vaccines—February 18, 2020) until the most updated data regarding these projects (last update based on the WHO documents December 8, 2020), what comprised 10 months of analysis and data collection.

The methodology used for the study is exploratory and is divided into two stages according to Fig. 2. In the first stage, the monitoring of COVID-19 candidate vaccines under development around the world, through access to reports and public databases, was sought and a study database was generated.

The criteria for select the main sources of data considered the reputation of the institution, reliability, and constant updating of the interest data. It is important to emphasize that the rapid pace, which the candidate vaccines forward in the development process, was not followed timely by the publication of scientific peer reviewed papers. So, the strategy adopted for this study was to use one main source to track and collect the vaccines under development data (WHO) together with complementary sources to capture detailed information, especially about the clinical trials. Regarding this complementary information, we collected data from official clinical trials registry platforms, considered by the most regulatory agencies as requirements to the clinical studies approval in their respective countries. Thus, the continuous monitoring and data collection of these sources of information enabled the construction of the study database, which was used as a basis to explore the accelerating factors in the development process of the COVID-19 cases.

Below is pointed out the sources used to generate the study database:

- WHO report on the panorama of candidate cases against COVID-19: DRAFT landscape of COVID-19 candidate cases, updated periodically;
- Nine online databases of clinical trials: Clinicaltrial. gov, Australian New Zealand Clinical Trial Registry (ANZCTR), Pan African Clinical Trials Registry, EU Clinical Trials Register, ISRCTN Registry, Chinese Clinical Trial Registry, Clinical Trial Registry India (CTRI), Indonesia Registry Web Portal (Clinical Research Registry), and Cuban Public Registry of Clinical Trials (RPCEC), which aimed at complementing the background overview information of the vaccine development projects, mainly with regards to the clinical development strategies adopted by developers.

In relation to stage 2, based on the database study and literature review on the topic, the authors proposed a framework of five blocks, called here the acceleration factors, that are used to describe and characterize the innovation ecosystem, in which the candidate vaccines pass through. This set of factors was created with the intention of grouping smaller elements, which present similar characteristics and purposes, what makes them belong to a common factor. The elements include, but are not limited to technological aspects, as types of vaccine technological platforms and their advantages; R&D strategies lead by developers; and programs, instruments, procedures, and strategies adopted by medicines regulatory agencies, governments, international organizations, and other stakeholders in order to foster and speed up the development

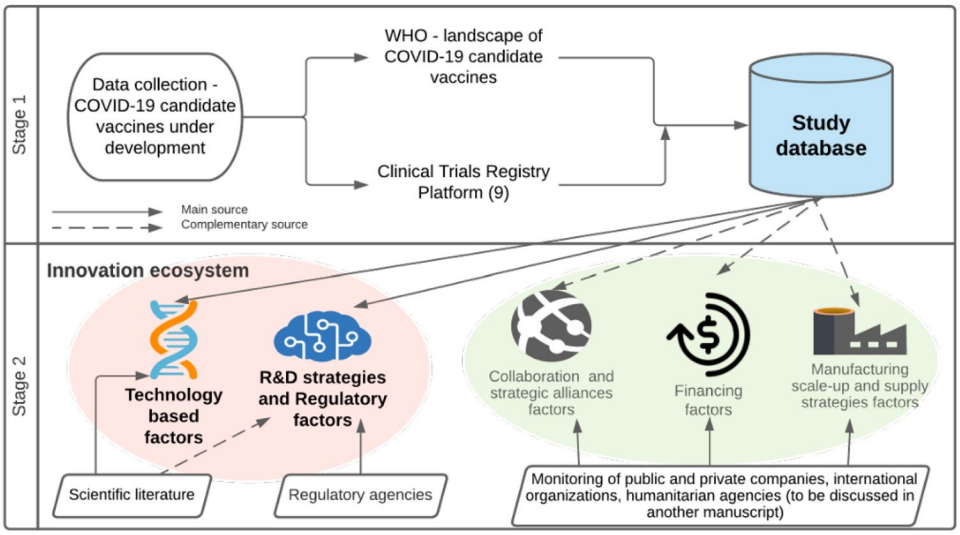

Fig. 2 Schematic presentation of the methodology applied to the study. Source: created by the authors (Lucidchart®)

processes of COVID-19 cases. The 5 acceleration factors, as presented in the Fig. 2, are as follows: (1) factors based on technology, (2) regulatory and R&D strategy factors, (3) collaboration and strategic alliances factors, (4) financing factors, and (5) manufacturing scale-up and supply strategies factors.

As depicted in Fig. 2 the study database was used as the main source for those factors related to technology and R&D strategies (solid arrows). Additionally, scientific literature was used to track the main vaccine technological platforms and pre-clinical studies conducted in the COVID-19 vaccines candidate projects, especially to the technology-based factors, and for the regulatory and R&D strategy factors, the monitoring of clinical trials and medicine regulatory agencies were key aspects to understand this second factor. For the other acceleration factors, which focus on less technological aspects, the study database served as a driver, represented in Fig. 2 with dotted arrows. The main information to explore these 3 factors were obtained by monitoring of public and private companies, international organizations, humanitarian agencies, reference institutions in the area, governments, and other stakeholders. These acceleration factors will be discussed and addressed in a future article.

Therefore, the present manuscript attempts to give a comprehensive overview about the innovation ecosystem, in which the candidate vaccines are being developed, through identification of strategies and practices adopted by the developers and regulatory agencies that lead to shortening and accelerating the COVID-19 vaccine development process.

Results and Discussion

According to the methodology adopted in the present work, firstly, a strategy for monitoring the COVID-19 candidate vaccines under development was established, through access to different public databases, in order to generate the study database, which focused in the 51 candidate vaccines under clinical development. The reason to select this set of candidate vaccines for data collection and analysis is based on the existence and reliability of data, once the availability of information related to these types of projects become official as it enters in clinical trials, pushed by ethical requirements.

This first stage of the study provided a clear view of how fast the new projects emerged over the study period (10 months, from February to December 2020), as well as how many projects advanced to clinical stages (Fig. 1). These results served as input for the development of stage 2 of the research, by providing a more detailed view of the most advanced projects, focused at exploring the mechanisms and strategies adopted by the companies to accelerate the development of these vaccines.

As mentioned in the methodology, the authors preferred to separate this work into two manuscripts, for the sake of didactics and contents, once the actual panorama, inclusive in terms of data generation, is considered a complex theme presenting interfaces with different areas of knowledge and from worldwide efforts. For the present manuscript, the first two factors presented in the methodology section, of a technological nature and regulatory and R&D strategies, were explored in more detail. A future manuscript will explore the other three factors, which are related to aspects of financing, collaboration, and global coordination programs of the COVID-19 vaccines production and supply chain.

Therefore, in the next sections, an overview of the most advanced COVID-19 candidate vaccines will be presented followed by the two acceleration factors, as mentioned previously, in the scope of innovation management and in the perspective of pointing out future paths for the development of new vaccines to combat other epidemics and pandemics that may arise.

Overview of the COVID-19 Candidate Vaccines Most Advanced

According to the Fig. 3, the total number of clinical trial registered in the platforms monitored is 107, comprising approximately 534.921 participants expected to be enrolled. From these clinical trial, 33 are phase I, 37 phase I/II, 11 phase II, 3 phase II/III, and 23 phase III. This magnitude of clinical trials approved in a short time (10 months) for one unique purpose (to reach an efficacious and safe vaccine against COVID-19) reveals a noteworth global effort, both from the companies and governments involved, as well as from regulatory agencies and ethical approval bodies.

Based on the most advanced candidate vaccines, which are currently in clinical development, we identify a close dispute between the USA and China (Fig. 4), which emerges in the race to develop a COVID-19 vaccine, being the USA the main player with 15 candidate vaccines (25%), followed by China with 12 (20%) and Germany with 5 (8%).

In general, it is possible to note that most of the developer companies or institutions are located in developed countries or in traditional countries in the vaccine segment, as are the cases of Cuba, India, and Russia (Fig. 4). However, when we analyze the countries involved in the execution of clinical trials (recruiting countries, as shown in the Fig. 5), it is noted that there is greater heterogeneity, especially in phase III clinical trials, where the determinant for the choice of clinical research centers is conditioned to transmission rates of SARS-CoV-2 locally. For phase I, I/II, or II clinical trials, this characteristic is no longer so evident, since they focus on the safety and immunogenicity of the vaccines under study, with no protection (efficacy) assessment at this stage.

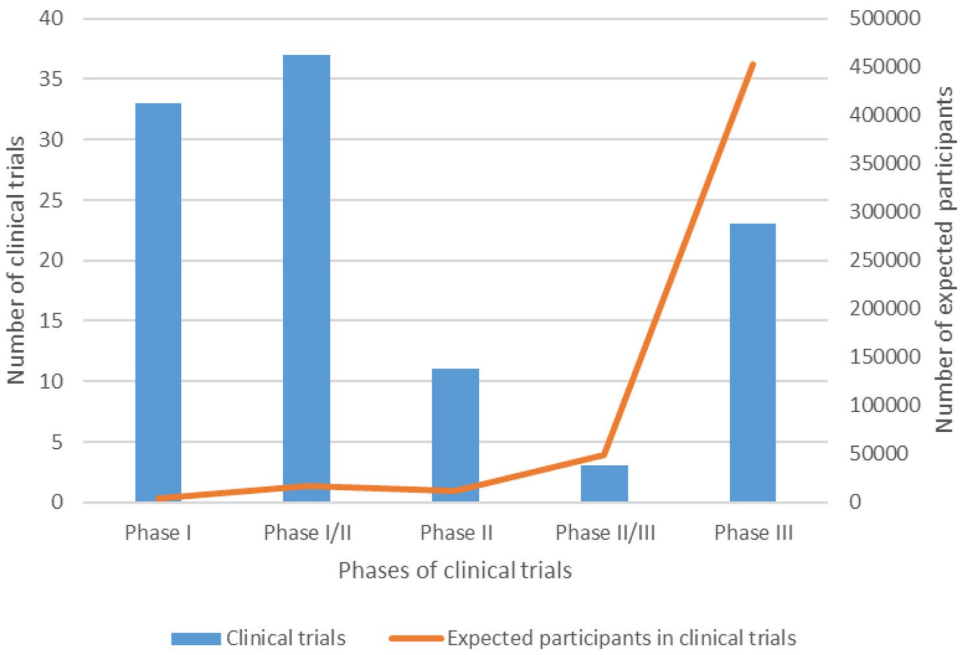

Fig. 3 Distribution of COVID-19 candidate cases clinical trials among phases

This geographical analysis demonstrates a wide involvement and effort of the 5 continents in the search for an effective and safe vaccine, unlike other epidemics and pandemics, in which the initiatives were adopted by a smaller number of companies, most of them recognized as belonging to the vaccine segment cluster. The emergence of new technological platforms enabled the entry of other companies outside the traditional vaccine segment in this race, mainly those focused on R&D and innovative technological platforms, such as those of nucleic acids and recombinant proteins, which is considered having great potential on research of therapeutic molecules. Moderna (USA), BioNtech (Germany), Inovio (USA), and Arcturus (USA) are examples of new entrants that build scientific bases on nucleic acid

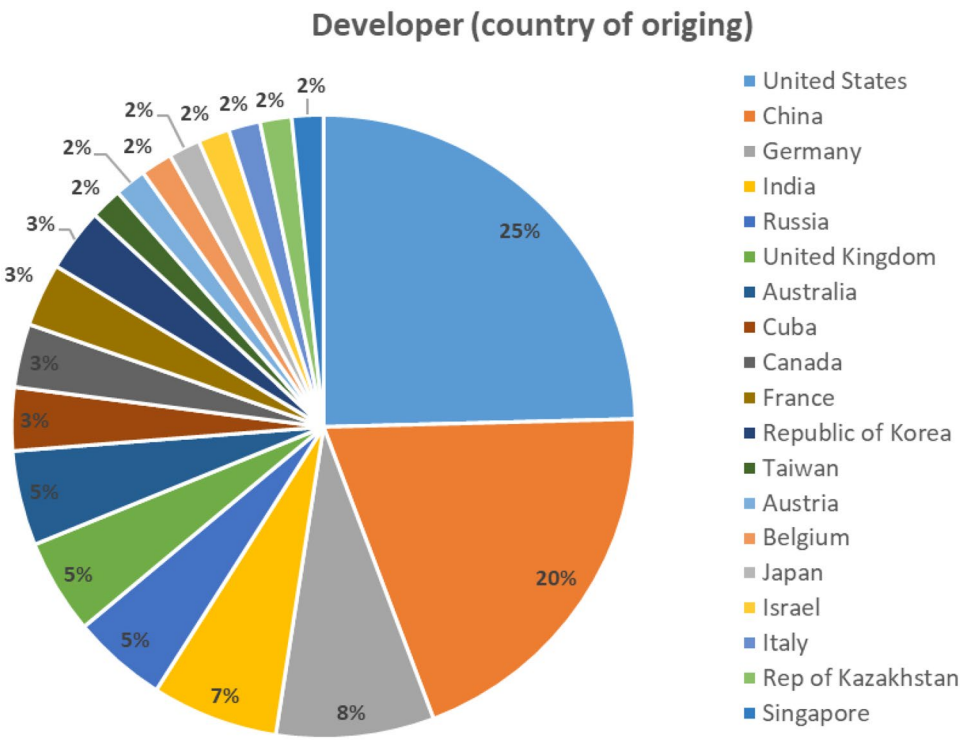

Fig. 4 Distribution of the COVID-19 candidate case developers based on the country of origin

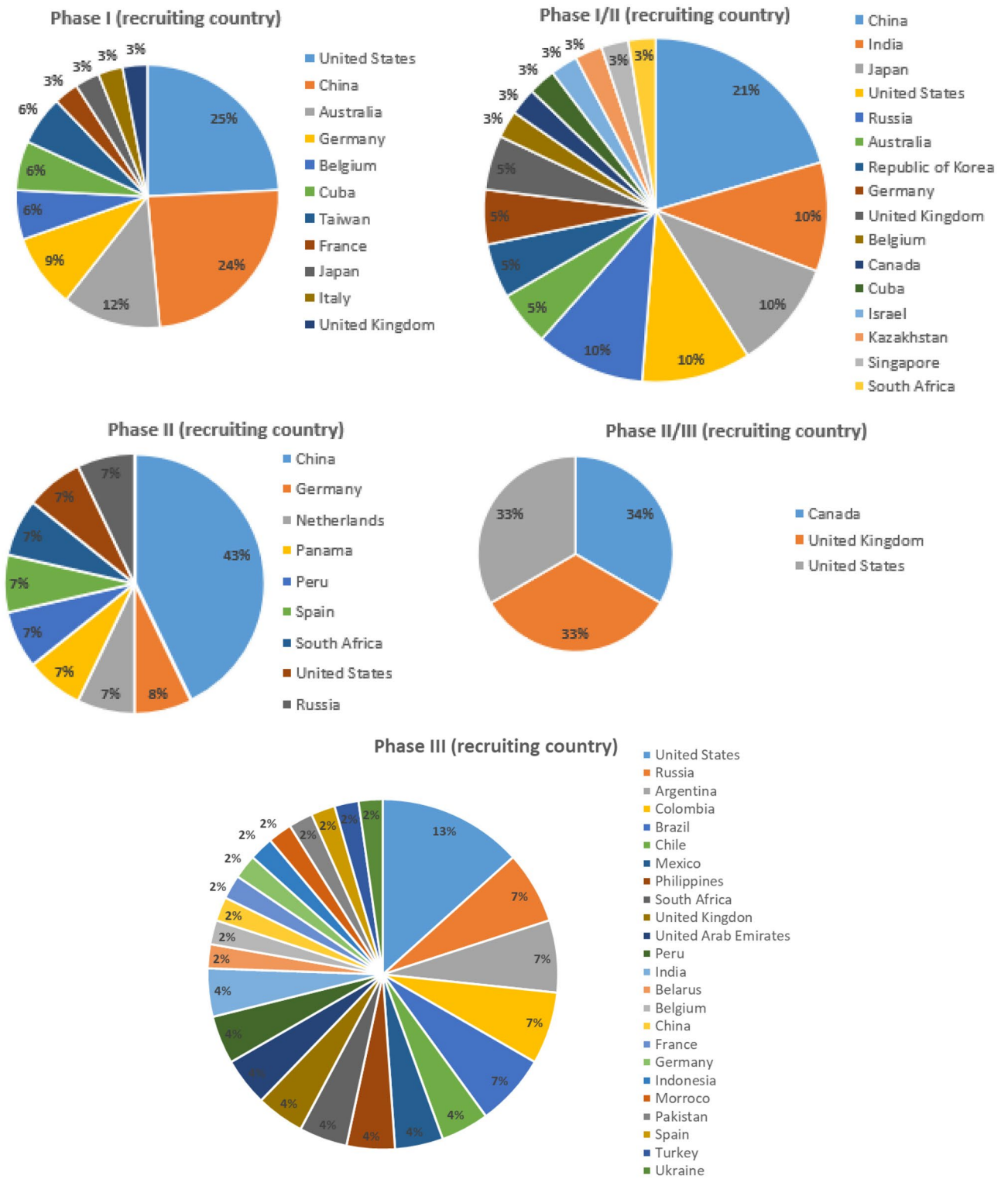

Fig. 5 Distribution of the recruiting countries based on the COVID-19 candidate cases clinical trials

platforms. Janssen (USA) and Astrazeneca (UK), by investing in viral vector platforms, demonstrate a movement of large pharmaceutical companies hitherto recognized for their position in therapeutic areas to also aggregate in their acting field the diseases preventable by vaccines [6–11].

to speed up current endeavor to reach a vaccine based on this platform. This technological approach tends to generate high protein expression in the body, inciting a strong immunogenic response, in addition to being considered safe [2, 17, 24].

For diseases such as HIV, Ebola, Zika, and Chikungunya, the use of vector-based vaccines including adenovirus (Ad), measles virus (VM), vesicular stomatitis virus (VSV), alphavirus, poxvirus, and herpesvirus, demonstrated the ability to stimulate cellular and humoral immunity allowing the insertion of 5 kb or more of the transgene. It is worth mentioning that these viral vectors are weakened and cannot cause diseases in humans but depending on the type of vector and their circulation in certain populations, pre-immunity may exist, which leads to less effectiveness of the vaccine [18].

The whole virus platforms, such as those of inactivated or attenuated vaccines, are considered traditional technologies, and despite the low representation in the current panorama of projects under development for COVID-19, they are considered as advanced in this scenario, with a total of 8 candidate vaccines in clinical phase, being 4 in late-clinical stage (phase III). Interestingly, China is the most relevant country in what concerns to develop COVID-19 candidate vaccines using inactivated approach, leading 6 projects out of 8. The broad knowledge of this technique may be one of the factors that provide a rapid advance in the development of these vaccines and, consequently, the entry into clinical studies. On the other hand, because inactivated vaccines require the handling of the live (wild) virus in the development process, as well as in the future production process, this may be one of the reasons that hinder its use. Compared with other technological platforms, this approach is being pursued by few companies, that venture into this strategy, since it would require biosafety levels 3 (BSL-3 containment), both for research laboratories and for manufacturing plants [25].

Two other innovative technological platforms that appeared latter among the candidate vaccines in the clinical development were those based on multi-peptides and VLP (Virus Like Particles). Vector Institute (Russia), University Hospital Tuebingen (Germany), and COVAXX (USA)/ United Biomedical Inc. Asia (China and Taiwan) represent those candidate vaccines based on multi-peptides under clinical development, while SpyBiotech (USA)/Serum Institute of India (India) and Medicago (Canada) represent the VLP approach, being the last in late-stage clinical trial. Important to highlight that these two technological platforms are also based on DNA recombinant techniques and molecular biology, considered ones of the knowledges in health and biology science that most advanced in the last decades.

Another particularly important factor in the rapid advance of research was the use of previous studies related to other coronaviruses and more specifically to the etiologic agents of two other diseases, which have caused in the last 20 years several outbreaks of severe respiratory syndromes associated with high mortality rates, SARS (severe acute respiratory syndrome coronavirus),and MERS [18].

Coronaviruses have a large genome of about 30 Kb (30,000 nitrogenous bases) forming a single strand of RNA surrounded by a helical nucleocapsid (N) and an outer envelope composed of matrix protein (M), envelope protein (E) and spike (S) proteins. Protein S, which occurs naturally in the trimeric form, contains the receptor-binding domain (RBD) responsible for binding to the angiotensin-converting enzyme 2 (ACE2) and for entering the cell. For SARS-CoV, during the outbreak in 2003, protein S was evaluated as a promising target for vaccine development, for its ability to stimulate the generation of neutralizing antibodies. Moreover, recent research has demonstrated that the linkage affinity of SARS-CoV2 S protein to ACE2 is 10 to 20 times stronger than SARs-CoV; this might explain the contagious nature of SARS CoV2 and poses as a potent target for a COVID-19 vaccine [18, 26, 27].

As no vaccine has been licensed to prevent SARS and MERS diseases, mainly because the outbreaks were limited and resolved before their development, the accumulation of knowledge generated was fundamental for the onset of new development projects for SARS-CoV-2 vaccine. Based on these previous studies, most of the COVID-19 vaccine development projects aimed at protein S (spike) as a target with immunogenic potential. Thus, the discovery process, a phase in which different targets are tested and the first proof of concepts is carried out in vitro, could be shortened as the developers target the S protein of SARS-CoV-2, even considering different technological platforms. This was possible because the gene that encodes the SARS-CoV-2 protein S is quite similar in sequence and structure to the SARS-CoV protein S gene sharing a global protein folding profile similar to that of the S protein of the MERS-CoV virus [28].

According to the Fig. 6, the most frequent route of administration used by the COVID-19 candidate vaccines under clinical development was the intramuscular route (82%), similar scenario to most vaccines current commercialized.

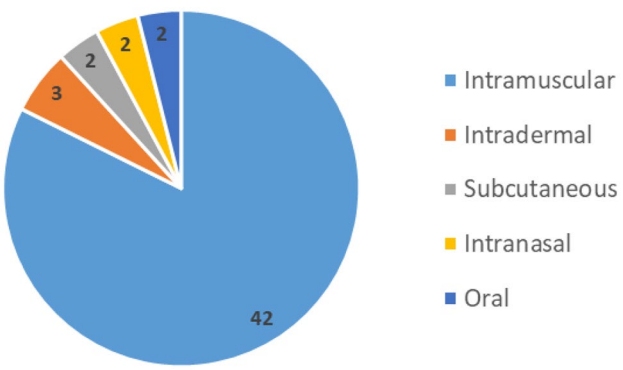

Fig. 6 Route of administration studied in the COVID-19 candidate vaccines under clinical development

The intradermal route (6%) is particularly important for those candidate vaccines containing DNA plasmids, because they are administered using electroporation devices, that increase the permeability of the cells to the DNA. Inovio Pharmaceutical (USA), Cadila Healthcare (India), and Providence Health and Services (USA) are companies following this strategy, despite some of them are also evaluating in the clinical trials the option without the device. As the RNA molecules cannot be stabilized into circular plasmids, the strategy adopted from the developers of this kind of vaccine is to incorporate them into lipid-particles or nanoparticles, as vehicle to deliver the RNA molecules to the cells.

Other routes of administrations, as oral (4%) and intranasal (4%), recently appeared in the clinical trials of candidate vaccines, which brings additional advantages mostly related to the manufacturing process and adherence of vaccination once it seems to be easier to take. Symvivo (Canada) and Vaxart (USA) represent the companies studying oral route, while Beijing Wantai Biological Pharmacy/Xiamen University (China) and Codagenix (USA) represent the intranasal strategy. Symvivo, through its bacTRL™ proprietary platform, enables oral and intravenous vaccines to selectively colonize hypoxic tissue, while simultaneously being cleared from healthy tissues. It uses a live genetically modified bacteria as a vehicle to carry the DNA plasmid, that according to the company, produce and deliver genetic material to the surrounding tissues, providing consistent and progressive levels of gene delivery and expression. Regarding subcutaneous route of administration (4%), ImmunityBio (USA) and University Hospital Tuebingen (Germany) are following this strategy [29].

Regarding the vaccination schedule, most of the developers's strategies rely on two doses, being 44 COVID-19 candidate vaccines studying this scheme. Among them, 30 candidate vaccines are only researching the two doses schedule, while 14 developers are still evaluating different schedules in their clinical development programs (10 are evaluating single or two doses and 4 two and three doses). It is possible to note that in the most clinical development programs, the definition of the vaccination schedule seems to be established in phase I or II, but some developers continue to evaluate different schedules even in phase III (what can be illustrated by the case of University of Oxford/AstraZeneca). With respect to the period between the doses, there is not a standard or schedule most adopted. The variation between the clinical development programs is great, and the types of schedules comprise 14, 21, 28, and 56 days apart between the doses. Interestingly, the COVID-19 candidate vaccine developed by the partnership between CanSino Biological Inc and the Academy of Military Medical Sciences of China is proposing in one of the study groups to evaluate an uncommon schedule, two doses at the same time in both arms of the participants. It may represent a strategy to increase the vaccine dosage without changing the formulation.

Another technological advance for accelerating studies in the area is the speed with which results from the RT-PCR (reverse-transcriptase polymerase chain reaction) used for testing SARS-CoV-2 infection are released. But the ability to analyze biological systems and processes is only part of that story. At the core of today's bio-revolution is our growing ability to "design" biology using modern gene-editing tools, such as CRISPR—Clustered Regularly Interspaced Short Palindromic Repeats [23]. These technologies may have accelerated the process of genetic modifications and recombination of cells, vectors, and other bio-based components that are involved in the process of developing new vaccines for COVID-19.

It is important to consider the risk of the rapid advance of these technological approaches without adequate monitoring of the impact on the environment and permanent assessments of genetically modified organisms, using advanced techniques of genetic editing. Biological systems are organically self-sustaining and self-replicating, increasing the risk of unknown impacts on the environment. Therefore, the evolution of biosafety approaches is extremely important, as genetic editing technologies advances [23].

Regulatory and R&D Strategy Factors

The elements considered in this group of factors were explored in two approaches: the first was related to the regulation of the pharmaceutical sector, through the monitoring of "fast track" procedures, by technical and guidance support from the main regulatory agencies, and the second is more related to the strategies adopted to accelerate the stages of R&D vaccine process, associated with regulatory flexibilities.

Regulatory Procedures

The role of regulatory agencies and international harmonization bodies are fundamental in combating the COVID-19 pandemic, as they guide the paths to be followed in the development of vaccines, while providing support and taking action in accelerating the approval processes of clinical studies and vaccine licensure for immunizers. Regulatory agencies face great pressure. As expectations to accelerate the stages of vaccine development are high, caution, and rigor in efficacy and especially safety assessments are necessary before moving on to human studies and licensing for commercialization. Although not addressed in this study but no less important, the research ethics review board carry out evaluations concurrently with the regulatory agencies, focusing on studies in human beings.

the studies, and not only at the end of the submission of the final licensure dossier.

In general, it is possible to note that the rapid regulatory response of the main agencies around the world has been facilitated due to closer monitoring of COVID-19 vaccine development projects, which provides regulatory bodies with a better understanding of the complex R&D development, enabling clarification of issues during the process. This follow-up, which used to happen only for the beginning of the clinical stages, started to occur also in the most preliminary stages, specifically in the preclinical development. Noteworthy is also the endeavor the regulatory agencies have allocated to expedite the COVD-19 vaccine development process, from the workforce mobilization to evaluate issues related to COVID-19 vaccines to international cooperation in the scope of ICH (International Conference of Harmonization) to avoid duplicate work, already done by other agencies, and so accelerate all the analysis process. The dedication and professionalism of regulatory agency staff members have played a vital role in this battle against this pandemic.

Strategies for the R&D Process

The conventional process of developing a vaccine encompasses numerous technical stages of high complexity, from existing knowledge about the target to be reached (pathogen), the selection of the most appropriate antigen, the development of production processes to obtain the respective antigen, formulation and analytical methodologies development, proof-of-concept studies in animal models, stability studies, until reaching at the complex and expensive clinical studies, which in the case of a new vaccine requires three phases. In the clinical stage, the vaccine under study must prove to be safe (phase I), which normally involves 6 to 12 months of data collection after the immunization of each patient. Phase II trials provide an understanding of the required dosages, and phase III is a complete efficacy study, with consolidation of the safety assessment. As companies gain more confidence that a vaccine will work, they are prepared for commercial launch. The entire process usually takes five to ten years [14, 35].

Because of the cost and high failure rates, developers generally follow a linear sequence between the main stages of development, with several breaks for data analysis or checks on the development of the manufacturing process. The accelerated development of a vaccine in pandemic situations requires a new paradigm in the R&D process. One of the main strategies adopted by COVID-19 candidate vaccine developers in this pressure times is the parallelism of phases; in other words, they initiate a sequential phase before the results from the previous phase. Figure 7, which comprises the fourteen candidate vaccines on phase III of clinical trials (most advanced COVID-19 candidate vaccines), clearly shows this parallelism concept, between the clinical phases. For this current analysis, the clinical trials from the same phase of a vaccine were added in terms of timeline, so they do not appear repeatedly.

The wide availability of financial sources and government incentives, which will be better discussed in the second article, has a critical role in the vaccine development process, especially in pandemic context. As it allows companies to take more risks in the parallelism of clinical phases, as well as the conduction of several other evaluation and studies at the same time, the required data about the candidate vaccine (related to efficacy, safety, and quality) can be generated in a shorter time. Based on this scenario of relevant financial incentives raised all over the world and mobilization of the business and scientific community, the data depicted in Fig. 7 clearly show the application of these strategies by the developer companies, which would certainly be difficult to happen in different contexts.

High financial risks, in addition to ethical-regulatory risks, must be considered. A good example is happening with vaccines coming from the same technological platform as others that have been previously tested in humans. These cases have enabled phase 1 clinical trials to proceed concurrently with tests on animal models [35]. Although this was a possible strategy even before the pandemic, it was not widely used, mainly because the regulatory agencies demand justifications for this acceleration, plausible in the current scenario.

More specifically in relation to clinical development, some factors accelerate the work of the teams involved in this stage, as they put pressure on taking advantage of the temporal opportunity of the pandemic, which in this case, is related to the dynamics of virus transmission and epidemiology of the disease. In this sense, companies fear what happened previously in other epidemics, as in the cases of SARS and MERS, in which vaccine candidates were under development, but clinical studies had to be interrupted, or did not advance to subsequent stages, due to the lack of a conducive transmission environment. This occurs when clinical studies evaluate vaccines for viruses considered to be new, for which protection correlates are not known yet, that is, there is no adequate biomarker that can infer protection, as are generally the protective antibody titers for known diseases. In this case, the most appropriate strategy to assess the effectiveness of a new vaccine is the infection rate of the vaccinated group in relation to the control group, considering that both are exposed to infection by the virus [34].

In addition to pressure from society, there is another more scientific aspect, which depends on the assessment of conditions for conducting a phase III clinical study, such as the curve of cases in a given population, the transmission

Developer	Nº of participants / Nº of Clinical trials*	Developer Country	Technological platform
Moderna / NAID	30720 (3)	United States	Nucleic acid (RNA)
CanSino/Beijing Institute of Biotechnology	46678 (6)	China	Viral vector
University of Oxford/AstraZeneca	62509 (8)	United Kingdon	Viral vector
Inovio Pharmaceuticals	7498 (4)	United States	Nucleic acid (DNA)
Wuhan Institute of Biological Products/Sinopharm	15920 (3)	China	Inactivated
Sinovac Research & Development Co., Ltd.	29378 (6)	China	Inactivated
BioNTech/Pfizer	45091 (7)	United States/Germany	Nucleic acid (RNA)
Beijing Institute of Biological Products/Sinopharm	18640 (3)	China	Inactivated
Novavax	50819 (4)	United States	Protein subunit
Gamaleya Research Institute	40286 (5)	Russia	Viral vector
Anhui Zhifei /Chinese Academy of Sciences	30216 (5)	China	Protein subunit
Medicago Inc.	30792 (2)	Canada	Virus Like Particule (VLP)
Janssen Pharmaceutical Companies	91845 (5)	United States	Viral vector
Bharat Biotech International Ltd	25800 (3)	India	Inactivated

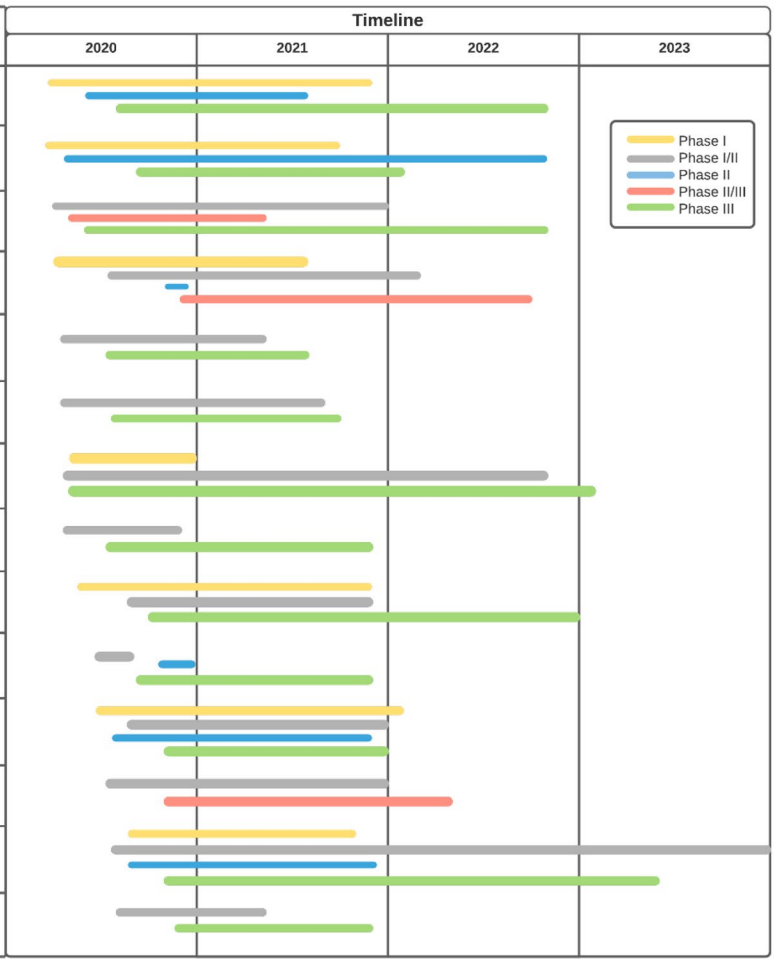

Fig. 7 Parallelism of clinical phases (most advanced COVID-19 candidate cases). Source: Created by the authors (Lucidchart®)

rate and the need to recruit research participants with SARS-CoV-2 negative serology, which becomes even more difficult as the virus spreads.

Another strategy most used by companies that are leading the vaccine race against COVID-19 is the so-called adaptive clinical trials. This type of study is based on an adaptative scientific concept for drug development and data generation that allows early and progressive patient access to medicines.

In this regard, Pfizer/BioNtech, interestingly, conducted one large study (NCT04368728), in an adaptive way, which included the three clinical phases at one unique clinical trial. Together with the reasons mentioned previously about the nucleic acid platform, this one-in-three adaptive clinical trial can be pointed out as an important factor that enabled accelerate the vaccine development process to be the first approved by relevant regulatory agencies, as FDA, Health Canada and MRHA (UK).

According to the EMA, adaptive pathways are based on the following principles:

- Iterative development, which means approval in stages, starting with a restricted population of research subjects and then expanding to larger populations, in a continuous process of assessment of a product's risk-benefit profile. After conditional approval based on initial data, substitute parameters are used, considered predictive of important clinical results;
- Collection of evidence through previous real-life studies that might supplement data from clinical trials;
- Early involvement of patients and health technology assessment bodies in discussions on drug development [36].

The efficiency of studies with adaptive designs depends on the time and frequency of interim analyzes. Decision making in this type of study requires availability of information from a sufficient number of research participants [37].