Universidade de Lisboa

Faculdade de Farmácia

CHARACTERISTICS ANALYSIS OF COVID-19 OBSERVATIONAL AND INTERVENTIONAL STUDIES REGISTERED IN PORTUGAL BETWEEN 2020 AND 2021

Jéssica Gouveia Maatar

Dissertation supervised by Professora Doutora Joana Batuca and co-supervised by Professora Doutora Sofia de Oliveira Martins

Biopharmaceutical Sciences

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1. RESUMO

A Doença por Coronavírus 2019 (COVID-19) é uma doença infeciosa causada pelo vírus SARS-CoV-2 que foi identificada pela primeira vez em Dezembro de 2019 na China, na cidade de Wuhan. Face à sua rápida disseminação e elevada escala de transmissão, em Março de 2020, foi declarada pandemia pela Organização Mundial da Saúde. Este vírus, nunca tinha sido identificado anteriormente e demonstrou poder causar pneumonia grave ou até morte. A partir deste momento, os estudos COVID-19 tornaram-se o principal foco dos investigadores para a descoberta de novas formas de diagnóstico, tratamento e prevenção a fim de regredir o mais rápido possível o avanço da pandemia. Mundialmente este vírus já causou mais de 6,04 milhões de mortes, totalizando 445 milhões de casos confirmados.

Aparentemente, a facilidade de disseminação do vírus SARS-CoV-2 nos humanos, deve-se ao facto de este se ligar com alta eficácia a uma proteína chamada enzima conversora de angiotensina 2 (ECA2) localizada na superfície de diversas células. Uma vez que não existia um tratamento específico e eficaz contra a COVID-19, recorreu-se a medicação para o tratamento sintomático da doença. Já foi demonstrada a eficácia de medicamentos antivirais para tratar o COVID-19, uma vez que estes são capazes de prevenir a entrada do vírus na célula hospedeira e consecutivamente evitar a replicação viral. Por outro lado, a vacinação é considerada a opção mais preventiva para a COVID-19 uma vez que permite atingir a imunidade da população.

A incrível pressão que a pandemia exerceu sobre investigadores, reguladores e decisores políticos, e reconhecendo o esforço coletivo de todos para conseguir desenvolver rapidamente mas em segurança numa época de tremenda incerteza opções terapêuticas eficazes numa escala mundial voltou a sublinhar a importância de investigação clínica, nomeadamente dos ensaios clínicos em grande escala estruturados de acordo com um protocolo metodologicamente bem desenhado, de forma coordenada e colaborativa para que os resultados obtidos sejam robustos, a importância de ter estruturas e incentivos para permitir uma partilha de dados mais rápida de conjuntos de dados anonimizados, ter mecanismos céleres de financiamento assim como a necessidade de proporcionar oportunidades semelhantes às dos países de elevado rendimento para a realização de ensaios clínicos em regiões de baixos recursos, com consideravelmente menos financiamento para a investigação clínica.

Desde o aparecimento da doença têm sido propostos o *repurposing* de vários medicamentos já aprovados para outras indicações terapêuticas e surgiram em menores números algumas terapêuticas inovadoras. O benefício risco de todas estas opções terapêuticas (medicamentos, vacinas) têm vindo a ser demonstrado em ensaios clínicos de várias fases e com desenho adaptativo que permite acelerar o processo de desenvolvimento.

Posto isto, o principal objetivo sempre passou pela realização de novos ensaios clínicos para o desenvolvimento de medicamentos com potenciais benefícios para tratamento e de vacinas para prevenção. Para uma melhor compreensão do envolvimento que Portugal teve nos estudos clínicos realizados para a COVID-19, dada a sua importância na saúde pública, seria relevante caracterizar e analisar os estudos registados em

Portugal e por sua vez, identificar os centros de pesquisa que mais estiveram envolvidos.

Assim, o principal objetivo deste trabalho é caracterizar o tipo de estudos (observacionais e de intervenção) registados nas bases de dados de registo que envolvem Portugal entre 2020 e 2021. O presente estudo tem como objetivo secundário analisar características como os tipos de promotores do estudo, os financiadores, ensaios nacionais ou internacionais), número de participantes recrutados, tipos de intervenção, publicação e centros nacionais envolvidos.

Para melhor compreender as adaptações que tiveram que ser realizada na implementação e condução de estudos clínicos em contexto pandémico, tanto a nível de autoridades reguladoras, como promotores, centros de ensaio, equipas de investigação e participantes começou-se por recolher os dados das publicações relativas às orientações nacionais e internacionais. Estas medidas excecionais foram sendo emitidas pela Agência Europeia de Medicamentos (EMA), e a nível nacional pela Autoridade Nacional de Medicamentos e Produtos de Saúde (INFARMED) e o Comité Nacional de Ética para Investigação Clínica (CEIC).

Para atingir o objetivo principal do estudo, foi realizada uma pesquisa sistemática dos registos entre 1 de janeiro de 2020 e 31 de dezembro de 2021 utilizando quatro plataformas de registo de ensaios clínicos - ClinicalTrials.gov, EUCTR ANZCTR e RNEC. A pesquisa nestas quatro plataformas de registo de ensaios clínicos, permitiu a identificação e caracterização de estudos observacionais (ClinicalTrials.gov) e com intervenção a decorrer em Portugal para a COVID-19. Após a identificação de todos os estudos registados em Portugal no período mencionado anteriormente, foi feita a análise e caracterização de todas as informações recolhidas. Para isso, os dados foram organizados e registados numa tabela do Microsoft Office Excel, divididos por diversos parâmetros (de acordo com as informações dos estudos mais relevantes para o trabalho.

Através desta análise, no presente estudo foram identificados em Portugal 29 estudos clínicos para a COVID-19 dos quais 14 são estudos observacionais e 15 são estudos de intervenção (ensaios clínicos). Durante o ano de 2020, Portugal esteve envolvido em mais estudos observacionais (n=11) do que estudos de intervenção (n=6). Em contraste, em 2021 Portugal registou mais estudos de intervenção para COVID-19 (n=9) do que estudos observacionais (n=3). Estes ensaios têm sido promovidos maioritariamente por universidades e companhias farmacêuticas. Os estudos observacionais foram promovidos maioritariamente por universidades, em que se destacaram a Universidade de Lisboa, a Universidade do Porto e a Universidade do Minho, e os estudos de intervenção por companhias farmacêuticas. Nos estudos com intervenção, em oposição aos estudos observacionais, verificou-se uma grande percentagem de estudos multinacionais, provavelmente por 60% por serem ensaios comerciais e possuírem maior capacidade de financiamento. Os tipos de financiadores vêm de encontro aos promotores, isto é, os estudos observacionais são maioritariamente financiados por organizações públicas e em estudos com intervenção por organizações privadas, principalmente empresas farmacêuticas com o objetivo da comercialização do produto.

Todos os estudos de intervenção feitos no âmbito da COVID-19, foram ensaios clínicos randomizados já que permitem entender e avaliar o efeito de cada intervenção realizada, uma vez que cada grupo recebe uma intervenção diferente. A análise de dados destes estudos revelou que 80% dos estudos registados em Portugal eram para estudar medicamentos capazes de tratar e regredir o avanço da doença. A identificação dos centros de investigação nem sempre era possível, pois nem sempre eram mencionados. No entanto, quando se trata de estudos de intervenção, utilizando o RNEC foi possível identificar a maior parte. As áreas com maior número de centros de investigação concentram-se nas grandes áreas metropolitanas de Lisboa, Porto e Braga, coincidindo com as áreas com mais estudos de COVID-19 registados em Portugal. No distrito de Lisboa, destacaram-se a Nova Medical School, da Universidade NOVA de Lisboa, o Centro Hospitalar Universitário Lisboa Central e o Centro Hospitalar Universitário de Lisboa Norte. No Porto, o Centro Hospitalar Vila Nova de Gaia e o Centro Hospitalar de São João foram os que mais participaram. Relativamente à publicação dos estudos, conclui-se que dos 29 estudos clínicos realizados para COVID-19 registados em Portugal entre 2020 e 2021, 66.67% dos que estão concluídos nos registos já deram origem a uma publicação.

Apesar de todo o esforço feito por muitas entidades reguladoras nacionais, Portugal ainda apresenta várias lacunas e falta de harmonização que atrasam a implementação de ensaios clínicos internacionais. Por conseguinte, o desenvolvimento da investigação clínica deve basear-se numa estratégia nacional que reúna as autoridades de saúde para promover um conjunto estimulante de políticas públicas e financiamento.

Palavras-chave: COVID-19, SARS-CoV-2, Estudos Observacionais, Estudos de Intervenção, Centros de Investigação

2. ABSTRACT

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus that was first identified in December 2019 in China, in the city of Wuhan. In view of its rapid spread and high scale of transmission, in March 2020, it was declared a pandemic by the World Health Organization. This virus has never been identified before and has been shown to cause severe pneumonia or even death. Therefore, COVID-19 studies have become the main focus of researchers for the discovery of new ways of diagnosis, treatment and prevention in order to reverse the advance of the pandemic as quickly as possible. Worldwide, this virus has already caused more than 6.04 million deaths, totaling 445 million confirmed cases.

The effectiveness of antiviral drugs to treat COVID-19 has already been demonstrated, since they are able to prevent the entry of the virus into the host cell and consecutively prevent viral replication. On the other hand, vaccination is considered the most preventive option for COVID-19 as it allows the population to be immunized. That said, the main objective has always been to carry out new clinical trials for the development of drugs with potential benefits for treatment and vaccines for prevention.

For a better understanding of the involvement that Portugal had in the clinical studies carried out for COVID-19, the main objective of this work is to characterize the type of studies (observational and interventional) registered in the registration databases involving Portugal between 2020 and 2021.

To achieve the primary objective of the study, a systematic search of registries was performed between 1 January 2020 and 31 December 2021 using four clinical trial registry platforms - ClinicalTrials.gov, EUCTR ANZCTR and RNEC. Research on these four clinical trial registration platforms allowed the identification and characterization of observational studies (ClinicalTrials.gov) and interventional studies taking place in Portugal for COVID-19. After the identification and characterization of all studies registered in Portugal in the aforementioned period, all data were registered and analyzed in Microsoft Office Excel.

Through this analysis, in the present study, 29 clinical studies for COVID-19 were identified in Portugal, of which 14 are observational studies and 15 are interventional studies (clinical trials). These trials have mostly been sponsored by universities and pharmaceutical companies. The areas with the highest number of research centers are concentrated in the large metropolitan areas of Lisbon, Porto and Braga. Regarding the publication of the studies, it is concluded that of the 29 clinical studies carried out for COVID-19 registered in Portugal between 2020 and 2021, 66.67% of those that are completed in the records have already given a publication.

Despite all the efforts made by many national regulatory entities to facilitate the approval processes for clinical trials, Portugal still has several gaps and lack of harmonization that delay the implementation of international clinical trials.

Key-words: COVID-19, SARS-CoV-2, Observational Studies, Interventional Studies, Research Centers

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6. INTRODUCTION

6.1. Coronavirus Disease 2019

Coronavirus Disease 2019 (COVID-19) was declared as pandemic by the World Health Organization on March 11th, 2020. COVID-19 is an infectious disease caused by the SARS-CoV-2 virus and was first identified in December 2019 in China, in the city of Wuhan, spreading around the world mainly due to the speed and scale of the transmission of the disease (Figure 1).[1]

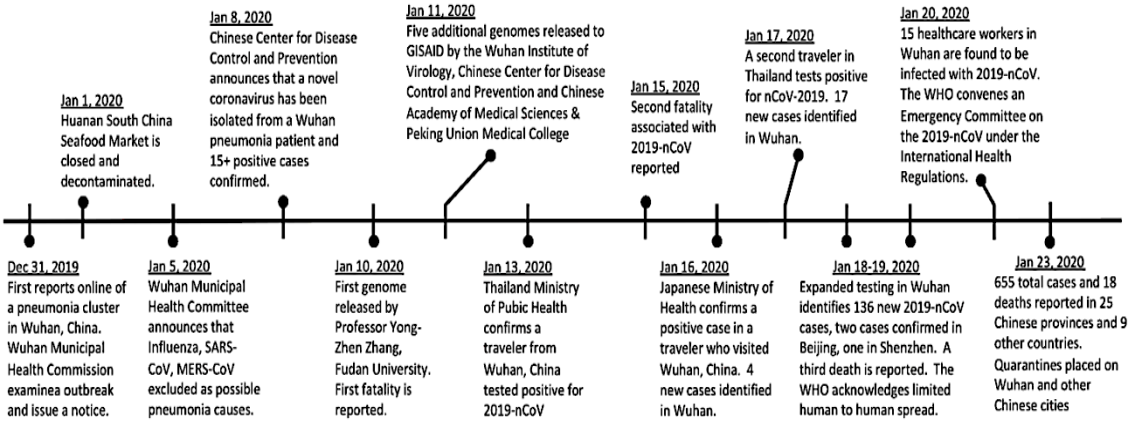

Figure 1 Timeline of COVID-19 events [2]

6.1.1. COVID-19 Epidemiologic Overview

Worldwide, until March 2022, this virus has already caused more than 6.04 million deaths, totaling 445 million confirmed cases. Epidemiological data in Portugal to date are summarized in 3.83 million confirmed cases and 21,285 deaths.

6.1.2 A Brief History of Coronavirus Family

Coronavirus belong to the *Coronaviridae* family, which integrate viruses that can cause infection in humans and other mammals and have been known since the 1960s. Currently, eight coronaviruses that infect and can cause diseases in humans are listed. They are usually associated with clinical manifestations of the respiratory system and may be similar to common colds or progress to a more serious disease, such as pneumonia.[3]

Of all types of coronaviruses that infect humans, SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus), MERS-CoV (Middle East Respiratory Syndrome-related Coronavirus) and SARS-CoV-2 have a zoonotic origin and have been transmitted to humans from the host. In the past decade, SARS-CoV and MERS-CoV have been shown to cause potentially lethal infections, while HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1 are associated with mild symptoms.[3,4]

There have been other outbreaks in previous years in which some *coronavirus* have been identified causing serious respiratory infections in humans. One occurred between 2002 and 2003 related to the severe acute respiratory syndrome that is caused by the coronavirus SARS-CoV and the other in 2012 by the coronavirus MERS-CoV.[3,5]

In a published study it was indicated that SARS-CoV-2 is very similar from a genetic point of view to others in the populations of bats of the species *Rhinolophus affinis*, with one of which it shares an identity of 96% (more specifically with the Bat-CoV-RaTG13), but which has no ability to infect human cells.[5]

Apparently, the facility with which this virus spreads so quickly and becomes so contagious among people is due to the fact that it binds with high efficiency to a protein called ACE2 - angiotensin converting enzyme 2 - located on the surface of several cell types.[4] Therefore, the conclusions of this study emphasize that the hypothesis that this virus may be a human construction that has been released into the environment on purpose is discarded, thus referring to a natural origin of the virus.

Initially designated as 2019-nCoV, the etiologic agent of COVID-19 was isolated and identified as a novel coronavirus. Later, the genome was sequenced allowing it to be related to the SARS-Cov coronavirus outbreak in 2003, thus being named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses.[1]

The new coronavirus, causing potentially severe pneumonia, has never been identified in humans before but transmission between people was almost immediately confirmed.[4,5]

6.2. Clinical Studies

A clinical study involves research using human volunteers, with the main objective of obtaining greater medical knowledge related to the diagnosis and treatment of diseases.[6]

There are two main types of clinical studies: interventional studies (also called clinical trials) and observational studies (Figure 2).

According to World Health Organization (WHO), clinical trials *"are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes."* [7]

6.2.1. Types of Clinical Studies

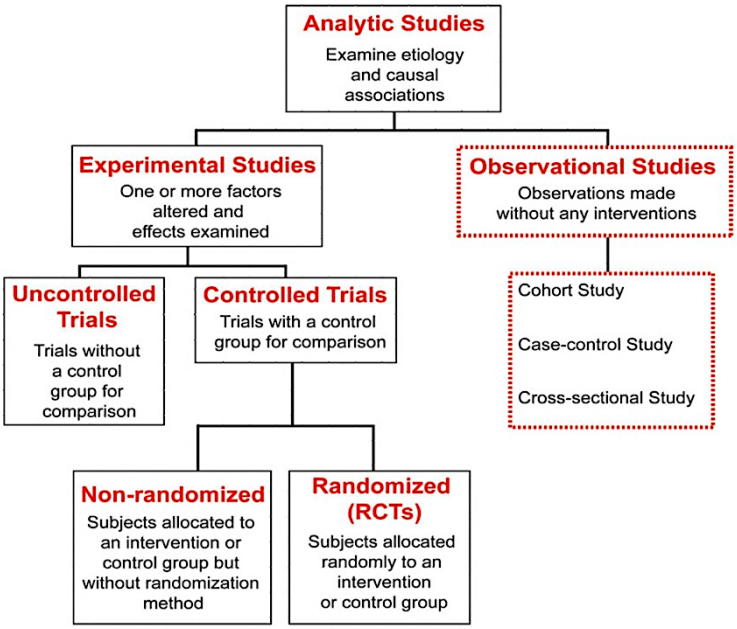

Figure 2 Classification of clinical studies [8]

6.2.1.1. Observational Studies

Observational studies are a type of studies where the investigator does not intervene, that is, the investigator does not alter the exposure status, but simply observes individuals and assesses the strength of the relationship between an exposure and the disease.[8]

The results and analyzes of these studies show how many people develop a disease or condition over time. Thus, it is possible to deepen and describe the characteristics of the disease, which can generate hypotheses about the cause of the disease.[9] These types of studies are able to provide similar results to randomized controlled trials. In order to make it possible to assess possible associations and causes, they must always have a comparison group.[8,9]

In observational studies, it is necessary to verify whether the study has a comparison or control group. If confirmed, the study is called analytical. Otherwise, it is a descriptive study. When the study is analytical, it can be divided into three groups: cohort studies, case control studies and cross-sectional studies (Figure 2).[9] In all three types, the researcher is looking at the natural relationships between factors and outcomes, all of which may have a distinct temporal direction.[9,10]

Cohort and case-control studies offer advantages in determining the occurrence of the disease and its association with an exposure, offering a temporal dimension. On the other hand, cross-sectional studies examine the data between disease and exposure at a given time, do not have an inherent temporal dimension (Figure 3).[8]

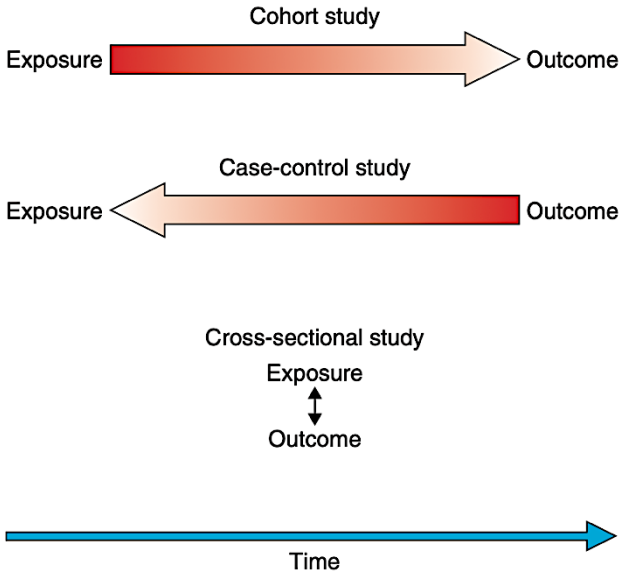

Figure 3 Schematic diagram showing temporal direction of three study designs [9]

When a cohort study is well designed, it can provide excellent results. In these studies, the investigator will first identify a disease-free study population with an exposure of interest and one(s) without the exposure. That said, it will follow them in time until the disease or outcome of interest occurs to determine the results. Cohort studies can be further divided into two groups: prospective and retrospective. In prospective cohort studies, all groups - exposed and unexposed - are identified and followed up in time for the results. In the case of retrospectives, the researcher can go back in time to identify exposure groups through existing records in order to be able to follow them to the results. They have the great advantage of determining that the exposure preceded the outcome, since the exposure is identified early. On the other hand, they include the need for a large sample size, a longer duration of the study design and, consequently, a slower achievement of results.[8,9]

A case-control study consists of identifying the study participants based on their case status, that is, diseased or not diseased, undergoing or not undergoing surgery, among other examples. Once the status is identified, the control cases can be categorized. Data on exposure to risk factors can be collected through interviews or research. These studies have been termed retrospective studies because of the study execution and nature of the design. If we compare case-control studies with cohort studies, several advantages are distinguished such as: they are faster, they require fewer participants, they are relatively cheaper to implement and they allow multiple exposures to be evaluated for an outcome. Case-control studies are appropriate for investigating rare outcomes.[8,10]

Cross-sectional study is when the investigator measures the outcome and the exposures in the study participants at the same time. These studies are used to assess the prevalence of diseases in clinic-based samples. An example of this type of study could be to study the association between sedatives or talking on a cell phone and being

involved in an automobile crash. These studies are inexpensive and can be conducted relatively faster.[10,11]

6.2.1.2. Interventional Studies

In observational studies the researcher is limited to analyzing exposures and outcomes, without intervening or altering the course of natural events. On the other hand, in the case of interventional studies, the researcher interferes at some point in the study, in order to then be able to determine the effect of the intervention.[10,12] Participants can receive a series of interventions such as: vaccines, drugs, medical devices, changing the diet, performing a therapeutic procedure, among others.[12] This will allow the investigator to study various pharmacological effects and even identify adverse reactions.

As previously mentioned, this type of study can be divided into two large groups: randomized controlled trials (RCTs) and nonrandomized controlled trials (Figure 2). However, the most common and used in interventional studies is randomized controlled trials.[10]

Non-randomized trials are study designs that compare different groups, in which one group had intervention by the researcher and the other(s) had no intervention. In this type of study, it may be possible to relate the intervention and the result, since they are usually carried out prospectively. One of the disadvantages is it is susceptible to bias, as the participants belong to different groups.[10,12]

The randomized controlled trial is the only study known to be able to avoid and reduce the likelihood of bias in the determination of results and may have many modifications. It is similar to the cohort study in several respects, with the exception of the randomization of participants to exposures. [9,10]

RCTs are trials in which a homogeneous group of participants, who match the inclusion and exclusion criteria, are randomly divided into two separate groups. Each group receives a different intervention.[12] Theoretically, in a well-implemented randomization procedure, the only difference is the intervention. That said, any difference in the results between the groups is related to the effect of the intervention, which allows the study and comparison of several aspects. However, randomized controlled trials also have disadvantages such as the process of screening participants before inclusion, greatly reducing the number, not being able to be done for some cases due to ethical reasons and being very expensive.[9,10,12.]

6.2.2. Phases of a Clinical Trial

Researchers carry out research and preclinical studies of the drug in question at very small doses in order to make sure that it is not harmful to humans. In in the clinical phase of development there are trials that are divided into several phases.

Phase I is especially about ensuring that the treatment is safe in humans. The researchers spend several months analyzing the effects of the medication on a small

group of healthy volunteers, in order to control for possible serious adverse effects. In addition to evaluating the ideal dosage, it is also possible to conclude the best way to administer the drug. According to the FDA, approximately 70% of drugs are approved. [13,14]

In phase II it is already possible to determine the correct dosage of the drug in order to analyze the efficacy of the treatment. For this to be available, a greater number of volunteers is already needed at this stage compared to the previous stage. The FDA estimates that at this stage, about 33% of drugs move to phase III.[13,14]

Phase III of a clinical trial involves a much larger group of volunteers, up to about 3,000 participants, and has as its main objective the evaluation of the efficacy/safety of the new drug with the existing options for the same condition. As this phase lasts longer due to the greater number of participants, it makes it more likely to detect rare side effects. Approximately 25 to 30 percent of drugs move to phase IV. [13,14]

Phase IV, also known as Post-Marketing Surveillance, consists of conducting clinical trials after marketing authorization. Their main purpose is to obtain more information about the long-term risks and benefits that may not have been seen before.[14]

6.3. COVID-19 Clinical Trials

Covid-19 clinical trials have become the main focus of public health. That said, in 2020, researchers from all over the world started to carry out clinical trials on this new disease (Figure 4), in order to obtain more information - diagnosis, medicines, vaccines, interpretation of the disease, therapeutic strategies, others - to stop and face the pandemic.

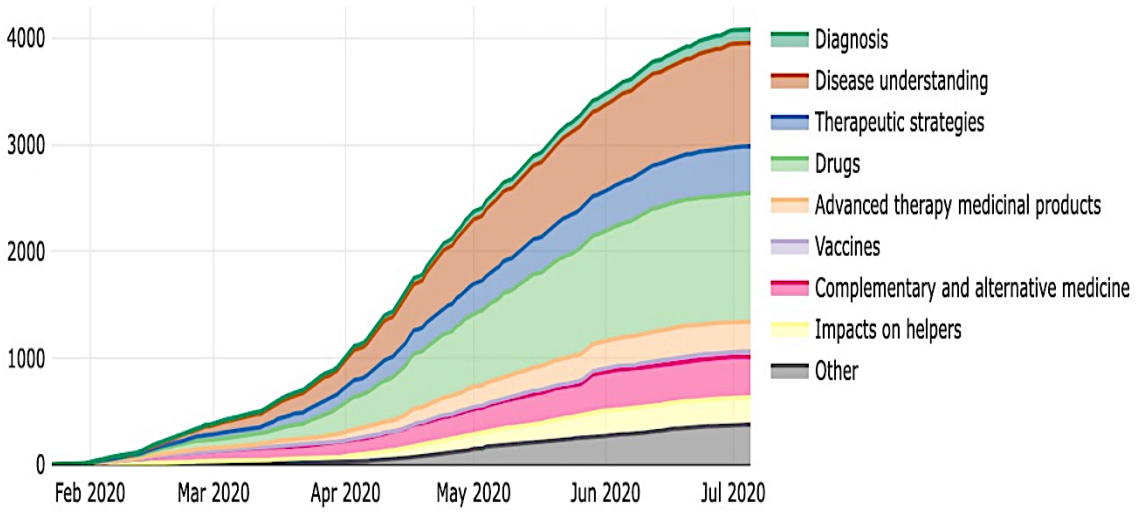

Figure 4 Cumulative number of registered COVID-19 clinical trials [15]

6.3.1. Impact of COVID-19 Pandemic in Clinical Trials

COVID-19 disease has drastically altered the lives of the entire world in many ways. Clinical trials were no exception and more than 1,000 clinical sites have been shown to indicate a negative impact of COVID-19, in which patient recruitment for ongoing trials has stopped and a large portion has consecutively delayed studies.[16]

During the pandemic, as for trials that were already underway, clinical trials that were early and smaller were more likely to pause compared to trials with larger projects. On the other hand, the launch of new clinical trials was greatly affected. An analysis was made of more than 62,000 trials started before and during the pandemic in the United States in which only 57% of those that would have started if the pandemic had not occurred were carried out.[17]

The COVID-19 pandemic has undermined the quality of clinical trials. Several factors contributed to this, such as: remote monitoring and monitoring, online meetings and express delivery of medicines. All this called into question the quality of the rehearsals, however it also allowed many to continue.[18]

Study sites were also targeted by this pandemic, due to difficulties in continuing studies, delay in registering participants and problems in monitoring. Pharmaceutical and therapeutic trials have been shown to be more resilient to the effects of the COVID-19 pandemic compared to academic trials from hospitals and medical centers. Researchers are also concerned about funding for new research organizations, given the whole situation.[16,19] Regardless of the situation caused by COVID-19, the safety of participants must be the top priority.[18]

Clinical research is the process that leads to the development of new drugs and potential treatments. In 2020, more than 79% of ongoing clinical trials were interrupted directly or indirectly by COVID-19 and many researchers together with their teams had to shift their focus to support related to this new disease.[20]

In a short time, researchers, members of the ethics committee, monitors and everyone involved in the progression and execution of clinical trials underwent a process of adaptation in view of the duration and persistence of the pandemic.

6.3.2. Platform Trials in the COVID-19 Pandemic

Platform trials are clinical trials that allow the evaluation of several interventions simultaneously in relation to a control group in a single protocol (Figure 5). This type of assay allows the control to be updated and new experimental arms to be added during the assay.[21]

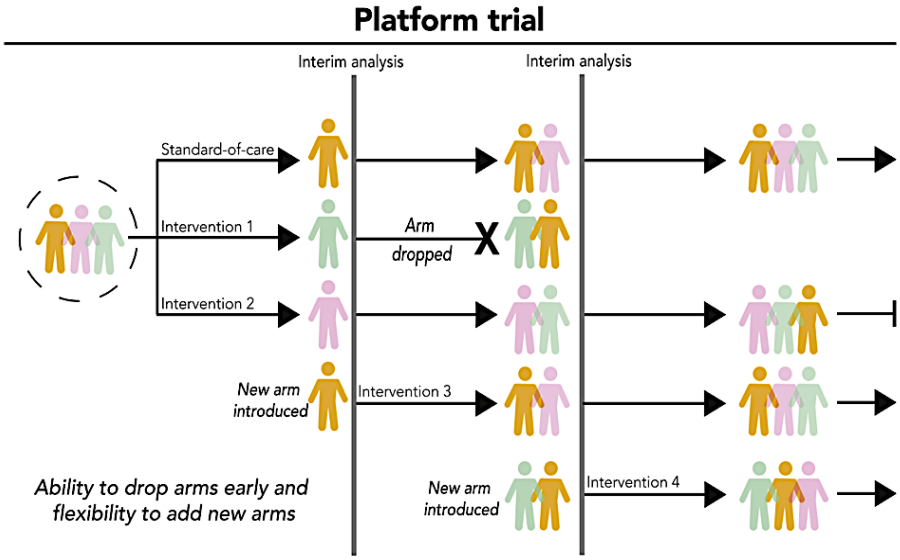

Figure 5 Illustration of a platform trial [17]

Compared to traditional trials, platform trials are more effective in terms of the sample size needed, thus shortening the recruitment time. In these studies, it is possible to perform pairwise comparisons between each of the intervention arms and the control arms, not depending on indirect comparisons. [21,22]

Shortly after the World Health Organization declared a global pandemic, more than 1,000 interventional trials were registered. Platform clinical trials have attracted significant attention as they allow the study and identification of effective therapies in a single protocol. The success of platform tests with the addition of new arms during the COVID-19 pandemic may have replaced the need for new tests with distinct designs. Since the platforms were already well defined, they made it possible to find effective treatments, thus increasing the use of these studies. [23]

Platform trials have proven to be an asset and one of the most suitable resources for new discoveries based on COVID-19. Thus, funding was accelerated during the pandemic by facilitating the rapid start of testing. However, this remains the biggest obstacle to their realization and advancement.

6.3.3. Treatments for COVID-19

After the outbreak of the COVID-19 virus around the world, the main focus became to study and find effective treatments for this disease in order to regress as quickly as possible the advance of the pandemic.

Since there was no effective specific antiviral treatment for COVID-19, medication was resorted to for symptomatic treatment. However, the goal has always been to conduct new clinical trials for the development of antiviral drugs with potential benefits and vaccines to achieve herd immunity.[24]

6.3.3.1. Drugs

According to EMA, a drug *"is a substance or combination of substances intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action."* [25]

Several *in vitro* and *in vivo* studies based on experience with SARS-CoV and MERS-CoV have demonstrated the effectiveness of specific antiviral drugs to treat COVID-19. However, this type of medication should only be used in patients with mild symptoms, since in patients with comorbidities and more severe symptoms due to COVID-19, it may increase the risk of mortality.[26] Antiviral drugs are believed to be effective at various stages of viremia, more specifically in preventing viral entry into the host cell and viral replication.[27]

One of the first drugs to prove effective in patients with COVID-19 was remdesivir in China. Remdesivir prevents viral replication through an adenosine analogue that is incorporated into viral RNA. In several studies carried out, clinical improvement was observed in 68% of patients with the use of remdesivir and it was shown to be active acting on the viral polymerase of coronavirus.[26,27] Initially, tocilizumab and immunoglobulin were also studied and demonstrated some efficacy against COVID-19. [28]

After evaluation by the European Medicines Agency (EMA), several treatments have already been authorized in the European Union to treat COVID-19. Most treatments can be administered to adults and adolescents from 12 years of age and weighing at least 40 kilograms. [29]

Sotrovimab, casirivimab and imdevimab, regdanvimab and ritonavir have already been authorized for the treatment of patients who do not require supplemental oxygen or who are at increased risk of the disease becoming severe. On the other hand, remdesivir and tocilizumab are more indicated for patients with severe disease and who already need respiratory support, as they are more effective. However, they can also be a form of treatment in moderate disease against COVID-19. EMA also authorized a drug with the combination of tixagevimab and cilgavimab capable of preventing the disease. A study involving more than 5,000 people showed that it reduced the risk of COVID-19 infection by 77%. [29]

6.3.3.2. Vaccines

Vaccination is considered the only definitive and preventive treatment option for COVID-19. Since the beginning of the pandemic, when the seriousness of the situation in terms of public health was realized, several clinical trials of vaccines began to be conducted worldwide.[28]

After several months of study and research, according to EMA, the following vaccines are authorized for use in the European Union:

- Comirnaty (Pfizer): vaccine that contains tozinameran, a messenger RNA (mRNA) molecule with instructions for producing a protein from SARS-CoV-2. Can be administered to people aged 5 years and older.

- Nuvaxovid (Novavax): vaccine that contains a version of a protein found on the surface of SARS-CoV-2 (the spike protein), which has been produced in the laboratory. Can be administered to people aged 18 years and older.

- Spikevax (Moderna): vaccine that contains elasomeran, a messenger RNA (mRNA) molecule with instructions for producing a protein from SARS-CoV-2. Can be administered to people aged 6 years and older.

- Vaxzevria (AstraZeneca): vaccine made up of another virus (of the adenovirus family) that has been modified to contain the gene for making a protein from SARS-CoV-2. Can be administered to people aged 18 years and older.

- Janssen: vaccine made up of another virus (of the adenovirus family) that has been modified to contain the gene for making a protein found on SARS-CoV-2. Can be administered to people aged 18 years and older.[30]

At this time, all vaccines mentioned above are being administered in Portugal, except for Nuvaxovid (Novavax).[31]

6.3.4. Measures, Guidelines and Recommendations

In addition to the impact of COVID-19 on the healthcare system and society at large at large at various levels, there has been a major impact on the advancement and initiation of clinical trials and their participants, as mentioned above. Therefore, extraordinary measures will have to be implemented and followed.[32]

Research teams and clinical centers must follow these measures in order to guarantee the safety and rights of clinical trial participants. Those responsible for trials must adopt measures and recommendations appropriately for each clinical trial, analyzing the risks of each decision. The implementation of the guidelines by member states contributes to delaying the interruption of clinical research in Europe during the public health crisis.[32,33]

The mission of EMA and INFARMED is to promote scientific excellence in the supervision of medicines for human use, for the benefit of public and animal health in the European Union (EU). They must also ensure access to safe, quality medicines and health products.[34,35] CEIC is an independent body made up of health professionals whose mission is to ensure the protection of the rights and safety of participants in clinical studies, by issuing an ethical opinion on the research protocols to which they are submitted.[36]

6.4. Commercial vs Non-Commercial Clinical Trials

Clinical trials can be divided into commercial trials and non-commercial trials also referred to as academic or investigator-initiated clinical trials (IICTs), in accordance with the sponsor.

A commercial study is a study sponsored by a pharmaceutical company. Usually, the main interest of the company is the development and approval of a drug. When compared to non-commercial trials, these occur on a larger scale as they are conducted simultaneously by several countries worldwide.[37]

Investigator-initiated clinical trials are trials sponsored by a non-profit institution (independent researcher, academic institution or study group) for non-commercial purposes. They are usually led by researchers working in hospitals or universities.[37] It is crucial that non-commercial clinical trial sponsors invest in developing appropriate administrative and management skills for trials. Thus, there would be greater support for non-commercial clinical research, whose relevance to global health is increasingly evident.[38]

Often, the interests of the pharmaceutical industry when new drugs are developed do not meet the current needs of clinical practice and therefore it is necessary to support independent clinical research. In Europe, between 10-30% of clinical trials are led by academic/non-commercial sponsors.[39] In this dissertation, commercial and non-commercial clinical trials of COVID-19, planned or in progress, carried out in Portuguese institutions between 2019 and 2021 will be registered and analyzed.

6.4.1. Importance of European and National Infrastructures in Response to the Pandemic

Many academic sponsors do not have the financial capacity to carry out clinical trials, even more so now with the demand for discovery of new treatments for COVID-19. Thus, to facilitate multinational clinical research, the European Network of Clinical Research Infrastructures (ECRIN) and the Portuguese Network of Clinical Research Infrastructures (PtCRIN) were created.

6.4.1.1. European Clinical Research Infrastructure Network (ECRIN)

European Network of Clinical Research Infrastructures (ECRIN) is a not-for-profit intergovernmental organisation that supports the conduct of multinational clinical trials in Europe. ECRIN links scientific partners and networks across Europe to facilitate clinical research. ECRIN was created as an ERIC (European Research Infrastructure Consortium) in November 2013, viewed as an ESFRI landmark since 2016 and has reached operational and financial maturity Portugal is one of the five founding members of ECRIN, together with France, Italy, Spain and Germany. Hungary, Norway, Czech Republic and Ireland have also since joined ECRIN as Members. Poland, Slovakia and Switzerland.is at the moment an Observer Country.

ECRIN works with national networks of clinical trials units (CTUs), with Portugal being one of the countries that signed the ECRIN statutes as a member country. [40] In this way, with all the connections and knowledge, ECRIN facilitates understanding between researchers, greatly facilitating the process and consecutively achieving success in the clinical trials they propose. ECRIN offers researchers support for conducting and implementing multinational trials though their partners clinical trials units (CTUs). Areas of support include funding requests, trial management, quality assurance, tools needed to address regulatory and ethical issues, risk assessment, and more. ECRIN has a vast portfolio of 60 multinational clinical research projects with an average of 6.3 countries per study.[40]

European Research infrastructures (RIs) such ECRIN mobilization in response to COVID-19 RIs to provide support to the research community was unprecedented and allowed a quick response.

Since the beginning of the pandemic, ECRIN has been committed to supporting the global to provide expert advice and resources for clinical trials on COVID-19. In order to accelerate research, it joined other European research infrastructures such as EATRIS, ELIXIR and BBMRI. [40]

6.4.4.2. Portuguese Clinical Research Infrastructure Network (PtCRIN)

Portuguese Network of Clinical Research Infrastructures (PtCRIN) is the national hub of ECRIN in Portugal.

PtCRIN aims to improve clinical research by promoting a more efficient implementation of multinational investigator initiated clinical trials (IICTs). Multinational clinical trials provide the highest level of evidence to accelerate the approval of innovative health technologies (drugs, cell therapies, devices, food, and behavior) and to support clinicians and decision makers in the adoption of a therapeutic decision that are safer and more cost effective. However, require specific infrastructures - clinical research centers (CRC) that provide technical support clinical investigators teams to conduct clinical studies, and clinical trial units (CTUs) that manage the studies from the design, regulatory approvals, monitoring, publication, etc.

PtCRIN is a consortium of 26 national institutions, Health Care Units, Universities, Research Institutes that host CTUs, CRCs and clinical investigators. PtCRIN CTUs provide services at a not-for-profit rate to public sponsors and SMEs (Figure 6).

The PtCRIN is made up of a non-profit network made up of CRCs, CTUs and Universities with expertise in the area of clinical research. This organizational model guarantees the commitment of health units to clinical research.[41]

Given the pandemic and all the countries involved in hundreds of studies, PtCRIN made it possible to more easily answer several questions. That is, it was the key for national

and international researchers to be able to communicate and share information and knowledge, increasing the robustness of the studies.

Figure 6 PtCRIN Members

7. SCOPE AND AIM

In order to understand the involvement that Portugal had in COVID-19 clinical trials, given its relevance to the discovery of effective treatments as it has reached the whole world, it would be important to characterize and analyze the studies registered in Portugal and also to identify the research centers that most were involved.

This work aim characterizes the type of studies (observational and interventional) that have been conducted in Portugal between 2020 and 2021. The objective is identifying the main characteristics of the studies: type of studies (commercial or non-commercial; interventional or noninterventional; national or international trials), number of patients recruited, funding and publication through a systematic search in registry databases.

8. METHODOLOGY

8.1. Inventory COVID-19 Guidelines

European Medicines Agency (EMA), national competent authority INFARMED (National Authority for Medicines and Health Products) and National Ethics Committee for Clinical Research (CEIC) release exceptional measures related to carrying out clinical trials during the period of the COVID-19 crisis. Most of the European countries have put in place accelerated procedures ("Fast track" procedure) for the evaluation and authorization of clinical trials related to the management of the pandemic COVID-19. In many countries the regulatory authorities have issued official guidelines for the accelerated procedure. Some of them cover also the ethical review process by the Ethics committee. For a better interpretation and understanding of the evolution of measures throughout the pandemic, the main national and international guidelines were collected.

8.2. Research and Characterization of COVID-19 Observational and Interventional Studies registered in Portugal between 2020 and 2021

The selection of clinical trials required that they were registered in Portugal between 1 January 2020 and 31 December 2021 and were identified by the methodology described below.
For the collection and selection of information, three international databases were used, namely ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR) and the Australian New Zealand Clinical Trials Registry (ANZCTR) and one national database, namely the National Registry of Clinical Studies (RNEC).

8.2.1. Search methodology

INCLUSION CRITERIA:

- Clinical studies of COVID-19
- Clinical studies registered after 1 January 2020 until 31 December 2021
- Clinical studies with recruitment centers in Portugal

EXCLUSION CRITERIA:

- Clinical studies not related to COVID-19
- Clinical studies registered before 1 January 2020 and after 31 December 2021
- Clinical studies without recruitment centers in Portugal
- Duplicate clinical studies

STEP 1

First, all studies - both observational and interventional - were searched on the ClinicalTrials.gov platform. To make the search more detailed in line with our goals, the terms "COVID-19" and "SARS-Cov-2" were placed in the advanced search fields. The search was carried out from 01 January 2020 to 31 December 2021, selecting Portugal as a country in the advanced search field, as we only want clinical trials registered in Portugal.

STEP 2

Then, a search was carried out on the EU-CTR platform, where only intervention studies are registered. This step consisted of finding studies that might not be on the platform used previously and to complement information. In the advanced search, Portugal was also selected, the term "COVID-19" and the same period of time mentioned above.

STEP 3

With the ANZCTR, the search was carried out in the aforementioned time interval and using Portugal as the recruitment country. The registration number corresponds to the ClinicalTrials.gov platform code.

STEP 4

To complete the information of the clinical trials, mainly on the source of funding, the platform of the National Registry of Clinical Trials (RNEC) was also used. In this case, the search was performed by the EudraCT number in the advanced search field, making the search more direct and efficient. Only interventional trials are registered on this platform.

8.2.2. Data Extraction

STEP 5

All information was analyzed and extracted manually. They were organized and recorded in a Microsoft Office Excel table, divided by several parameters according to the information that was relevant for the data analysis.

STEP 6

The table was organized and divided by the following parameters: codes (NCT and EudraCT), title, type of study, sponsor, country of sponsor, type of institution, study status, start date, completion date (month and year, when applicable) or estimated completion date, therapeutic area, clinical trial characteristics (randomized, controlled, masking, etc.), type of intervention, population study (number of patients recruited, ages, health status, patients recruited in Portugal), recruitment sites in Portugal, countries involved in the clinical trial, funder, type of funding, funding agencies and publications of completed studies. All information was extracted manually.

8.2.3. Duplicate Identification

STEP 7

Through the sponsors, titles and codes of the studies, duplicates were identified in the various databases. Thus, the duplicates were discarded and removed from the search. All the remaining studies were gathered in a Microsoft Office Excel table with all the information extracted from the different databases.

8.2.4. Additional information

STEP 8

After all studies were filtered and completed, a search was performed to obtain additional information, which was added to the respective parameter in the table in Microsoft Office Excel.

STEP 9

Clinical trials were manually distinguished into commercial trials and IICTs through sponsor analysis. On different platforms, the funder is often not explicit. Therefore, the sponsor was considered as a financier. In EU-CTR the funder was identified in the field “Sources of Monetary” and in Clinicaltrials.gov the funders were identified in the field “Sponsor and Collaborators”. In the ANZCTR, there was a field duly titled “Financier”.

8.2.5. Search of publications

STEP 10

To check whether the trial was already published, PubMed was used using the title or EudraCT as a search engine. Through a Google search, other publications of the study were also found. Information such as date of publication, Portuguese authors and journal published were taken from studies already published.

8.3. Data analysis

All collected data were organized and analyzed in Microsoft Office Excel for Windows. Relative and absolute frequencies were calculated and values are presented as percentages and averages.

9. RESULTS

9.1. Inventory COVID-19 Guidelines

Following the declaration of a pandemic by the World Health Organization due to SARS-CoV-2 infection, a set of exceptional measures related to clinical trials were issued. We can see in Figure 7 a table with the dates in which they were published and the respective responsible entities.

TITLE	WHO PUBLISHED?	PUBLICATION DATE
Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic – **VERSION 1**	EMA	**20/03/2020**
COVID-19: Exceptional measures regarding clinical trials execution during the period of risk to public health - **VERSION 1**	INFARMED	**26/03/2020**
Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic – **VERSION 2**	EMA	**27/03/2020**
Informação CEIC sobre Ensaios Clínicos ou Estudos de Intervenção com DM face à conjetura atual da COVID-19	CEIC	**31/03/2020**
COVID-19: Exceptional measures regarding clinical trials execution during the period of risk to public health - **VERSION 2**	INFARMED	**15/04/2020**
Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic – **VERSION 3**	EMA	**28/04/2020**
COVID-19: Exceptional measures regarding clinical trials execution during the period of risk to public health - **VERSION 3**	INFARMED	**11/05/2020**
Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic – **VERSION 4**	EMA	**04/02/2021**

Figure 7 Inventory COVID-19 Guidelines issued by EMA, INFARMED and CEIC

To safeguard the safety of participants, a series of measures were implemented in the context of COVID-19. The main measures that were changed were based on the following parameters:

- Interruption of treatment;
- Suspension of recruitment;
- Scheduled visits - clinical evaluation and study procedures using telematic methods;
- Centralized monitoring and review of source data;
- Direct dispensing of experimental drugs at home;
- Conditions for transfer between test centers.

9.2. Research and Characterization of COVID-19 Observational and Interventional Studies registered in Portugal between 2020 and 2021

9.2.1. Analysis of Observational Studies

9.2.1.1. Number of COVID-19 Observational Studies initiated each month

A total of 14 observational studies were and organized considering the month and year of the trial initiation to understand their distribution over the months during the pandemic (Figure 7).

Although COVID-19 appeared in 2019, this graph only starts in 2020, as there are no observational studies recorded in Portuguese institutions in the year 2019. Figure 8 shows that during the study period, April, May and June 2020 were the months with the highest number of observational studies initiated. Both in 2020 and in 2021 there was no record between July and December.

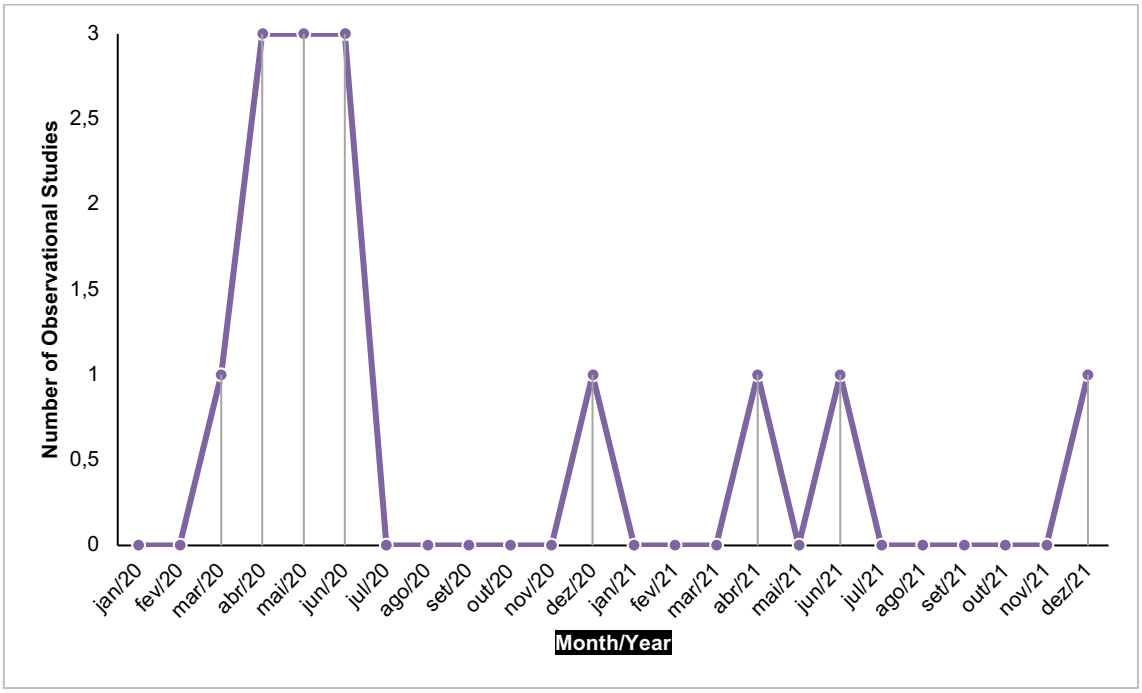

Figure 8 Number of planned or ongoing COVID-19 observational studies registered in Portuguese institutions from 2020 to 2021, according to the records of ClinicalTrials.gov and ANZCTR.

9.2.1.2. Country and Type of Sponsor of COVID-19 Observational Studies

The analysis of the nationality of the sponsor organisation, it was observed that half of the sponsors were Portuguese (50%), which translates into a large representation. The remaining non-national sponsoring organizations were all from Europe (42.86%), except for one from the USA (Figure 9).

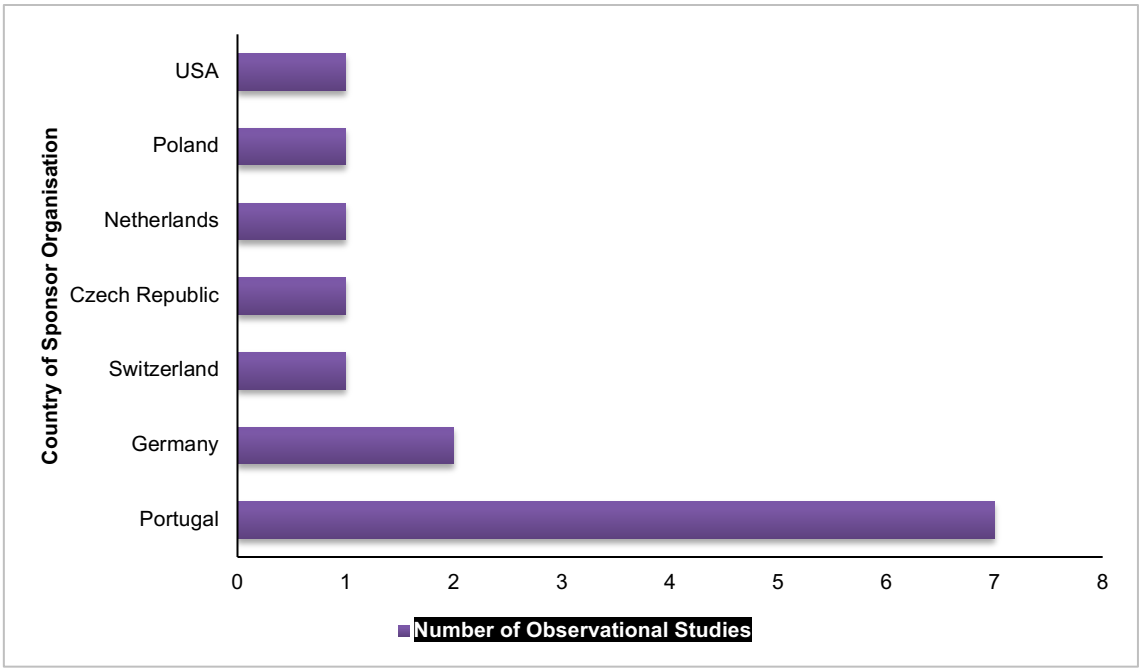

Figure 9 Nationality of the sponsor organization of COVID-19 observational studies registered in Portugal between January 2020 and December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

Regarding the type of sponsor organisation, we observed that the majority 64.29% (n=9) were sponsored by universities. The remaining 21.43% by hospitals (n=3) and 14.29% (n=2) were sponsored by pharmaceutical companies (Figure 10).

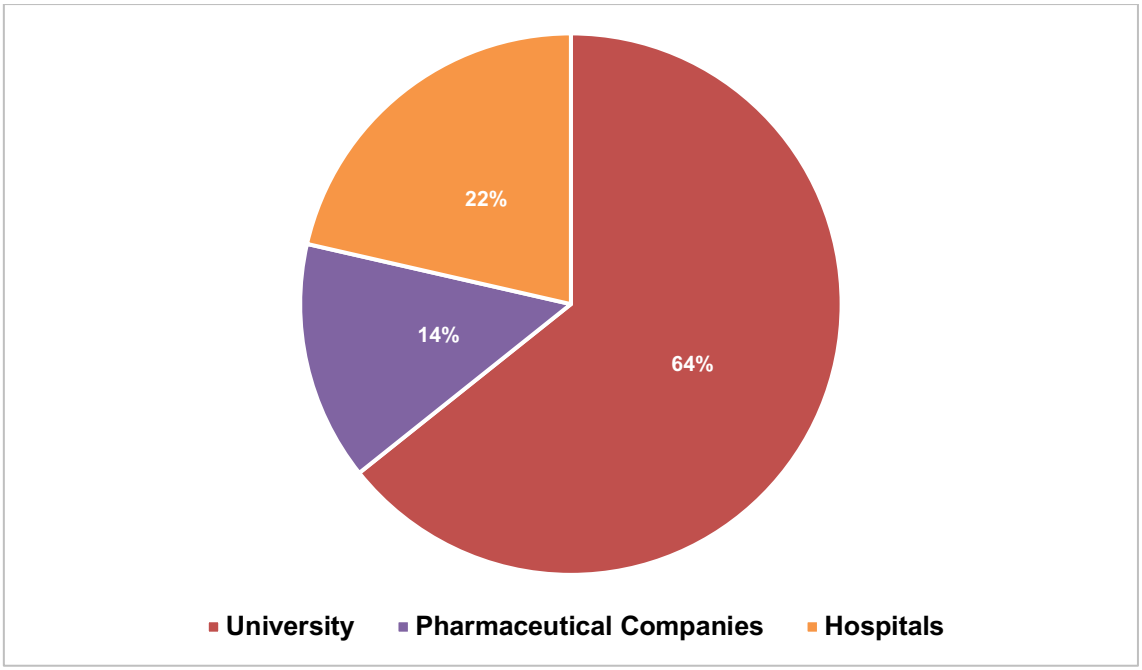

Figure 10 Type of the sponsor organization of COVID-19 observational studies registered in Portugal between January 2020 and December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

This allows us to conclude that 86% correspond to non-commercial trials since they are trials sponsored by universities, that is, public non-profit organizations. For commercial trials, the pharmaceutical industry was identified as the only source of funding in the remaining studies, specifically in 14% of trials.

The portuguese university that have been sponsoring more COVID-19 observational studies was the University of Lisbon (28.57%). The University of Porto is the second Portuguese university that most sponsored studies, corresponding to 14.29%. The University of Minho stands out, as it was the third and last in the country to sponsor another study (Figure 11).

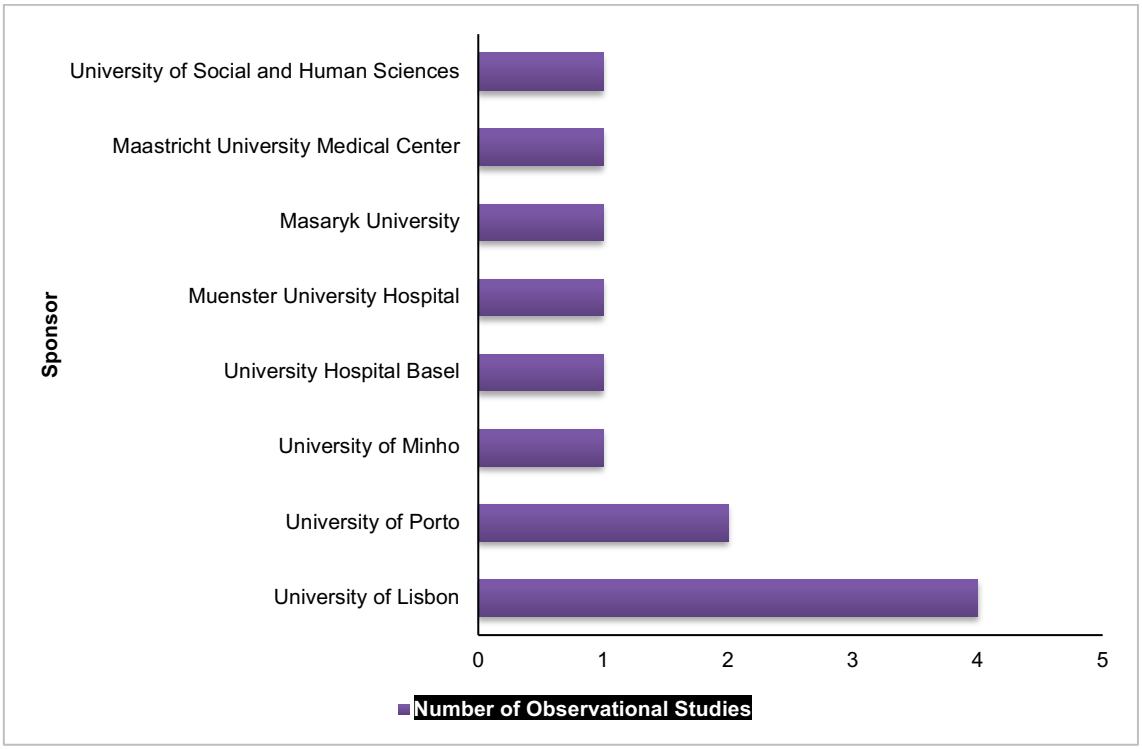

Figure 11 Universities sponsors of COVID-19 observational studies registered in Portugal between January 2020 and December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

9.2.1.3. Study Population Analysis of COVID-19 Observational Studies

In the population analysis of observational studies, it was observed that 42.86% (n=6) had COVID-19 infection as the main inclusion criterion at present. Undoubtedly, this was the most requested inclusion criterion for participation in the studies.

Excluding this criterion, 28.57% were healthy individuals (including pregnant women, individuals already vaccinated for COVID-19 and physicians from intensive care hospitals). The rest included patients with other diseases, with the aim of relating and evaluating their conditions when in contact with the SARS-CoV-2 virus.

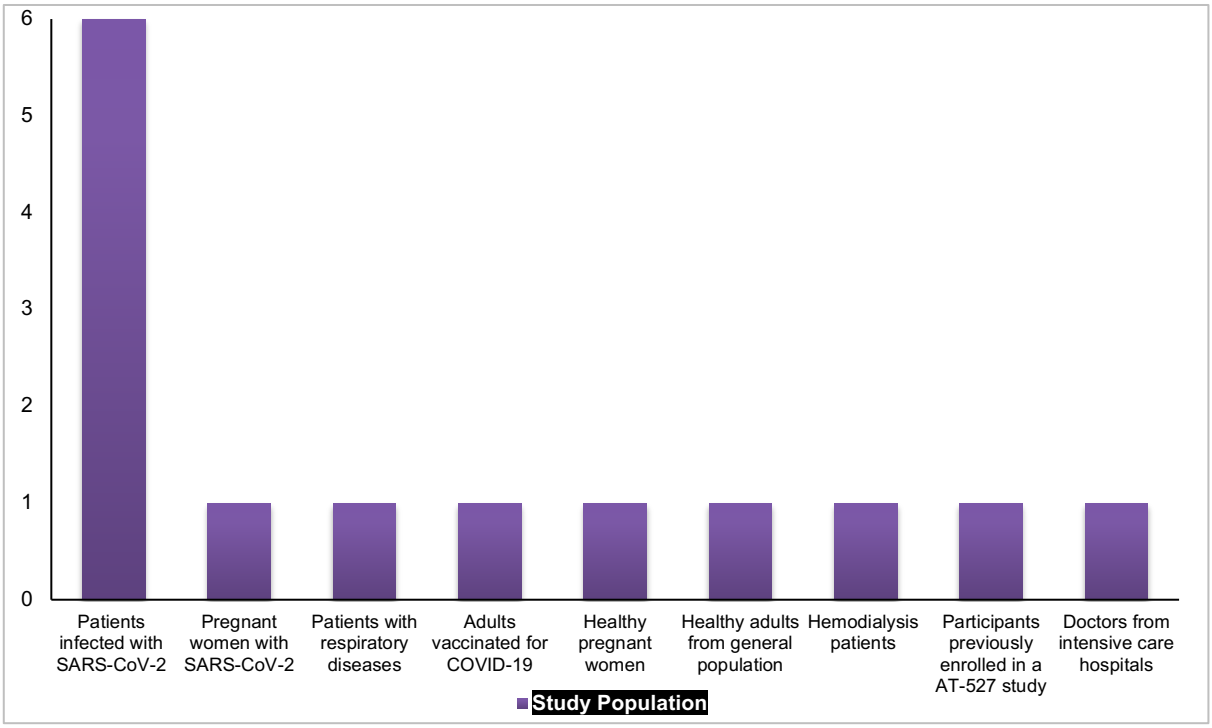

Figure 12 Study population of COVID-19 observational studies registered in Portugal between January 2020 and December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

Regarding the age range, in Figure 13, we observe that most studies required the age of participants to be over 18 years old (n=9). In 14.29% of the studies, anyone, that is, of all ages, could participate.

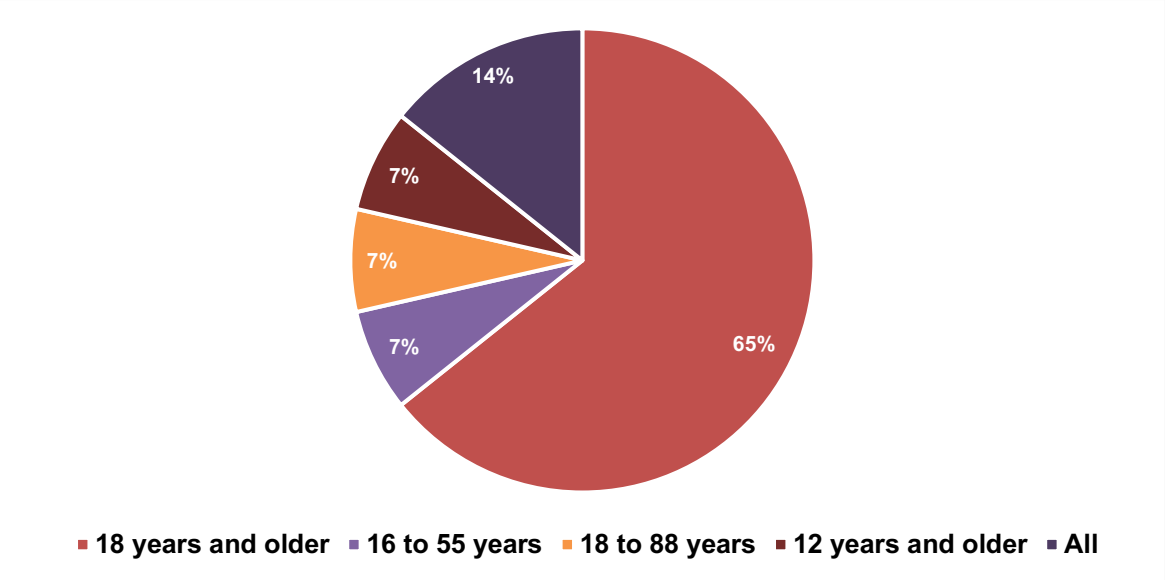

Figure 13 Age range of study population of COVID-19 observational studies registered in Portugal between January 2020 and December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

9.2.1.4. Portuguese Principal Investigators (PIs) and Clinical Research Centers (CRCs) conducting COVID-19 Observational Studies in each district of Portugal

According to the data collected, as we can see in Figure 14, principal investigators and research centers were identified in 7 different districts.

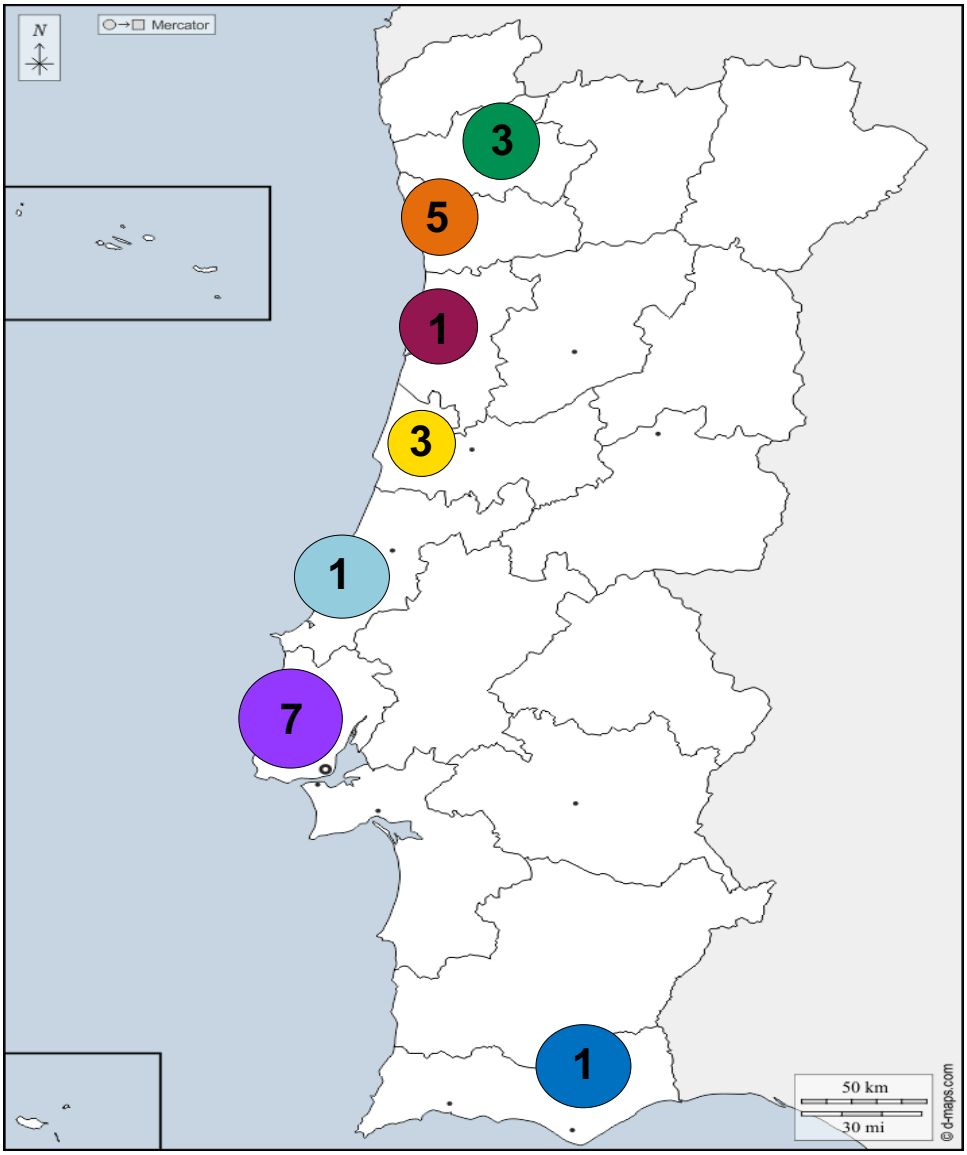

Figure 14 National distribution of the various Clinical Research Centers (CRCs) of COVID-19 observational studies in each district registered in Portugal between January 2020 and December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

In total, 21 different Portuguese centers involved in the COVID-19 observational studies were distinguished. Of all, Lisbon is the district with the majority corresponding to 33.33% (n=7) where Nova Medical School and University of Lisbon stood out. In Porto, 23.81% of the centers involved in the studies were identified, with emphasis on the Hospital Sao Joao. Regarding the Portuguese PIs, 16 were identified in all studies. For data protection reasons, they are not identified.

In the 14 COVID-19 observational studies in which Portugal is involved, 57.14% (n=8) are multinationals. The remaining 42.86% are carried out exclusively by Portuguese institutions, with only one of the studies sponsored by Portugal being multinational.

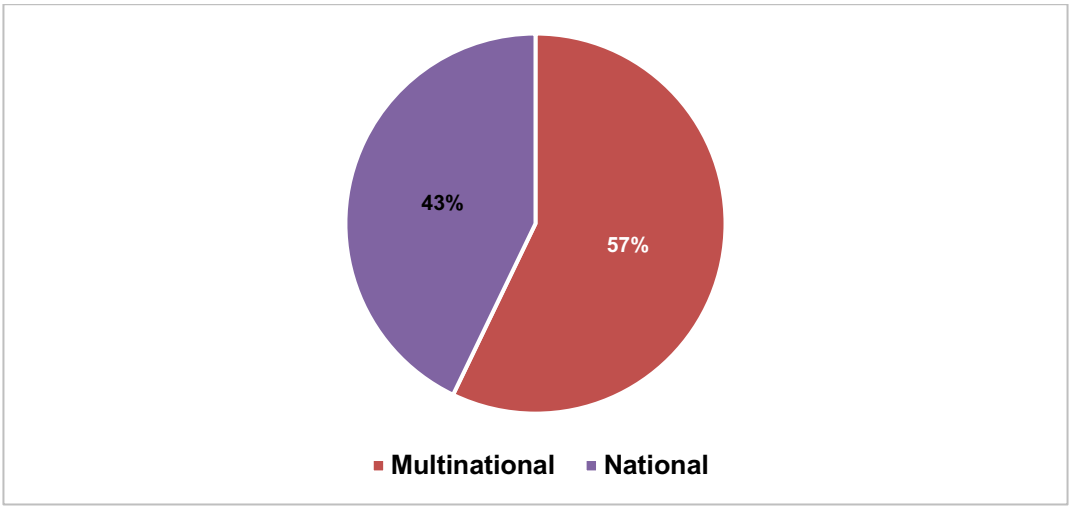

Figure 15 Distribution of multinational and national COVID-19 observational studies performed in Portugal from January 2020 to December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

Of the 8 multinational studies, the average number of countries that participated per study was 14. As we can see in the following graph, there was a study with the participation of only 2 countries, while another study had 27 countries involved (Figure 16).

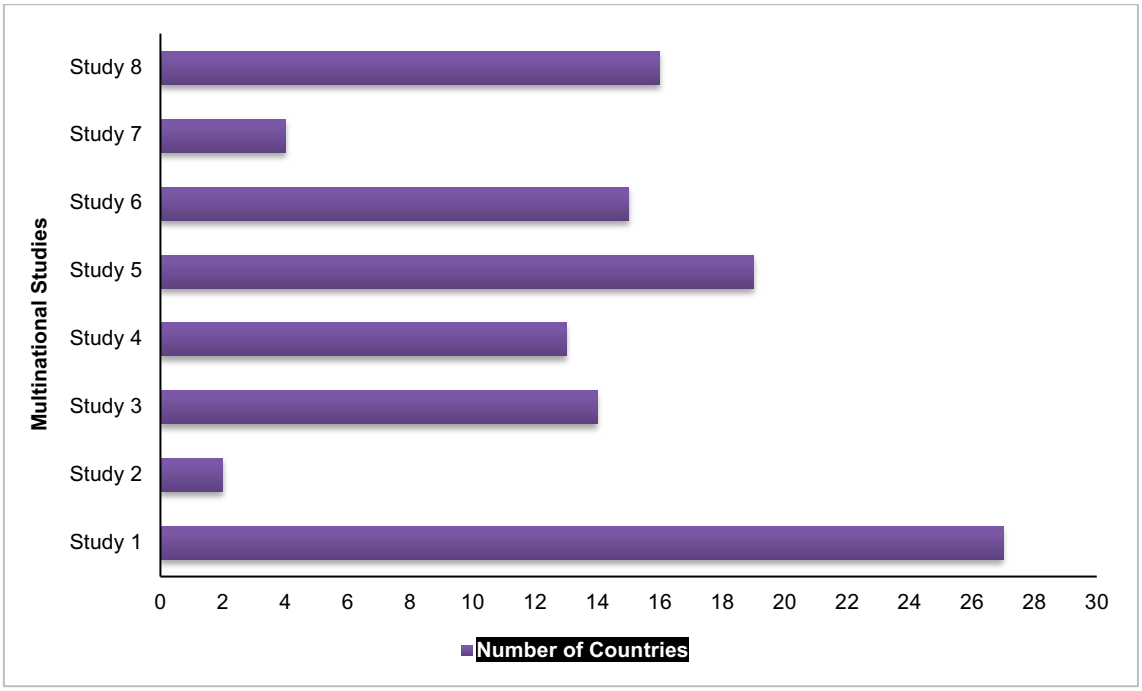

Figure 16 Number of countries involved in multinational COVID-19 observational studies performed in Portugal from January 2020 to December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

9.2.1.5. Type of Funders of COVID-19 Observational Studies

Regarding the identification of funders of observational studies, the founder was considered the same as the sponsor since no explicit information was found on the platforms used. That said, 86% (n=12) of the studies were funded by public organizations (universities and hospitals). The remaining 14% by private organizations (pharmaceutical companies).

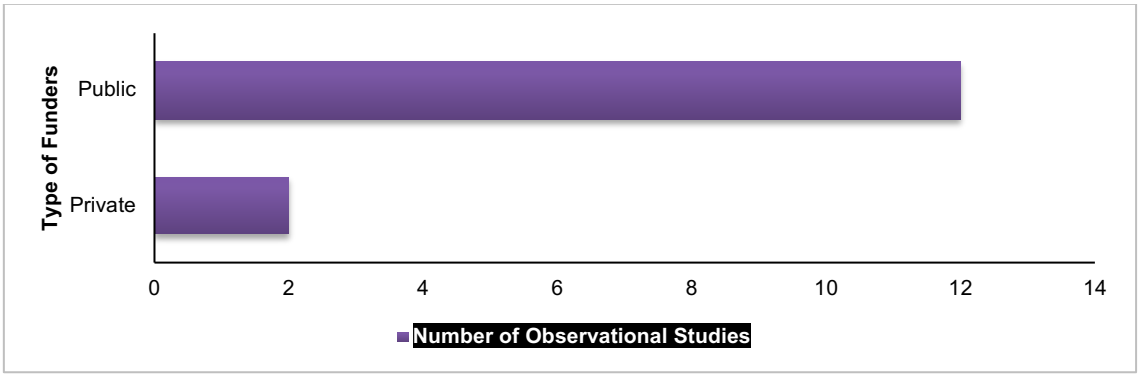

Figure 17 Type of funders of COVID-19 observational studies registered in Portugal between January 2020 and December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

9.2.1.6. COVID-19 Observational Studies Published in Scientific Journals

Of all studies (n=14), 42.86% (n=6) were considered completed according to the records of the four CTRs. After searching PubMed and Google, it was found that 50% of the completed trials had already been published. As for the rest, 35.71% of trials are still recruiting and 21.43% are active but not recruiting (Figure 18).

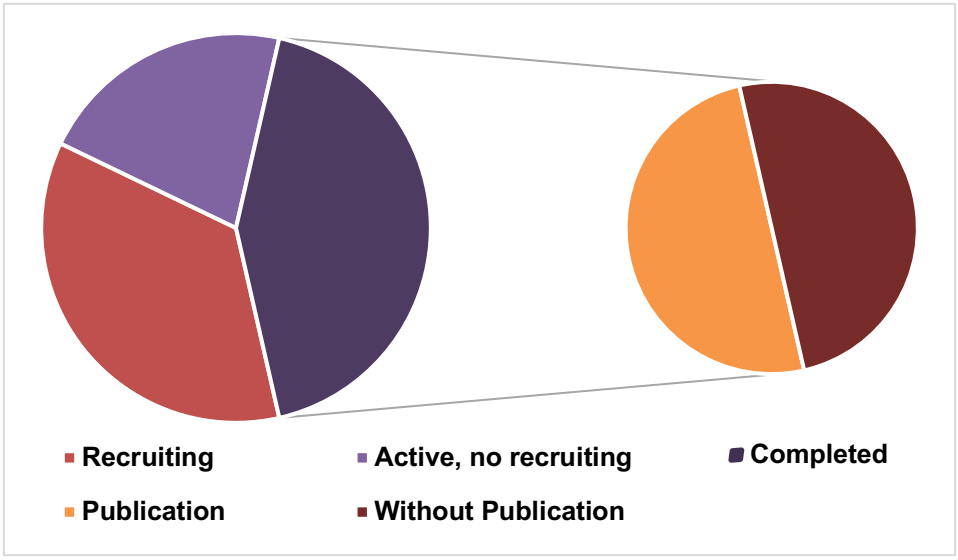

Figure 18 Number of completed, published and still ongoing COVID-19 observational studies performed in Portugal from January 2020 to December 2021, according to the records of ClinicalTrials.gov and ANZCTR.

9.2.2. Analysis of Interventional Studies

9.2.2.1. Number of COVID-19 Interventional Studies initiated each month

A total of 15 interventional studies were identified and organized considering the month and year of trial initiation to understand their distribution over the months during the pandemic (Figure 19).

Figure 19 shows us that during the first few months of the pandemic, there was only one intervention trial to be started each month. In the year 2021, there is already a growth, and April was the month in which more COVID-19 interventional trials were started, involving Portugal.

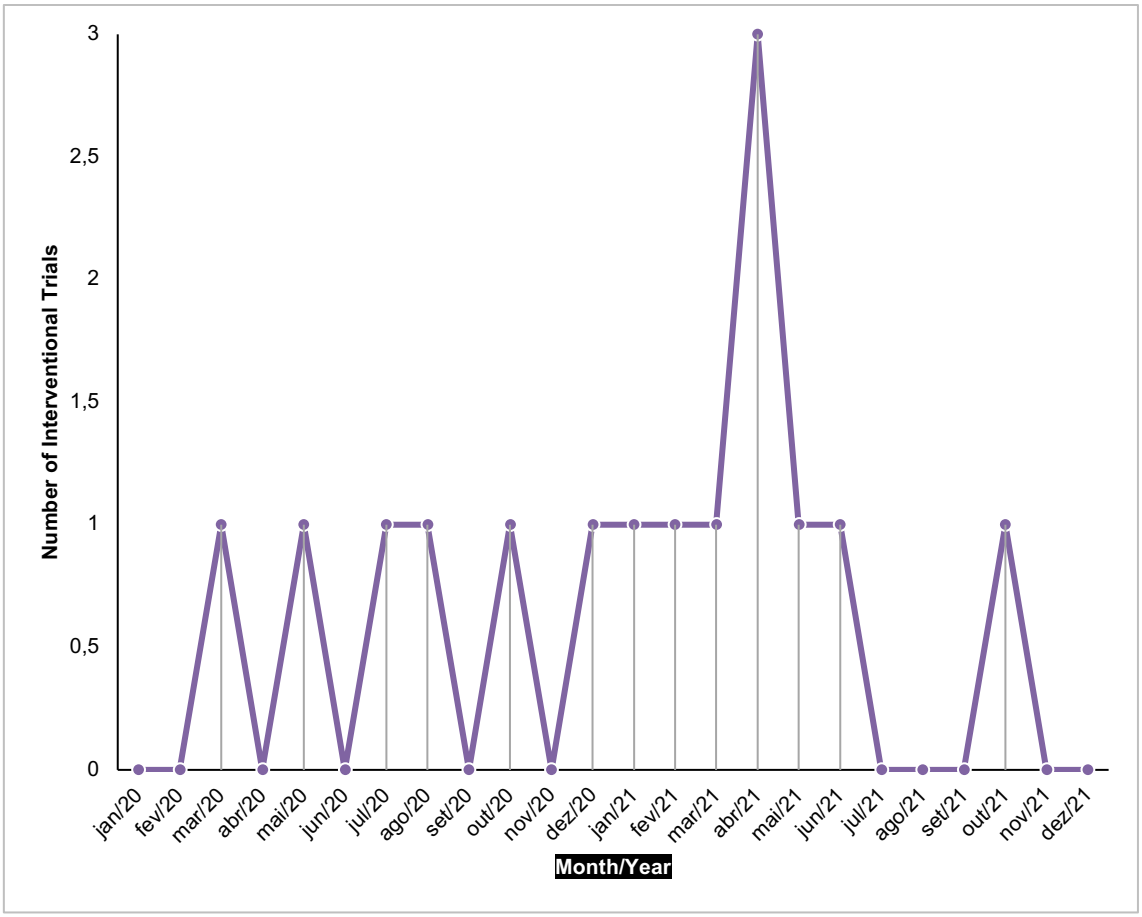

Figure 19 Number of planned or ongoing COVID-19 interventional studies registered in Portuguese institutions from 2020 to 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

9.2.2.2. Country and Type of Sponsor of COVID-19 Interventional Studies

The analysis of the nationality of the sponsor organisation, demonstrate that 33.33% (n=5) of the sponsors, the majority, were from Portuguese institutions. The USA represents 20% of the sponsors and the remaining (n=7) 6.66% each (Figure 20).

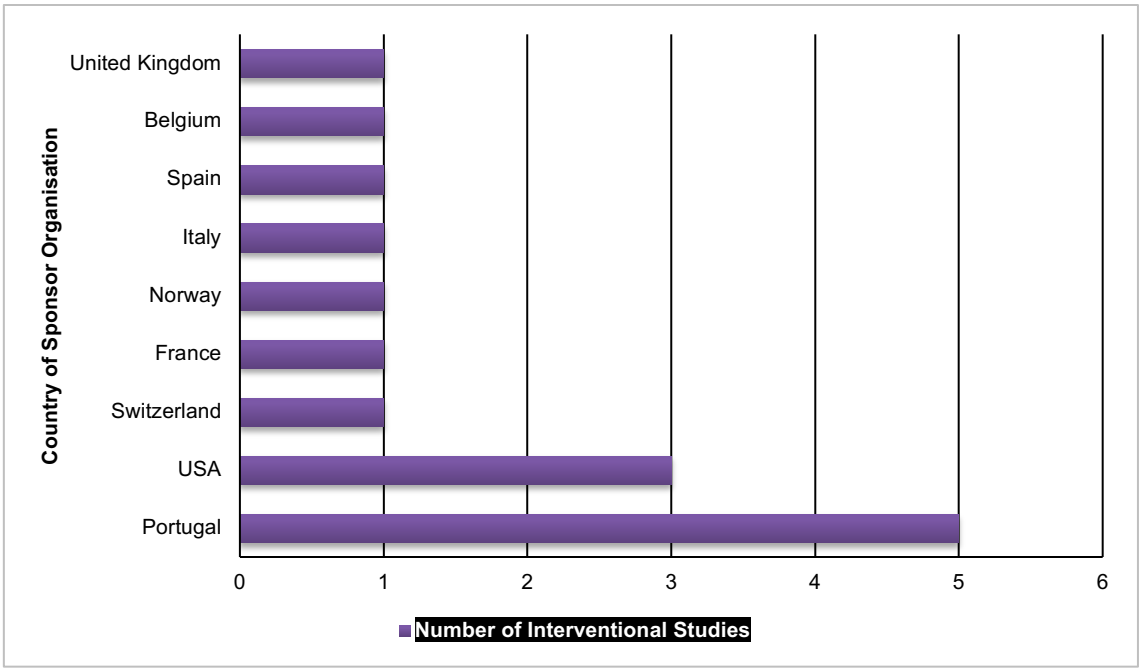

Figure 20 Nationality of the sponsor organization of COVID-19 interventional studies registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

Regarding the type of sponsor organisation, we observed that the majority 60% (n=9) were sponsored by pharmaceutical companies. Universities had sponsored 26.67% of the COVID-19 interventional studies and the remaining were sponsored by public agencies and institutes.

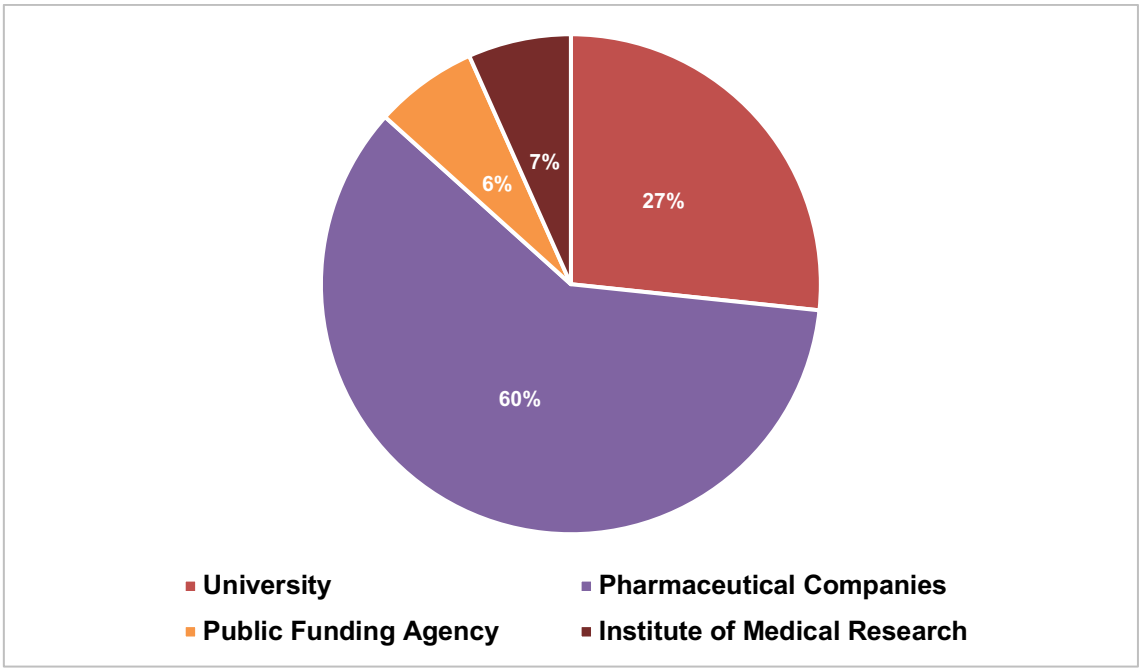

Figure 21 Type of the sponsor organization of COVID-19 interventional studies registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

Figure 21 allows us to conclude that 60% (n=9) of the studies are commercial trials, since they were sponsored by pharmaceutical companies. The remainder corresponds to the 40% of studies that are non-commercial trials, as they are trials sponsored by public organizations such as universities and public funding agency.

Of the 15 COVID-19 interventional studies that Portugal is involved, 3 are sponsored by Portuguese institutions. In the following chart we can see that of the 3 studies, 2 are sponsored by universities and 1 by a public funding agency (Figure 22).

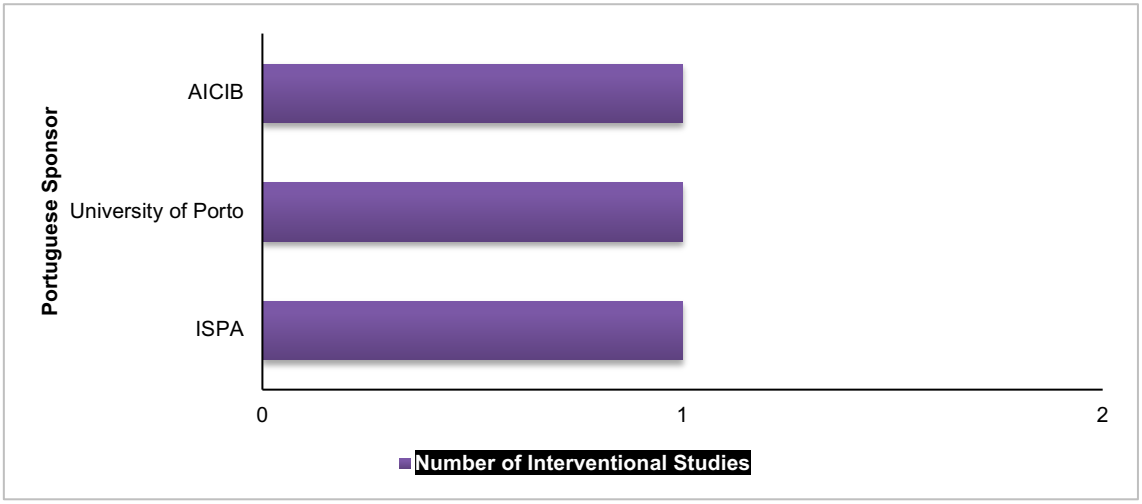

Figure 22 Portuguese sponsors of COVID-19 interventional studies registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

Most COVID-19 interventional studies are multinational and represent 86.67% (n=13). The remaining 13.33% correspond to trials planned and developed exclusively by Portuguese institutions.

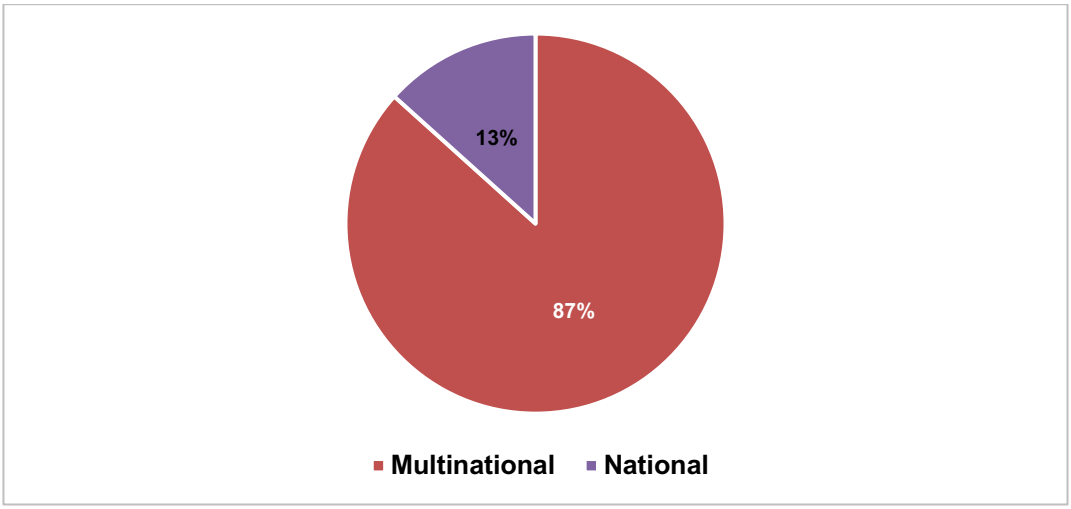

Figure 23 Distribution of multinational and national COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (EU-CTR, ClinicalTrials.gov, ANZCTR and RNEC).

The average number of countries that participated per study was 13. As we can see in the following graph, there was a study with the participation of only 4 countries, while another study had 52 countries involved (Figure 24).

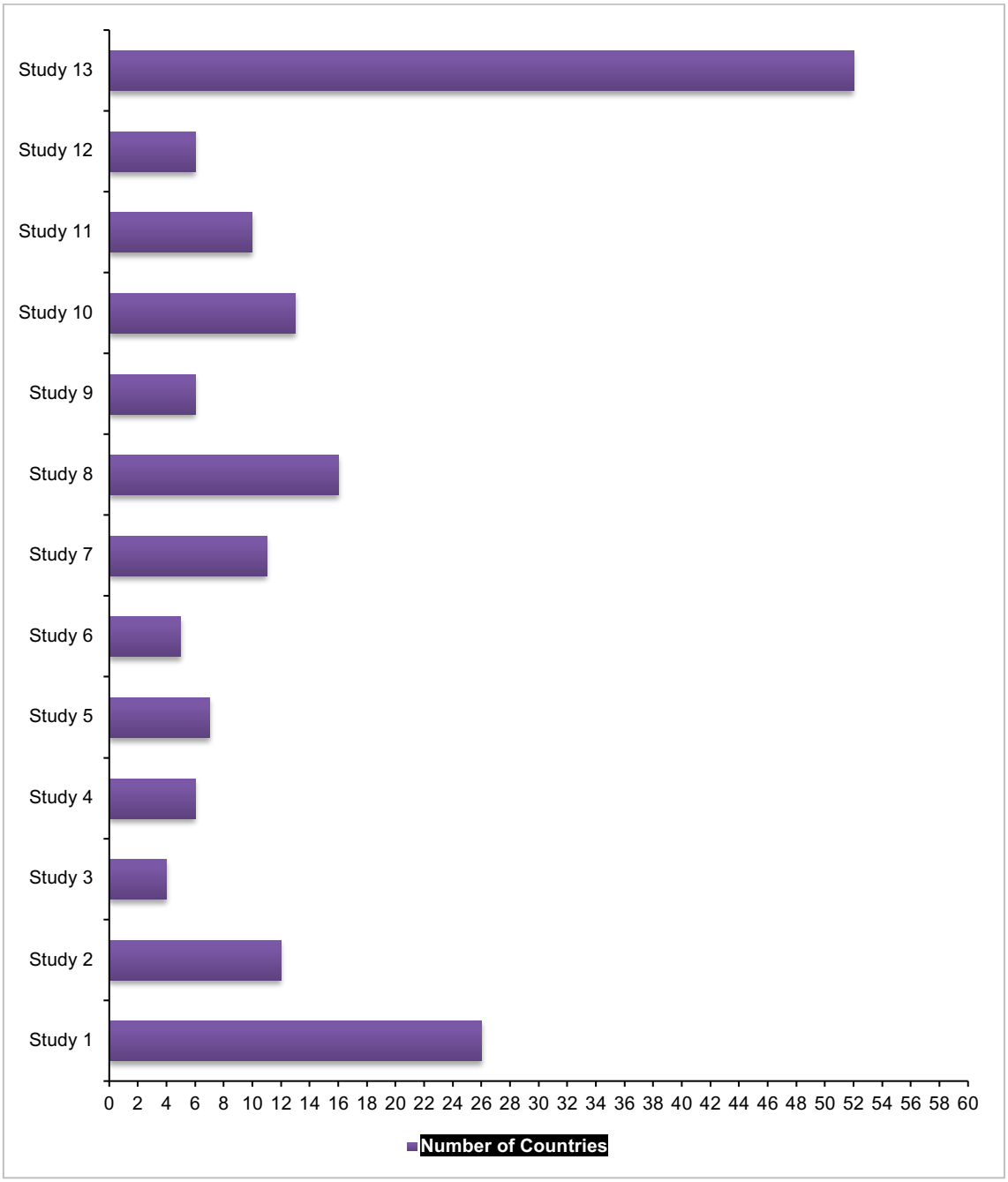

Figure 24 Number of countries involved in multinational COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the three CTRs (EU-CTR, ClinicalTrials.gov and ANZCTR).

Of the 13 multinational studies, 60% (n=9) are sponsored by pharmaceutical companies. This demonstrates that all studies that pharmaceutical companies sponsored (Figure 21) were multinational studies. With Portuguese sponsors, three multinational studies were identified, according to the data collected.

9.2.2.3. Design Analysis of COVID-19 Interventional Studies

All COVID-19 interventional studies in which Portugal is involved are randomized controlled trials. All have a comparison group (control group) and receive different treatments (Figure 25).

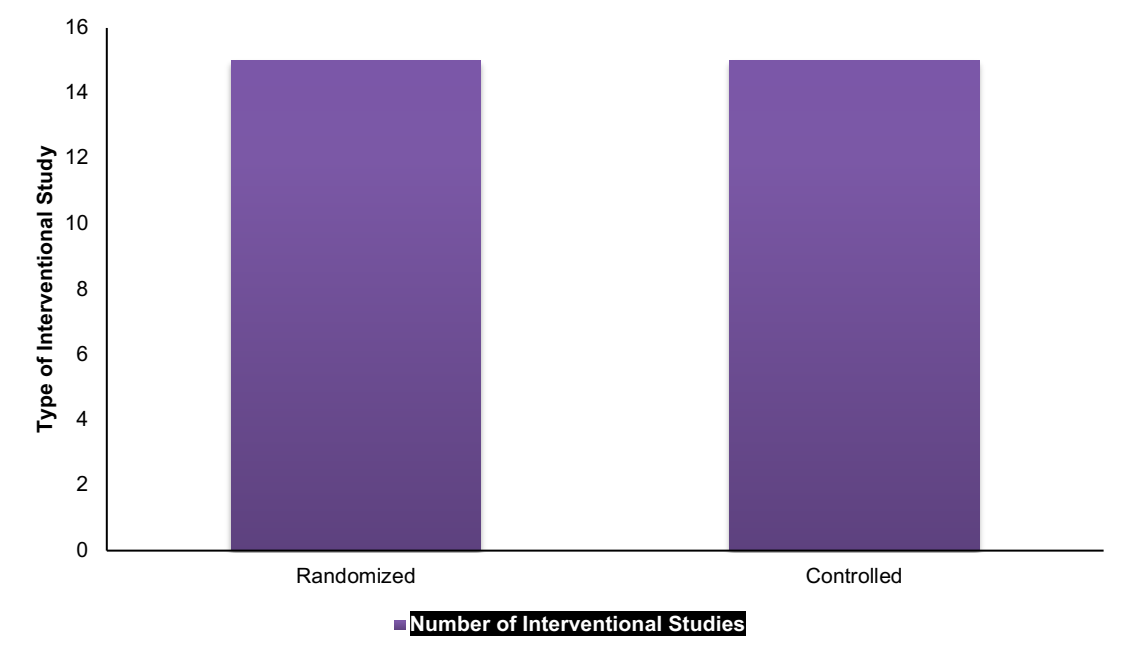

Figure 25 Type of COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (EU-CTR, ClinicalTrials.gov, ANZCTR and RNEC).

Regarding the treatment structure, in Figure 26 we observe that 93.33% (n=14) of the trials are parallel since each group of participants receives only one treatment. In only one trial (6.67%), participants received each of the treatments, so it's a crossover trial.

On the other hand, Figure 27 shows us that 33.33% (n=5) of the studies are Open-Label since the researchers know which of the groups were allocated.

The remaining studies are all Blind Studies. In 46.67% (n=7) both experimenters and participants are blinded, so they are Double-Blind studies. Classified as Single-Blind (only the participants are blinded) and Triple-Blind (participants, experimenters and researchers are blinded), one study was found each (6.67% each).

Exceptionally, there was a study in which it was classified as being Open-Label and Double-Blind.

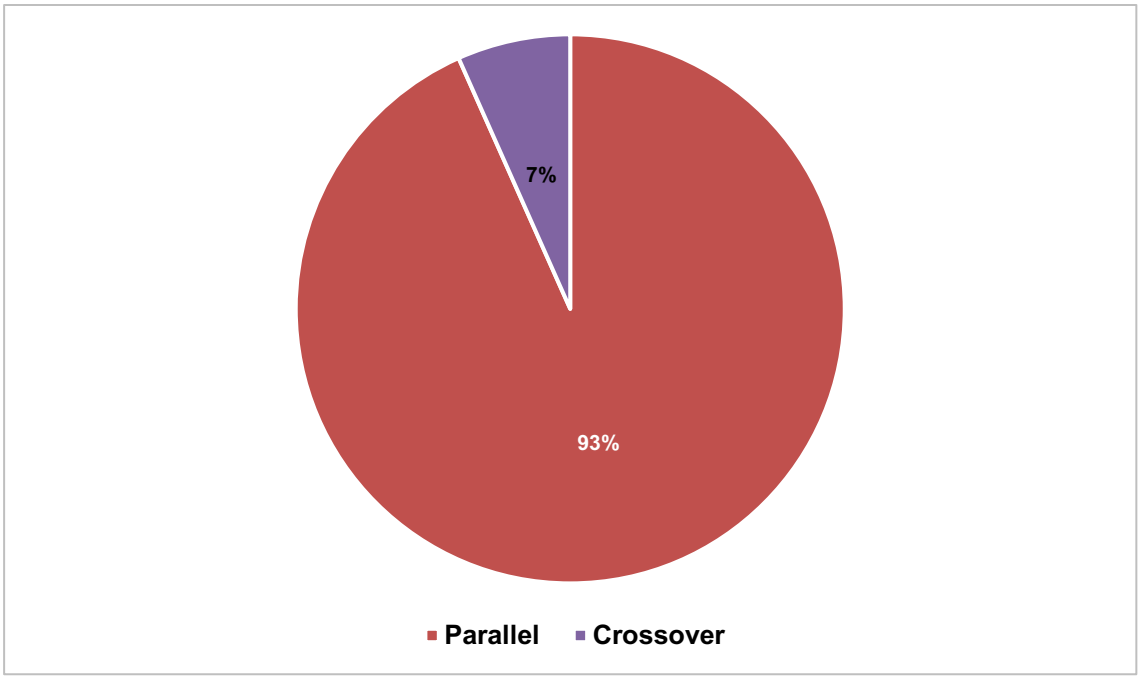

Figure 26 Classification of the treatment structure of COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (EU-CTR, ClinicalTrials.gov, ANZCTR and RNEC).

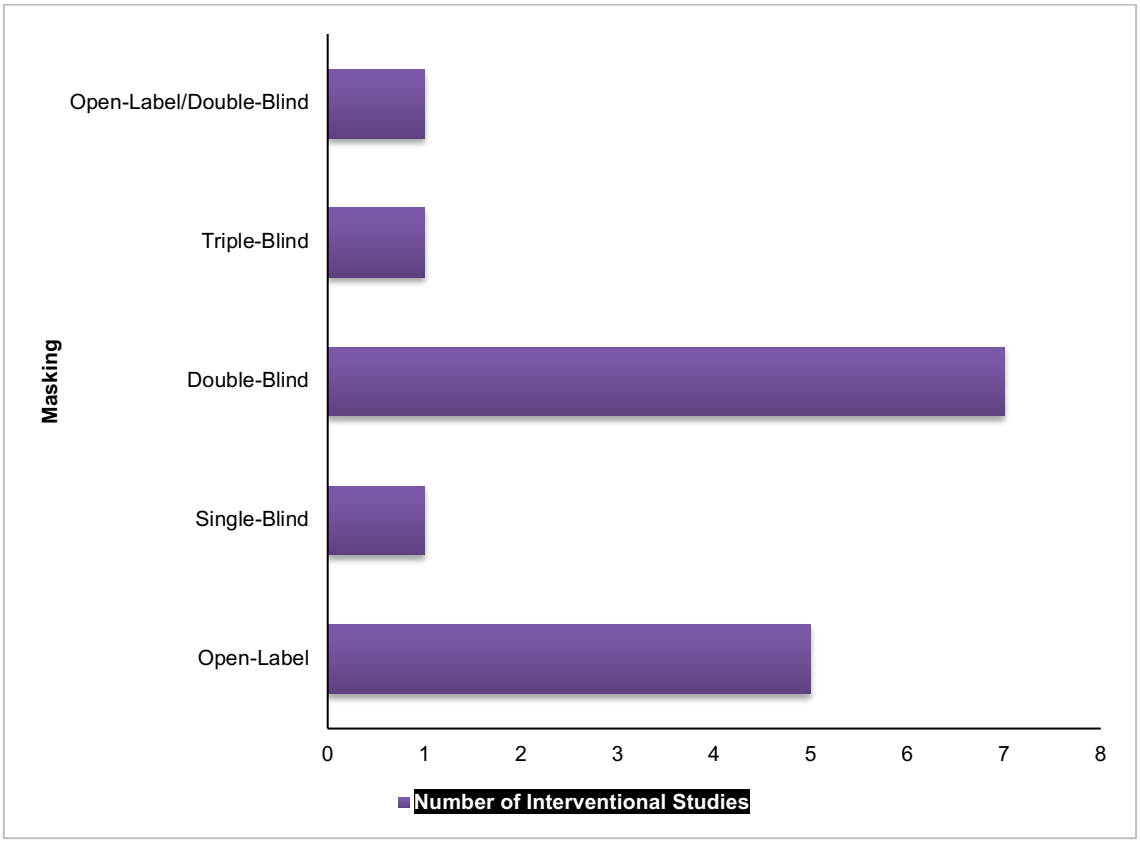

Figure 27 Masking of COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (EU-CTR, ClinicalTrials.gov, ANZCTR and RNEC).

According to the data collected regarding the comparator group of the COVID-19 interventional trials, placebo was the most used, representing 60% (n=9). In 13.33% (n=2) of the studies, the Standard of Care was used as a clinical trial comparator. In only one study (6.67%) a Medicinal Product was used as a comparator (Figure 28).

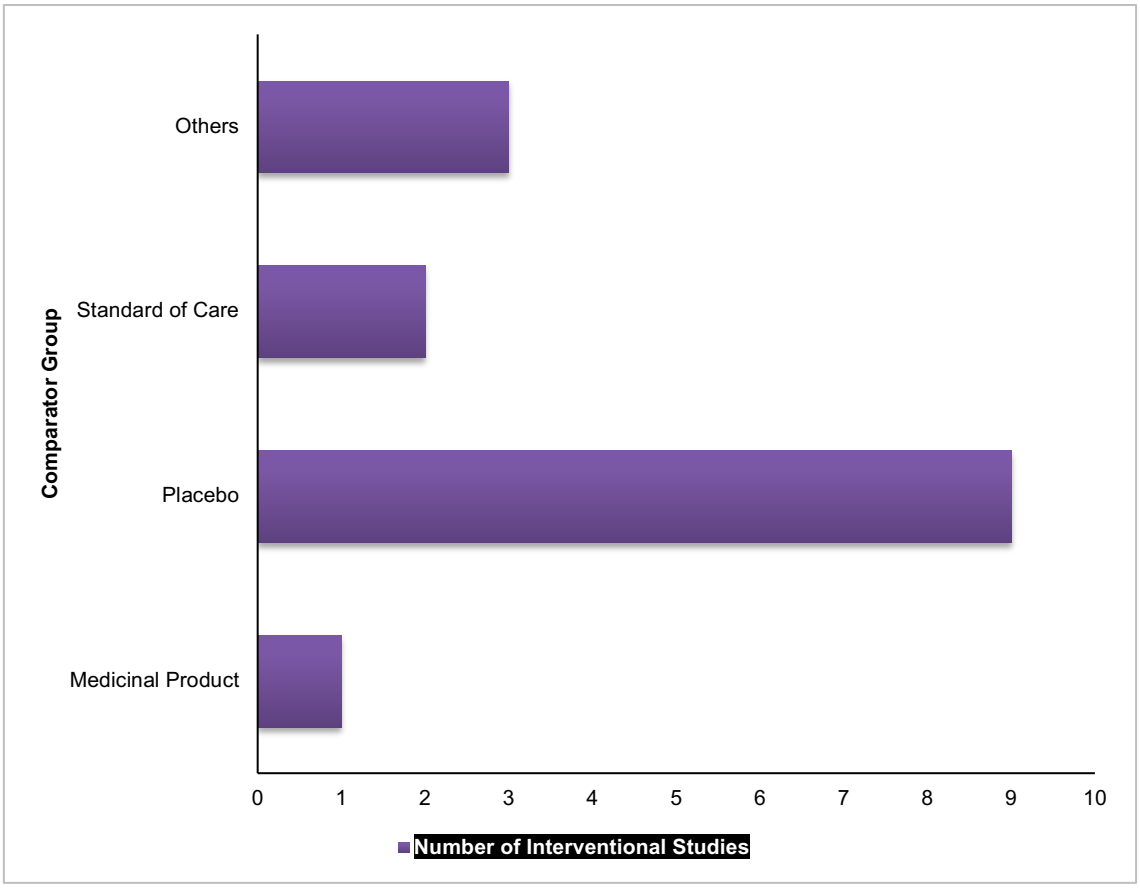

Figure 28 Comparator Group of COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (EU-CTR, ClinicalTrials.gov, ANZCTR and RNEC).

9.2.2.4. Type of Intervention of COVID-19 Interventional Studies

In this type of studies, the objective was to observe the effects of certain types of intervention for COVID-19. According to the data collected, 3 platform trials were identified for COVID-19, namely *SOLIDARITY*, *DisCoVeRy* and *SolidAct*, thus allowing the evaluation of several interventions simultaneously.

Figure 29 describes an analysis of the type of intervention performed in each study. The majority, more specifically 80% (n=12), correspond to Investigational Medicinal Product (IMP). The remaining types of intervention (n=3) correspond to 6.67% each, more properly classified as Procedure, Behavior and Device. Drugs studied in COVID-19 intervention studies were bemnifosbuvir (AT-527), interferon beta-1a, remdesivir, baricitinib, hydroxychloroquine, BI767551, PTC299, XVR01, dexamethasone, favipiravir, lopinavir/ritonavir and alteplase.

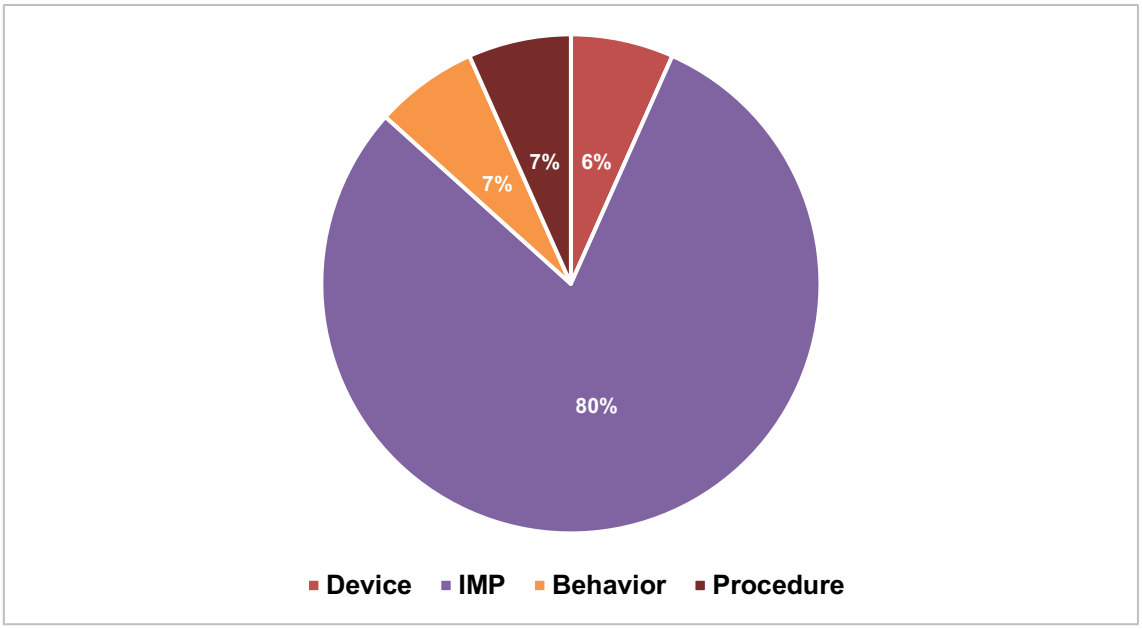

Figure 29 Type of Intervention of COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (EU-CTR, ClinicalTrials.gov, ANZCTR and RNEC).

Regarding the mode of administration, most IMPs were administered by intravenous use (33.33%, n=5). Of the remaining, in 20% (n=3) of the studies, IMPs were administered by oral use and in 13.33% (n=2) by inhalation. In two trials (13.33%), administration was by intravenous and oral route and in another trial by intravenous and inhalation route (Figure 30).

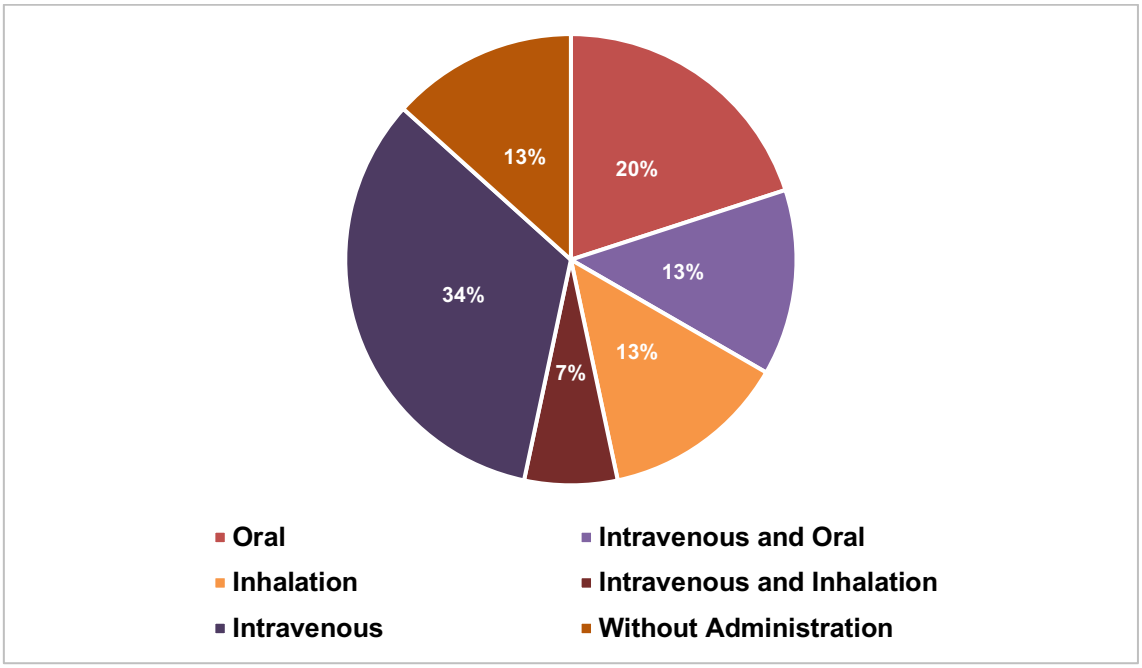

Figure 30 Mode of Administration of COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (EU-CTR, ClinicalTrials.gov, ANZCTR and RNEC).

9.2.2.5. Study Population Analysis of COVID-19 Interventional Studies

In the population analysis of interventional studies, it was observed that 86.67% (n=13) had COVID-19 infection as the main inclusion criterion at present. Undoubtedly, this was the most requested inclusion criterion for participation in the studies (Figure 31).

Excluding this criterion, 6.67% were healthy individuals from general population. The rest included participants with normal physiological state or any kind of comorbidity (also vaccinated or infected with COVID-19).

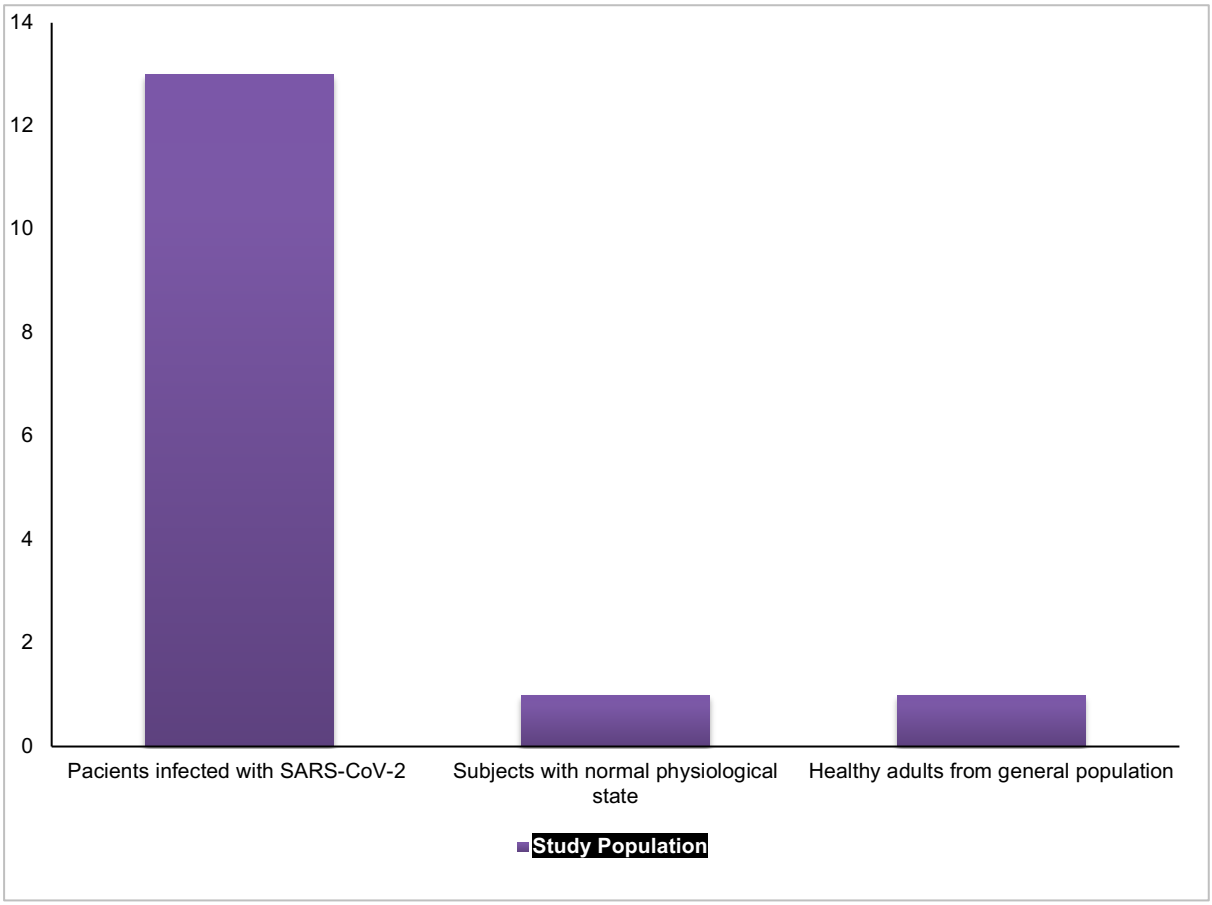

Figure 31 Study population of COVID-19 interventional studies registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

The number of participants involved varies greatly for each study, with the minimum number of participants recruited for the COVID-19 interventional studies was 40 and the maximum was 100.000, according to information from the platforms.

Regarding the age range, in Figure 32, we observed that most studies, 66.67%, required that the participants age be over 18 years old (n=10). In 26.67% (n=4) of the studies, participants were 12 years old or older. The remaining 6.67% corresponded to participants aged 14 or over.

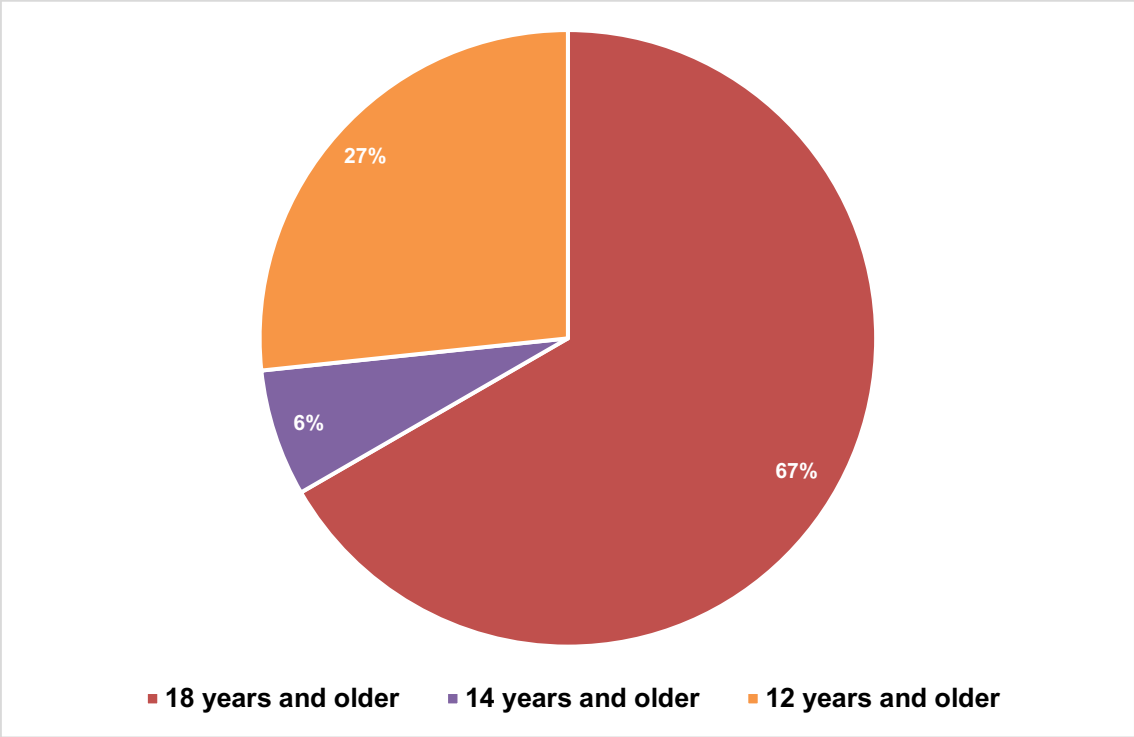

Figure 32 Age range of study population of COVID-19 interventional studies registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

Considering the study population and their respective ages, an analysis was also carried out to understand and compare the studies that needed hospitalized patients or could be in an outpatient setting (Figure 33). Therefore, in 40% (n=6) of COVID-19 interventional studies, patients did not need to be hospitalized, they were outpatients. The remaining 60% were hospitalized patients, 20% of whom would have to were hospitalized and with oxygen saturation (O2) ≤ 94% in room air.

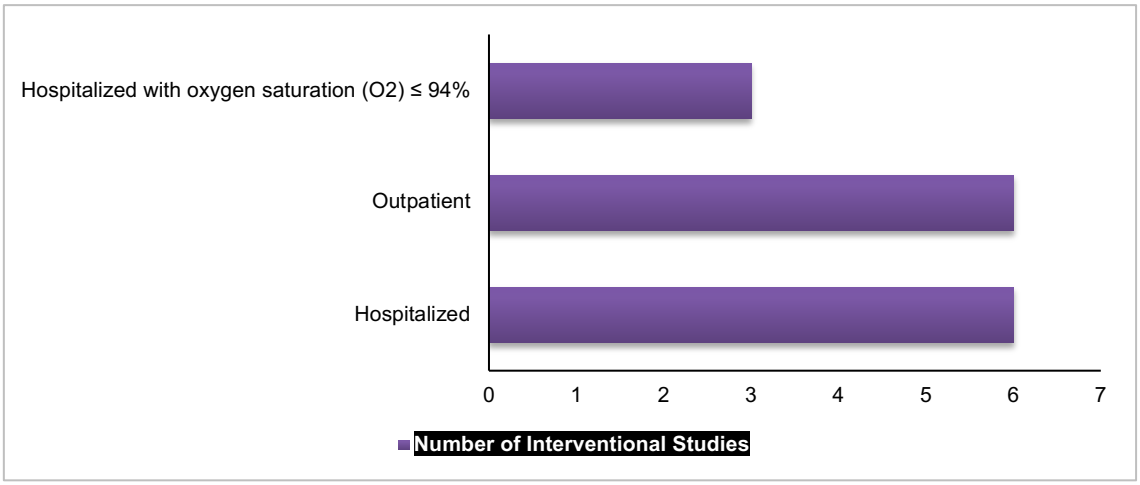

Figure 33 Analysis hospitalization of study population of COVID-19 interventional studies registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

9.2.2.6. Portuguese Principal Investigators (PIs) and Clinical Research Centers (CRCs) conducting COVID-19 Interventional Studies in each district of Portugal

According to the data collected, as we can see in Figure 34, principal investigators and research centers were identified in 10 different districts and in one 1 archipelago.

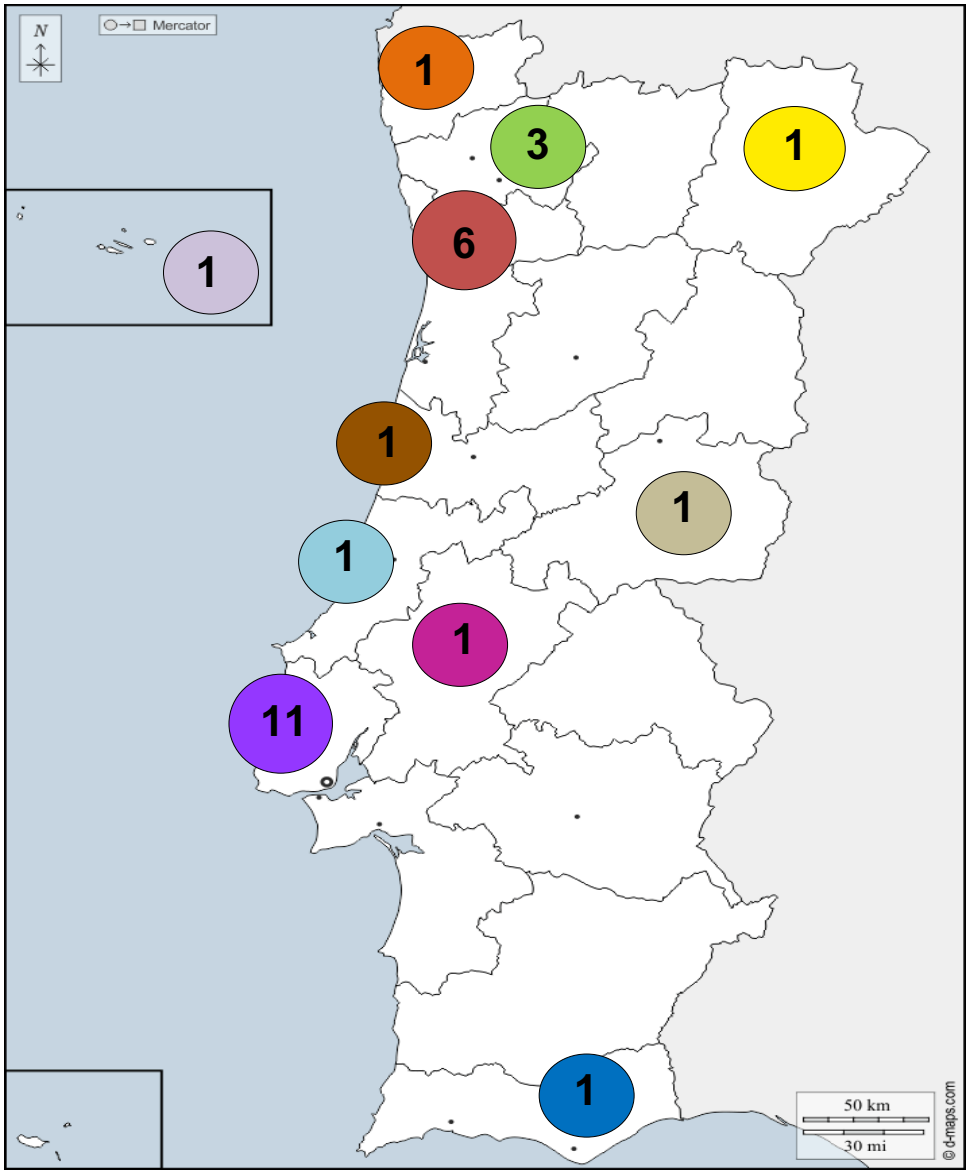

Figure 34 National distribution of the various Clinical Research Centers (CRCs) of COVID-19 interventional studies in each district registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

In total, 28 different Portuguese centers involved in the COVID-19 interventional studies were distinguished.

Of all, Lisbon is the district with the majority corresponding to 39.29% (n=11) where Curry Cabral Hospital and University Hospital Center Lisbon North stood out. In Porto, 21.43%

of the centers involved in the studies were identified, with emphasis on the Vila Nova de Gaia Hospital Center. Braga was the third district where more studies were carried out (n=3), more specifically at Hospital da Senhora Da Oliveira in Guimaraes.

Regarding the portuguese PIs, only 4 were identified, of which 2 belong to the pharmaceutical company Boehringer Ingelheim, another one to the Abel Salazar Institute of Biomedical Sciences of the University of Porto and the last to the Institute of Applied Psychology. For data protection reasons, portuguese PIs are not identified.

9.2.2.7. Type of Funders of COVID-19 Interventional Studies

The main funders of COVID-19 interventional trials are private organizations with 60% (n=9), more specifically pharmaceutical companies. By public non-profit organizations, 33.33% (n=5) of the studies were funded. Of the 15 studies, 6.67% (n=1) were identified as being funded by two sources of funding, one public and one private. In 20% of studies (n=3) the sponsor was considered the funder according to ClinicalTrials.gov records (Figure 35).

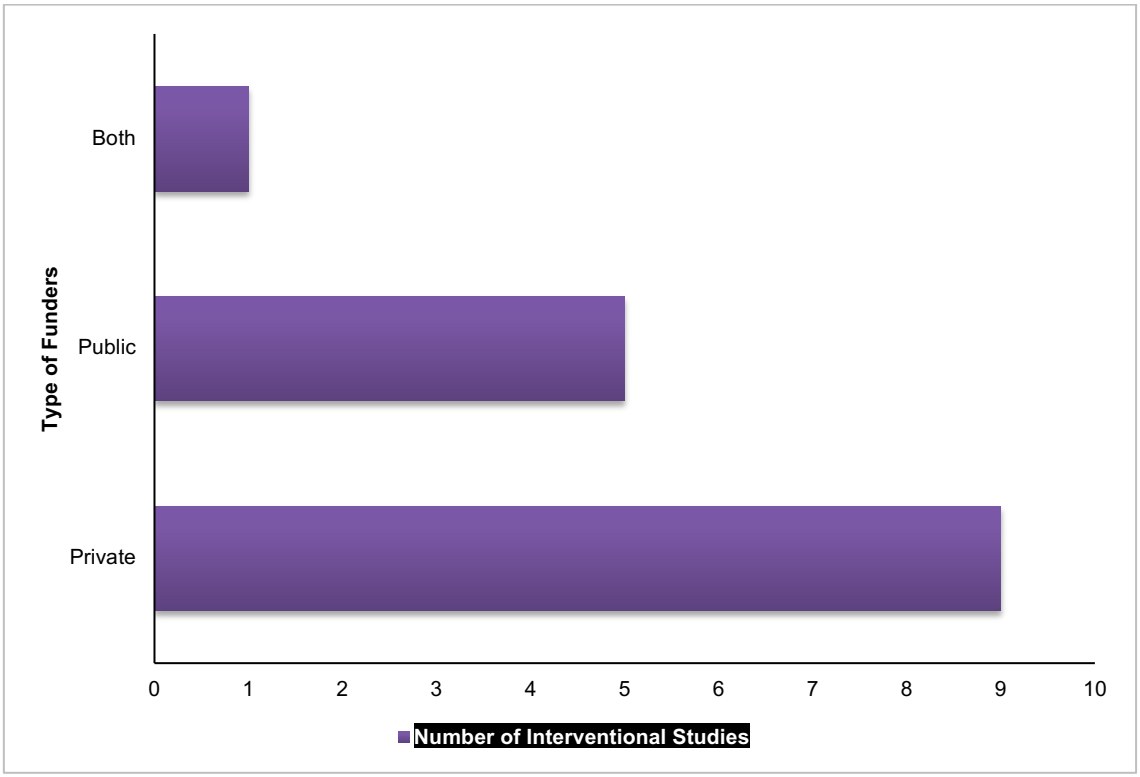

Figure 35 Type of funders of COVID-19 interventional studies registered in Portugal between January 2020 and December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

Of the studies that are funded exclusively by public organizations (33.33%), according to the data collected, it was observed that 20% (n=3) are funded by universities, 6.67% (n=1) by a public funding agency and the remaining 6.67% by a European Commission program (Horizon 2020).

9.2.2.8. COVID-19 Interventional Studies Published in Scientific Journals

Of all studies (n=15), only 20% (n=3) were considered completed. After searching PubMed and Google, it was found that 100% (n=3) of the completed trials had already been published. As for the rest, the majority, 60% of trials are still recruiting and 20% are considered terminated due to investigator decisions or safety concerns (Figure 36).

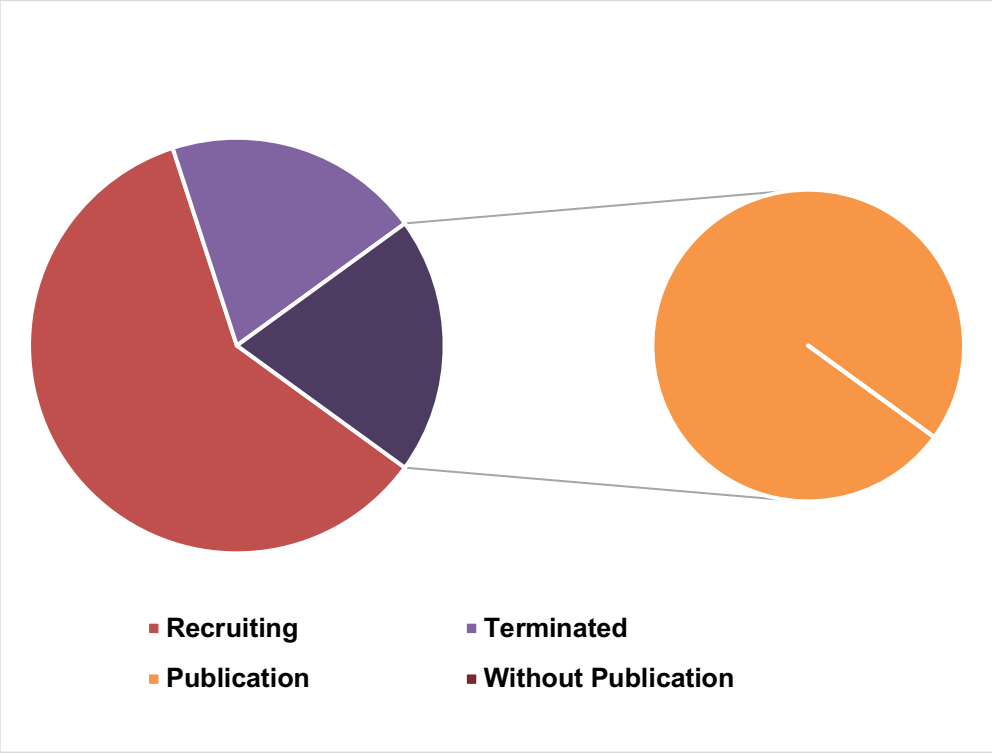

Figure 36 Number of completed, published, terminated and still ongoing COVID-19 interventional studies performed in Portugal from January 2020 to December 2021, according to the records of the four CTRs (ClinicalTrials.gov, EU-CTR, ANZCTR and RNEC).

10. DISCUSSION

In this study, an analysis was carried out of all interventional and observational studies for COVID-19 registered in four CTRs, with the main objective of identifying and characterizing the studies in which Portugal is involved during study period. The search started on January 2020 as Portugal was not involved in any studies in this year, since COVID-19 appeared at the end of 2019 in China and, being such a recent event, few studies were done that same year.

In Portugal, we identified a total of 29 different studies for COVID-19, of which 14 were observational studies and 15 were interventional studies. Over the months, new studies appeared, which is why the time span of the research was extended to December 2021, making the analysis more complete.

During 2020, considered the first year of a pandemic, Portugal was involved in more observational studies (n=11) than interventional studies (n=6). In turn, in 2021, the opposite was already observed, since Portugal registered more interventional studies for COVID-19 (n=9) compared to observational studies (n=3). This might be relating the interventional studies are more complex and its preparation and implementation can take longer, in addition interventional studies become more expensive and therefore Portugal may not have had this support to allow involvement in these studies since the beginning of the pandemic.

Universities have been the main sponsor of interventional and observational studies registered in Portugal for COVID-19. Of the 29 studies registered in Portugal, 12 were organized by Portuguese sponsors of which 9 were universities. Among them, the University of Lisbon stood out, being responsible for the largest number of studies (n=5), followed by the University of Porto and finally the University of Minho.

Half of the COVID-19 observational studies registered in Portugal were sponsored by national organizations, more specifically universities and hospitals. Even so, of the total, only one of the Portuguese organizations sponsored multinational COVID-19 studies, the others all sponsored studies carried out only at national level. This result is in line with a 2019 study by PwC and APIFARMA, as it reported lower international funding than most other European countries and, consequently, insufficient tax incentives to attract multinational companies, thus making it a less competitive country.[42] On the other hand, COVID-19 interventional studies have already shown greater representation in multinational studies.

This is based on the fact that the majority (60%) are commercial trials and therefore have pharmaceutical companies as funder and sponsors that obviously have a greater ability to obtain funding. In interventional studies, Portugal was also the country that sponsored the largest number of studies (n=5). Of the 29 studies registered, 72.41% (n=21) are multinationals, which confirms the interest on the part of several countries in new research for COVID-19. The number of countries involved in these multinational studies was very variable. The minimum corresponded to 2 countries per study and the maximum to 52 countries (*SOLIDARITY* trial).

AICIB (Agency for Clinical Research and Biomedical Innovation) was registered in RNEC as Portuguese sponsor of one of the interventional studies. However, in the international registers the sponsor of *SOLIDARITY* trial was WHO and of *DisCoVeRy* trial (European branch of the *SOLIDARITY* trial) was INSERM. Several of the researchers interviewed in the study carried out by APIFARMA mentioned that many of the barriers (support structures for research, complexity of the processes involved in clinical trials, strategy to promote clinical research in Portugal, autonomy for hiring human resources and financial management, professionalized research teams, different information systems in the various health units, among others) to clinical research could be mitigated through the action of this new agency.[42] At an international level, pharmaceutical companies sponsored most of the studies for COVID-19, with special emphasis on interventional studies, responsible for 60%.

In the population analysis of the registered studies, it was observed that 65.52%, more specifically 13 interventional studies and 6 observational studies, had the present infection by COVID-19 as the main inclusion criterion. Undoubtedly and with complete sense, this was the most requested inclusion criterion for participation in the studies. Excluding this criterion, the majority of the remainder were healthy individuals from the general population or with any type of comorbidity (also vaccinated or infected with COVID-19 in order to relate and assess their conditions when in contact with the SARS-CoV- 2). Regarding the age range, the one that was most identified in the inclusion criteria was 18 years or older. It was found in 65.52% (n=19) of the studies. It is therefore concluded that the researchers demanded more this age group to carry out both types of studies.

Regarding the study design, all interventional studies in which Portugal was involved were RCTs as they are trials that meet the inclusion criteria. In addition to the fact that the key criterion was the infection by COVID-19 for the development of the studies, these all also allow to understand the effect of each intervention made since each group receives a different intervention.

Concerning how the trials were conducted, we could observe that 93.33% of the participants in the interventional studies received only one treatment. Most studies (46.67%) are Double-Blind studies, as neither the participants nor the researchers know who is receiving the treatment. Conversely, in 33.33% of the studies it was shown that the investigators know which of the groups was allocated, so they are Open-Label studies.

Since the beginning of the pandemic, all researchers around world had as their main objective to find the best ways to treat and prevent COVID-19 in the shortest possible period of time. That said, through the analysis of interventional studies this came to be confirmed, since 80% (n=12) of the studies registered in Portugal were to study IMP (Investigational Medicinal Product). Several drugs were studied, as already mentioned in the results, in which remdesivir was included in most studies. According to the data collected, 3 platform trials were identified for COVID-19, namely SOLIDARITY, DisCoVeRy and SolidAct, thus allowing the evaluation of several interventions simultaneously. According to the data collected regarding the comparator group of the COVID-19 interventional trials, placebo was the most used, representing 60% (n=9). The

most used mode of administration was intravenous (33.33%, n=5) and in two trials (13.33%), administration was by two routes (intravenous and oral; intravenous and inhalation).

Identifying CRCs by searching for CTRs was also difficult as they were not always mentioned. On ClinicalTrials.gov, only the city where the CCR was located or the corresponding zip code could be mentioned. In turn, in the EUCTR, as a rule, they were never identified and in the ANZCTR only the location of the CRC was mentioned. However, when it came to interventional studies, using the RNEC it was possible to identify many of them. It also happened, in some cases, to identify the center or university where the study was taking place, through the contacts of the associated Portuguese researchers.

According to data collected from interventional studies, principal investigators and research centers were identified in 10 different districts and in 1 archipelago. In the observational studies, a decrease was observed, and they were only identified in 7 different districts. So, it was then possible to notice that the areas with the highest number of CRCs are concentrated in the large metropolitan areas of Lisbon, Porto and Braga, coinciding with the areas with the most COVID-19 studies recorded in Portugal. One of the reasons may be that these are the Portuguese cities with the highest number of universities and hospitals. In the Lisbon district, the Nova Medical School, the University of Lisbon, Curry Cabral Hospital and the Hospital Center of Lisbon Norte stood out. In Porto, Hospital Center Vila Nova de Gaia and Hospital Center of São João were the ones that participated the most.

As for the identification of funders of studies registered in Portugal for COVID-19 in the years 2020 and 2021, it was not always easy and straightforward, especially on ClinicalTrials.gov, where the funder was almost never mentioned. In observational studies, the funder was considered the same as the sponsor.

The main funder of observational trials in Portugal has been public organizations (86%, n=12), namely universities, following the principle that it has been referred to as the funder being the same as the sponsor. However, through further research, it was possible to conclude that some of these observational studies (at least 2 out of 14) were funded by the main Portuguese funding agency, Foundation for Science and Technology (FCT). Its mission is to promote in our country the advancement of knowledge in science and technology in order to achieve the highest international standards of quality and competitiveness.[43] In interventional studies, the main founders were once private organizations (60%), mainly pharmaceutical companies. Even so, the European Commission, the EU Research and Innovation program (Horizon 2020) and the AICIB were some of the public non-profit organizations that funded COVID-19 interventional studies in which Portugal was involved. When the study is funded or supported by a pharmaceutical company it is not indicated in the four selected CTRs, who owns the results, thus it was not possible to perceive or analyze these data.

Finally, regarding the publication of studies, of the 29 interventional and observational studies carried out for COVID-19 registered in Portugal in 2020 and 2021, only 31.03%

(n=9) were considered completed in the records. Of this total, 66.67% (n=6) have already been published.

10.1. Study Limitations

The search in the four CTRs was not always easy because a lot of information was missing and did not always coincide. Since the research started by being carried out on ClinicalTrials.gov, there were soon difficulties since the identification of funders of COVID-19 interventional and observational studies was not always indicated. This meant that there was a lack of information, which did not allow for a complete data analysis. So, in these cases the sponsor was considered the funder of the study in question.

Another limitation of this work was also the fact that observational studies may be underrepresented since their registration is not mandatory. Thus, they may not have been identified on the registration platforms.

The identification of the researcher's contacts and the delays in responses due to the pandemic situation did not allow the progress of the survey that was initially stipulated in the dissertation project. Furthermore, in some studies, only reference is made to the institutions that sponsor them and not to their respective researchers.

Thus, it became impossible to proceed with the survey and consecutively resulted in a lower achievement of results for a more complete analysis.

11. CONCLUSION

The urgent quest for safe and effective COVID-19 treatments required international co-operation for conducting clinical trials to test and compare existing and new therapeutics. Although all effort made by many national regulatory authorities, namely INFARMED and CEIC to set up streamlined and fast-track clinical trial approval processes, Portugal still has several gaps and lack of harmonization that delay the implementation of international clinical trials.

Portugal like other countries have several clinical studies for COVID-19 launched at the national level, and being conducted by universities/ health research institutions within a single center. However, EMA and medical community indicated early on that many of these national initiatives, often of limited amplitude, do not provide the robustness that is necessary to effectively validate treatments.

For this reason, a number of international trials have been launched with the goal to recruit enough patients in hospitals from multiple countries to test a diversity of potential treatments to come up with robust enough statistical data to inform relevant regulatory and health authorities.

Fortunately, based on a national strategy Portugal was able to participate in 3 of the largest international therapeutic platform trials: *SOLIDARITY* being fostered by the WHO, *DisCoVery* led by the French National Institute for Health and Medical Research (INSERM) and *SolidAct* led by the Oslo University Hospital. The last two are integrated in EU-RESPONSE project funded by the European Union's Horizon 2020. The 3-platform trial are running in Portugal in eleven clinical sites and AICIB and PtCRIN are in charge of the management of the trial, this example should be replicated in the future.

Clinical research development should be based on a national strategy that gather together health authorities and all stakeholders to promote a comprehensive and stimulating set of public policies and funding.

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