REGULATORY APPROACH

REGULATORY APPROACH AND ANALYSIS OF CLINICAL PHARMACOLOGY STUDIES BY THE NATIONAL ADMINISTRATION OF DRUGS, FOOD AND MEDICAL DEVICES DURING COVID-19 PANDEMIC

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ABSTRACT
The Department of Clinical Trials of the Office of Evaluation and Registration of Drugs of the National Administration of Drugs, Food and Medical Devices (ANMAT) carries out activities concerning the evaluation and monitoring of clinical pharmacology studies within the enforcement remit and scope of ANMAT Regulation 6677/10.
The pandemic declared by the World Health Organization, as a result of SARS-COV-2 emergence, required a swift adaptation by the world regulatory agencies to propose measures and offer responses at the speed required by the health emergency.
On the one hand, the understanding of the epidemiology and clinical spectrum of coronavirus disease evolved, and the knowledge of the disease burden stressed the urgent medical need to develop vaccines and drugs as prevention and treatment strategies. This situation drove clinical pharmacology research to take a leading role in finding scientifically sound responses to the disease in the shortest possible time.
On the other hand, the quality clinical research activities underway had to be preserved, while protecting the safety and wellbeing of study subjects and avoiding viral spread and the saturation of the health system.
For all the above, this work proposes a description of the measures adopted during the pandemic by the Department of Clinical Trials of ANMAT, as well as an analysis of the COVID-19 clinical pharmacology studies submitted to and authorized by ANMAT in the period: May 1st, 2020 - August 3rd, 2021.

Keywords: clinical trial, COVID-19 disease, pandemic.

INTRODUCTION

In December 2019, some severe pneumonia cases of an unknown origin were reported in Wuhan, Province of Hubei, China. On January 7th, a new strain of coronavirus (CoV-2, as differentiated from the strain that caused an outbreak in 2003, CoV-1) was isolated from lower respiratory tract specimens obtained from four cases. Said strain belonged to the same family as the viruses causing the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). On January 30th, 2020, the World Health Organization declared that the SARS-CoV-2 outbreak entailed a public health emergency of international concern and, by February 28th, over 80 000 cases had been reported worldwide. On March 11th, 2020, the World Health Organization declared the coronavirus 2019 disease (COVID-19), caused by SARS-CoV-2, a pandemic. By May 12th, 2020, over 4,2 million COVID-19 cases had been confirmed across the world and over 290 000 deaths attributed to the disease[1-3].

COVID-19 pandemic health crisis required an unprecedented fast development of treatments and preventive vaccines on a global basis, maximizing efficiency and productivity. Clinical research has adapted to such end. Scientists have used artificial intelligence technologies to screen candidate drugs in order to raise drug repositioning strategy success rate. Also, data follow-up centers and tools have been designed to collect and share the developmental status of candidate drugs and to update clinical trials results. Amid the pandemic, the academia, non-for-profit organizations, governments and pharmaceutical companies collaborated with each other eagerly to address the public health crisis at a global level[3,4].

Studies to evaluate the efficacy and safety of treatments and vaccines against SARS-CoV-2 were conducted at an unprecedented rate. By May 12th, 2020, over 1 300 clinical trials were recorded in the most important database, Clinicaltrials.gov, and, by March 19th, 2021, a total of 2 803 clinical trials on treatments were underway across the world. Predefined platform studies emerge as an efficient approach to acquire new knowledge. In this line, WHO planned the SOLIDARITY platform trial, which compared four COVID-19 treatments (remdesivir, chloroquine and hydroxychloroquine, lopinavir-ritonavir and lopinavir-ritonavir plus interferon-beta)[3,4].

Finally, and, as part of the response to drug development challenges and changes, regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have tried to operate in a more flexible way without undermining research process scientific grounds. Over the years, EMA has provided guidance and support for the development of pharmacology research, that include scientific information and, also, provide a regulatory framework for the design and conduct of clinical trials, compliance standards and the obligations attached. Similarly, FDA has published official regulatory guidance documents about the development of biological products, drugs and medical devices, as well as a general guide about the design of scientific research studies. During the pandemic, both EMA and FDA have established emergency working groups or programs to support the development of drugs and make fast regulatory decisions.

For example, EMA established the COVID-19 EMA pandemic Task Force (COVID-EFT) and the EMA COVID-19 Steering Group for a preventive approach of possible delays in the review of COVID-19 treatments and vaccines. On its part, FDA has accepted data from various sources to inform its regulatory decisions to combat the pandemic. In June 2020, in collaboration with the National Institute of Health (NIH), FDA formed the CURE *Drug Repurposing Collaboratory* (CDRC), a partnership that launched the COVID-19 pilot program to collect real world data to identify possible treatments. The CDRC has used real world data to support and boost randomized clinical trials with difficulties to enroll a sufficient number of COVID-19 patients[3-6].

In Argentina, ANMAT is the regulatory body that, through its Department of Clinical Trials, evaluates and monitors clinical pharmacology studies, as governed by its Regulation 6677/10. Due to the pandemic, ANMAT had to adapt itself and take actions at the pace required by the situation, therefore, it adopted measures to protect research activities within a health emergency context and to support efficient and quality COVID-19 clinical research. Said measures and recommendations were coincident and simultaneous with those implemented by other regulatory agencies such as EMA and FDA.

During the pandemic, ANMAT signed a collaboration agreement with EMA[7] that, as well as other agreements signed with FDA, favored the exchange and cooperation between agencies, with a view to protecting the health of their populations.

REGULATORY APPROACH OF THE DEPARTMENT OF CLINICAL TRIALS OF THE OFFICE OF EVALUATION AND REGISTRATION OF DRUGS OF ANMAT

Within the framework of clinical studies with drugs, on March 20th, 2020, ANMAT published on its official website the document "Measures and recommendations for clinical pharmacology studies during COVID-19 pandemic"[8], to preserve the clinical pharmacology studies activities during the pandemic, while protecting and prioritizing studies subjects´ safety and wellbeing. The document was intended for both ongoing studies and those to be submitted for evaluation and aimed at reducing the risk of viral spread and the saturation of the health system, that would experience an increased demand. This document was and is applicable to the pandemic period and the recommendations and measures it provides are dynamic, in accordance with the changing health-epidemiologic context inherent to the existing health crisis. It is to be noted that the measures and recommendations provided were in agreement and simultaneous with those applied by high health vigilance countries[9,10].

Some measures included in the document were as follows:

- Risk mitigation plans

Sponsors of clinical pharmacology studies were required to develop and submit Risk Mitigation Plans (RMPs) to strengthen

measures to prevent COVID-19 infection and spread, as well as the saturation of the health system in the country. A requirement was established for RMPs to be reported to investigators, research sites, ethics committees and ANMAT and to be included in the documentation file of every study. As a result, through the Distance Procedures Platform (acronym in Spanish: TAD), 199 RMPs were submitted, out of which 85% (169) were specific to the study or drug and the rest accounted for sponsors general plans applicable to all their studies.
Mostly, RMPs provided for measures related to the informed consent obtainment process, study visits and procedures, investigational product shipping and dispensing and ongoing studies monitoring.

- Recruitment

Another measure adopted by this Administration was the suspension of recruitment for clinical pharmacology studies with healthy subjects as a study population, except for COVID-19 prevention and treatment studies. Said restriction was lifted by this Administration on November 16th, 2020[11], as a result of the change of the Social, Preventive and Mandatory Isolation for a Social, Preventive and Mandatory Distancing, ruled by Decree 875/2020; but, a requirement remained for all the parties involved (sponsor, investigator, research sites and ethics committees) to evaluate, on an ongoing basis, the feasibility to resume and continue studies recruitment, by considering the different variables that could have an impact on it, such as the local social, health and epidemiologic context, personnel availability, research sites location and conditions, ethics committee decisions and sponsors´ monitoring capacities. Decisions had to be made accordingly and had to be consistently adapted to the recommendations of the Ministry of Health of the Nation and of each jurisdiction.
The recruitment for clinical studies with a study population that included patients remained subject to an assessment by the sponsor and investigator, based on the characteristics of each protocol and situation of each site, to prevent unnecessary risks and ensure relevant healthcare. It was seen that most sponsors decided to suspend the recruitment temporarily, based on a benefit/risk assessment.

- Visits, procedures and access to the investigational product

Other aspects considered in developing the document were the difficulties that could stem from the restrictions expected both external, in relation to imports/exports, and internal, in respect of the transportation of drugs or samples and the circulation of study subjects. Therefore, recommendations were given to ensure enough medication for the study subjects and the continuity of their treatments, as well as to plan the visits and procedures under the consideration of possible restrictions and lockdowns. Hence, telemedicine use was allowed as well as home visits, procedures and delivery of investigational products. Said visits were to be paid by adequately trained personnel to be designated according to documented operational procedures for Good Clinical Practices (GCP) compliance purposes.

- Operational aspects

To optimize the response by the Department of Clinical Trials, it was established that all coronavirus-related procedures had to include a "COVID-19" lettering in the procedure subject or note, for identification purposes and to be evaluated in the health emergency framework.
Accordingly, ANMAT established clinical pharmacology studies to treat or prevent coronavirus disease as a priority, with accelerated evaluations that protected subjects´ safety and rights. Along with the submission of applications through the usual platform, for the purpose of a prompt follow-up, applicants were asked to send an e-mail to the Department of Clinical Trials of the Office of Evaluation and Registration of Drugs (DERM/INAME) stating: "URGENT: ECLIN COVID-19" (COVID-19 Clinical Trial).

Evaluation of COVID-19 clinical pharmacology studies

The evaluation process of clinical pharmacology studies is conducted by means of a virtual platform containing a sequential step-based circuit to be followed by the areas involved (**Figure 1**). This process had to be adapted to the need for accelerated evaluations of COVID-19 prevention and treatment studies, while maintaining the required scientific, ethical and methodological standards necessary to obtain reliable and robust results.
Therefore, it was established that, prior to submitting a study for evaluation, fluent and consistent communication was to be fostered between study sponsors and the Department of Clinical Trials, which included answers to consultations through the institutional electronic mail and virtual meetings intended for discussion (Circular 001 – virtual basis). Then, at the time of formal application submission, such pre-evaluations allowed sponsors to consider and comply with the requirements and observations previously discussed, which led the final evaluation procedure to be conducted in a shorter time.
Upon the submission of a COVID-19 clinical trial application for evaluation and, after documentation has been checked for compliance with regulatory requirements (quality review), the Department of Clinical Trials is to give notice of the new application to the different areas involved in the evaluation process for a simultaneous, coordinated, collaborative and expedite activity.
Should observations be made to a study, the Department of Clinical Trials makes said observations along and simultaneously with the Office of Legal Affairs, which requires additional communication, coordination, effort and collaboration, since this procedure is usually conducted by each area involved on a separate sequential basis (**Figure 2**).

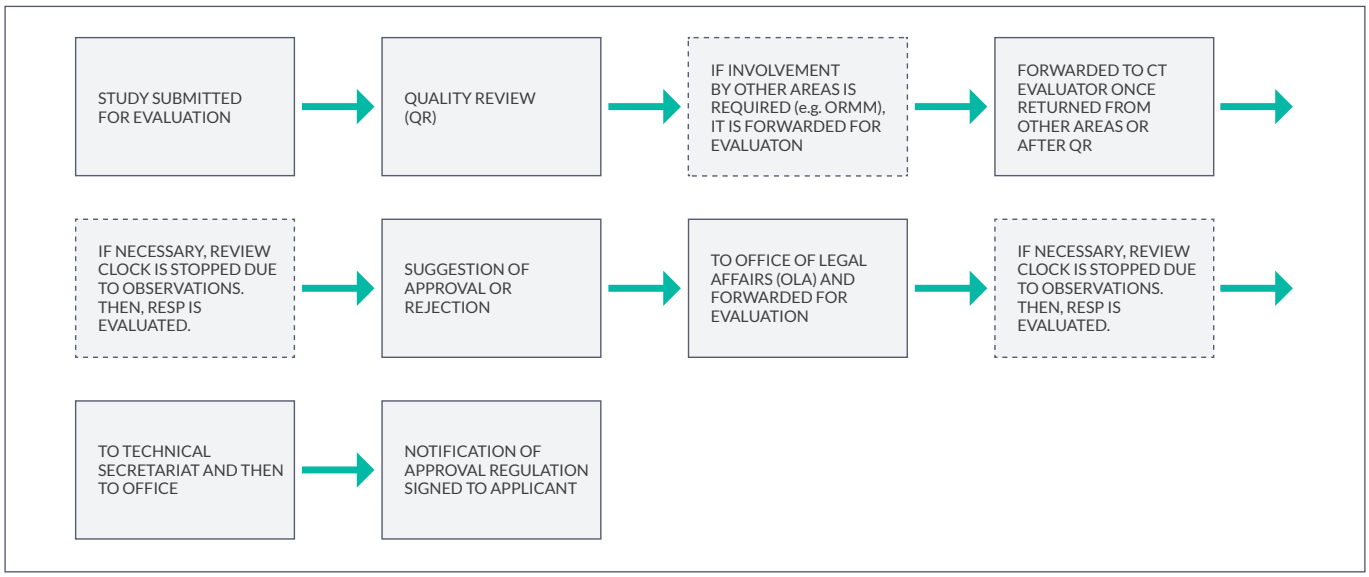

FIGURE 1: Clinical trial evaluation process.

QR= Quality review; ORMM: Office of Risk Monitoring and Management; CT: Clinical Trial; OLA: Office of Legal Affairs; RESP: Response

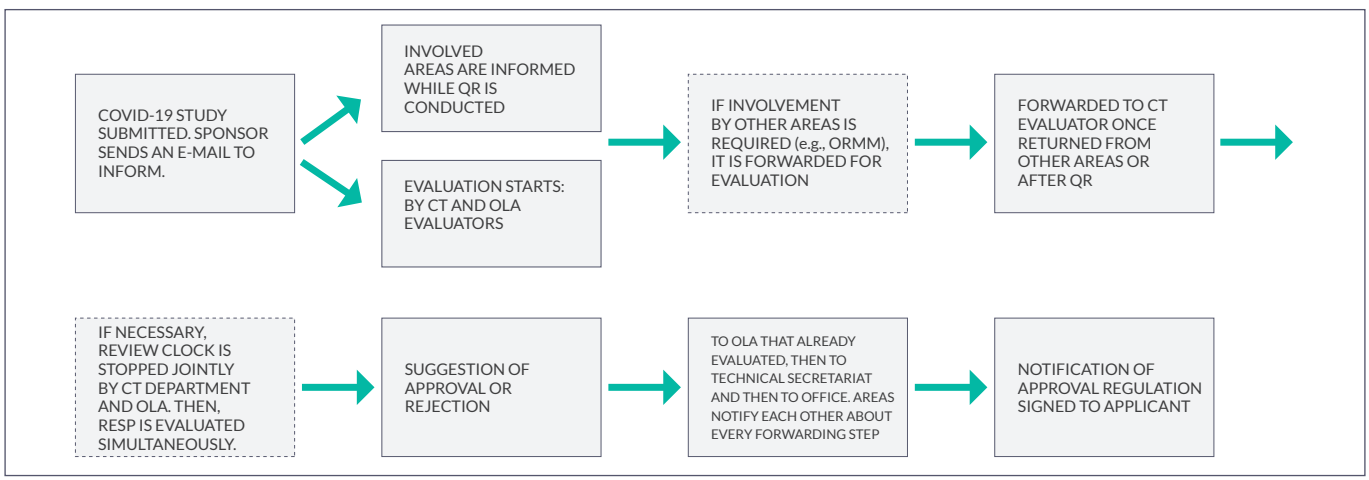

Figure 2: COVID-19 clinical trial evaluation process.

QR= Quality review; ORMM: Office of Risk Monitoring and Management; CT: Clinical Trial; OLA: Office of Legal Affairs; RESP: Response

In respect of evaluation timelines, ANMAT Regulation 4008/17 establishes that the technical areas involved in the evaluation of clinical pharmacology studies shall inform their decision within 60 administrative working days. Said timeline is reduced to 45 administrative working days in the case of ongoing studies approved by any of the countries included in Annex I to Executive Decree 150/92 (high health vigilance countries), by countries this National Administration opportunely deems regulatorily convergent and/or by countries recognized by the Pan American Health Organization (PAHO/WHO). In view of said regulations and the need to provide response, the Department decided to prioritize the evaluation of COVID-19 studies.

As to the evaluations of COVID-19 clinical pharmacology studies, in addition to assessing the same ethical and methodological aspects as in the case of any other pathology clinical studies, specific evaluations and recommendations inherent to the pandemic or the type of study were established, to minimize risks and protect the safety and rights of subjects, as well as the quality of the data to be obtained. For example, for vaccine trials on healthy volunteers, a requirement was established to describe the circuit subjects would follow in each site, to prevent contact between healthy volunteers and ill patients, as well as to minimize infection risks of coronavirus and other infectious diseases. Also, information was requested as regards logistics, such as the transfer of volunteers to the site, and specific recommendations were provided in terms of personnel required training.

Study designs were assessed for feasibility in the health context as well as for appropriateness to ensure the scientific validity of the analysis, since with no scientific validity, the investigation lacks social value and should not be conducted[12].

As an additional measure, it was decided that authorized COVID-19 clinical pharmacology studies were to be made public, for the information to be available and accessible for the public[13].

COVID-19 Clinical Pharmacology Studies follow-up and monitoring

- Follow-up by electronic mail: once a COVID-19 clinical pharmacology study has been approved, its sponsor is required to send an electronic mail reporting the study status (number of subjects enrolled / under treatment / followed-up / completed). This enables ongoing vigilance and monitoring, as well as the obtainment of information to plan inspections at adequate intervals, taking into account the fast enrolment characteristics of COVID-19 studies, and the characteristics of vaccines clinical pharmacology studies, that recruit a large number of subjects in a short period of time.
- Progress reports: due to the abovementioned characteristics of vaccines trials, upon authorization, a requirement was added for the submission of progress reports at a frequency higher than that established by the regulations, to optimize the trial follow-up and monitoring.
- GCP inspections: the aim of clinical pharmacology study inspections within the remit of ANMAT is to verify compliance with the Regime for Good Clinical Practices for Clinical Pharmacology Studies, as established by Regulation 6677/2010.

During COVID-19 pandemic, with a view to reducing the risk of viral contact among persons, including sponsors, investigators, site personnel, as well as ANMAT GCP inspection team members, the Clinical Trials Inspection Service developed a new tool to conduct inspections remotely, the Procedure for Good Clinical Practices Remote Inspections, in accordance with Regulation 6677/10. The overall purpose and the documentation checked in a remote inspection remain unchanged as compared to an in-person inspection.

The first remote inspection was conducted in August 2020. Due to the positive results obtained from the procedure to the time being, remote inspections are planned to be continued beyond the pandemic.

Likewise, pursuant to regulations of the Ministry of Health, a document was developed to detail protection measures and cautions to conduct safe in-person inspections during the pandemic[14].

ANALYSIS OF COVID-19 CLINICAL PHARMACOLOGY STUDIES SUBMITTED TO AND AUTHORIZED BY ANMAT DURING THE PANDEMIC

This analysis includes COVID-19 clinical pharmacology studies applications submitted to ANMAT and authorized by it in the period between May 1st, 2020 and August 3rd, 2021.

Out of a total of 268 studies approved in the abovementioned period, 61 (22.7%) were COVID-19 studies. It is to be noted that a total of 75 COVID-19 studies applications were submitted and, in 6 cases, the sponsors decided to withdraw the application and 8 are still under evaluation to August 3rd, 2021.

Following is a description of the characteristics of the 61 studies approved by this Administration.

In terms of who submitted the studies (sponsors o legal agents in Argentina), it was observed that 34 applications (55.7%) were submitted by Contract Research Organizations (CRO); 20 applications (32.8%) were submitted by pharmaceutical companies and 7 applications (11.5%) by other type of institutions (foundations or scientific institutions).

The average number of administrative working days elapsed from procedure start to authorization granting is 19 working days, with an 18-day standard deviation (SD).

In respect of the investigational product developmental phase, most studies (42 of 61) approved by ANMAT in the period analyzed were phase III studies (68.8%), (**Table 1**). **Tables 1** and **2** exhibit the distribution of the studies per clinical phase and type of population included, respectively.

Figure 3 details the frequency of the intervention type used in the clinical studies evaluated, where various treatments for symptomatic COVID-19 were the most frequent ones.

Table 3 shows COVID-19 severity in clinical pharmacology studies participants. This severity classification is taken from the definition given in various studies based on WHO severity classification of COVID-19[15].

As to investigational products, 30 studies with biological agents were evaluated as well as 30 studies with non-biological drugs and 1 trial that included both types of agents. Most agents evaluated were protease inhibitors/other enzyme inhibitors (17), monoclonal antibodies (13) and vaccines (11). To a lesser extent, other investigational products included: antiparasitic, antiretroviral and antifibrotic agents, blood products (human and animal origin), corticosteroids and interferons, among others.

Most interventions studied in our country were drugs in developmental phase. It was observed that only 20%, that is to say, 13 out of 64 agents studied, had been authorized for other clinical indications. Among the latter were drugs used to treat rheumatic diseases (abatacept, infliximab, sarilumab, baricitinib), anthelmintic drugs such as ivermectin, glyphozines indicated for type 2 diabetes mellitus, antiretrovirals and inhaled corticosteroids.

Table 4 and **Figure 4** show the location per jurisdiction of the 274 investigational sites licensed in the authorized studies.

Out of the 274 research sites, 54 sites (20%) pertained to studies on vaccines for disease prevention, whereas the other 220 remaining sites (80%) were licensed for research studies intended for COVID-19 therapeutics.

When considering whether the investigational sites belonged to the public health subsystem or not, it was noted that 76 sites (28%) were public sites and 198 sites (72%) did not belong to the public health subsystem.

The period analyzed included 31 655 subjects, out of whom, 29 668 subjects (94%) participated in vaccines studies, whereas 1 987 participants (6%) were recruited in therapeutical purposes studies.

TABLE 1: INVESTIGATION PHASES OF AUTHORIZED COVID-19 CLINICAL PHARMACOLOGY STUDIES

Investigation phase	N (%)
Ib	1 (1,6%)
II	18 (29,5%)
II/III	14 (23%)
III	27 (44,3%)
I to III	1 (1,6%)

TABLE 2: POPULATION INCLUDED IN COVID-19 CLINICAL PHARMACOLOGY STUDIES

Hospitalized	Studies
Yes	34 (55,8%)
No	26 (42,6%)
Yes or No	1 (1,6%)

TABLE 3: SEVERITY OF COVID IN CLINICAL PHARMACOLOGY STUDIES SUBJECTS

Severity of COVID	N (%)
Non-applicable	14 (23%)
Mild	8 (13,1%)
Mild to moderate	4 (6,6%)
Moderate	9 (15%)
Moderate to Severe	24 (39,3%)
Severe	1 (1,6%)
Mild, moderate and severe	1 (1,6%)

TABLE 4: LOCATION OF SITES PER JURISDICTION

Location of sites per jurisdiction	N	Percentage
AUTONOMOUS CITY OF BUENOS AIRES	134	49%
BUENOS AIRES	63	23%
CÓRDOBA	30	11%
SANTA FE	20	7%
RIO NEGRO	9	3%
TUCUMAN	9	3%
MENDOZA	3	1%
CHACO	1	lower than 1%
CORRIENTES	1	lower than 1%
JUJUY	1	lower than 1%
NEUQUÉN	1	lower than 1%
SALTA	1	lower than 1%
SAN JUAN	1	lower than 1%
Total in country	**274**	**100%**

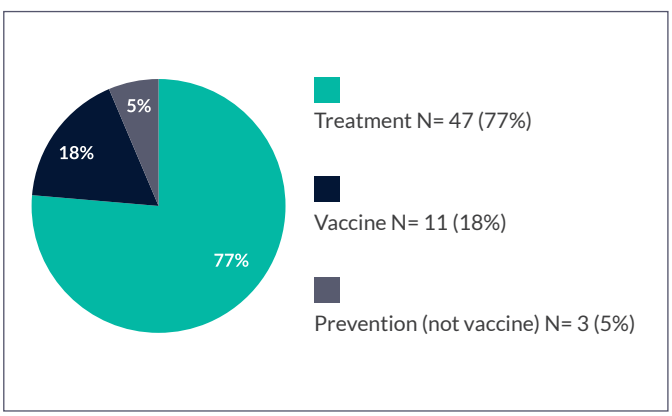

FIGURE 3: Type of intervention in COVID-19 Clinical Pharmacology Studies

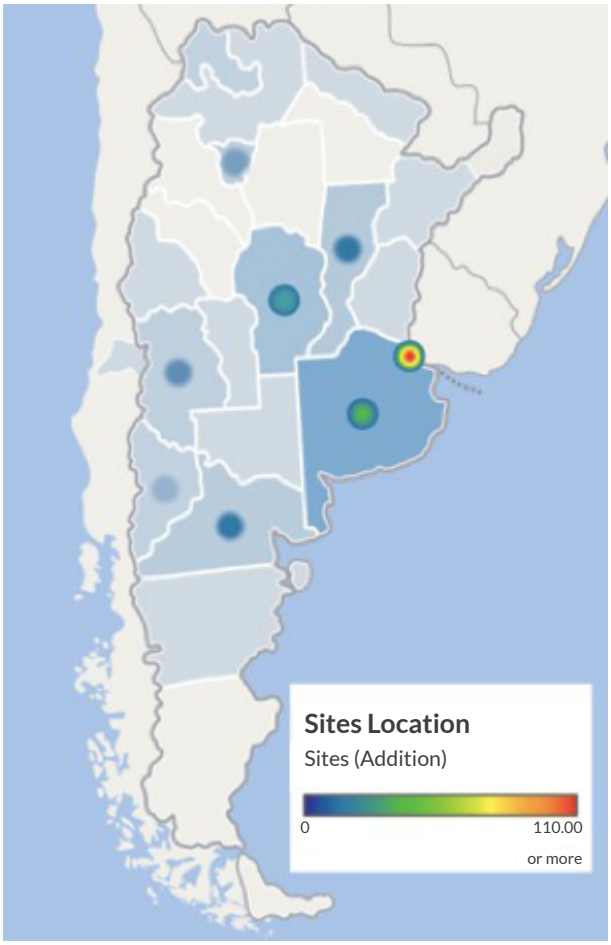

FIGURE 4: Map of authorized sites location in Argentina

CONCLUSION

During COVID-19 pandemic, ANMAT, through its Department of Clinical Trials, swiftly adapted to the situation and provided regulatory measures and responses to the health emergency.

The regulatory actions taken during the global public health crisis, even though endowed with certain flexibility and process simplification, enabled the maintenance of clinical trials integrity and the guarantee of participants´ rights, wellbeing and safety[9]. Efforts were focused on preventing viral spread and the saturation of the health system, that would be more stressed because of the health crisis. Along with the specific regulatory response to the pandemic, actions were taken to preserve the clinical research activities of the clinical studies underway.

It is to be underlined that the measures and recommendations for clinical pharmacology studies provided were in agreement with those implemented by other high health vigilance countries, both in terms of content and development and enforcement timing.

Based on the positive results obtained, some processes and tools implemented in the framework of the pandemic will be assessed for further continuation once the pandemic is over.

In view of the number of COVID-19 studies conducted and the number of subjects participating across the country, the Argentine Republic´s participation is to be highlighted for its data contribution to scientific evidence obtainment in SARS-COV-2 prevention or treatment in response to the pandemic.

Some accomplishments are:

- The articulation of various ANMAT areas involved in the clinical pharmacology studies evaluation process, with a view to carrying out a simultaneous, coordinated, collaborative and expedite activity.
- Streamlined evaluation processes for a safe access to new products and technologies.
- Strengthened multidisciplinary teams and teamwork.
- Optimized digital tools and platforms to streamline and conduct procedures and formalities.
- The strengthening of ANMAT as a high vigilance health agency and its positioning at the national and international level, based on openness to regulatory dialogue.

Some challenges ahead are:

- The need for a critical analysis of the decisions made and their impact.
- Human resources ongoing training to enhance knowledge and/or develop new skills.
- Continuous review of procedures and regulations at the pace of innovations.

Conducting a clinical investigation in pandemic conditions poses significant challenges, such as the need to generate knowledge fast, maintain public confidence and overcome practical hurdles while conducting the research. These challenges are to be carefully balanced with the need to ensure research scientific validity and uphold ethical principles throughout research conduct[12].

BIBLIOGRAPHY

1. Cucinotta D and Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed 2020; 91 (1): 157-60.

2. Bi Q, Wu Y, Mei S et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 2020; 20: 911–19.

3. Bierer BE, White SA, Barnes JM and Gelinas L. Ethical Challenges in Clinical Research During the COVID-19 Pandemic. Journal of Bioethical Inquiry. September 2020. https://doi.org/10.1007/s11673-020-10045-4.

4. Won JH and Lee H. Can the COVID-19 Pandemic Disrupt the Current Drug Development Practices?. Int J Mol Sci 2021; 22: 5457. https://doi.org/10.3390/ijms22115457.

5. EMA: European Medicines Agency. June 2021. Mandate, objectives and rules of procedure of the COVID-19 EMA pandemic Task Force (COVID-ETF). EMA/166423/2020.

6. Dodd S, Fish R, Gorst S et al. Representation of published core outcome sets for research in regulatory guidance: protocol [version 3; peer review: approved]. HRB Open Research 2021; 4 (45): 1-13.

7. ANMAT: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica [Internet]. La ANMAT firmó acuerdo de colaboración con la Agencia Europea de Medicamentos (EMA); Noviembre 2020. [Consultado el 30 de agosto de 2021]. Disponible en: https://www.argentina.gob.

ar/noticias/la-anmat-firmo-acuerdo-de-colaboracion-con-la-agencia-europea-de-medicamentos-ema
8. ANMAT: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica. [Internet]. Medidas y recomendaciones en los estudios de farmacología clínica durante la pandemia COVID-19; Marzo 2020. [Consultado el 30 de agosto de 2021]. Disponible en: https://www.argentina.gob.ar/noticias/medidas-y-recomendaciones-en-los-estudios-de-farmacologia-clinica-durante-la-pandemia-covid
9. EMA: European Medicines Agency [Internet]. Guidance on the Management of Clinical Trials during the COVID-19 (CORONAVIRUS) Pandemic [updated February 4th, 2021; accessed August 30th, 2021]. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
10. FDA: Food and Drug Administration [Internet]. Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards [updated: August 30th, 2021; accessed September 3rd, 2021]. Available at: https://www.fda.gov/media/136238/download
11. ANMAT: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica. [Internet]. Inicio o reinicio del reclutamiento de personas sanas para estudios de farmacología clínica; Noviembre de 2020. [Consultado el 30 de agosto de 2021]. Disponible en: https://www.argentina.gob.ar/noticias/inicio-o-reinicio-del-reclutamiento-de-personas-sanas-para-estudios-de-farmacologia-1
12. Organización Panamericana de la Salud y Consejo de Organizaciones Internacionales de las Ciencias Médicas. Pautas éticas internacionales para la investigación relacionada con la salud con seres humanos, Cuarta Edición. Ginebra: Consejo de Organizaciones Internacionales de las Ciencias Médicas (CIOMS); 2016.
13. Argentina.gob.ar [Internet]. Estudios clínicos autorizados para COVID-19. [Consultado el 30 de agosto de 2021]. Disponible en https://www.argentina.gob.ar/anmat/regulados/investigaciones-clinicas-farmacologicas/Estudios-autorizados-COVID19
14. Ministerio de Salud de la Nación Argentina [Internet]. Nuevo Coronavirus Covid-19. Recomendaciones para el uso de los Equipos de Protección [Consultado el 30 de agosto de 2021]. Disponible en: https://www.argentina.gob.ar/salud/coronavirus/recomendaciones-uso-epp
15. Marshall JC, Murthy S, Diaz J et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020; 20: e192–97.