



Urologic research in the COVID-19 Era: Challenges and Opportunities

Investigación urológica en la era COVID-19: desafíos y oportunidades

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Abstract

The Coronavirus (COVID-19) pandemic, typified as such in March 2020 by the World Health Organization (WHO), has exceeded the capacity of health systems to aid victims, and triggered a radical change in medical research, and in the monitoring of the enrollment for clinical trials in urologic fields around the world.

Last year, almost 90% of clinical sites closed patient enrollment, while at the same time, researchers around the world initiated almost 1000 COVID-19 clinical trials. This catastrophic pandemic has allowed us to expand our medical knowledge exponentially. The global urological community has created and published an infinity of scientific articles: establishing guideline reactions for diagnosis, treatment, and follow-up of the different urologic conditions across all areas of the field, reporting the experiences at urology services, and putting forward new strategies.

The *Confederación Americana de Urología* (CAU) has promoted international collaborative projects that have led to gaining insight into how the Latin American Urology Services faced the pandemic, including the challenges, strengths, and the areas of opportunity for urologic care. It also allowed us to increase the number and quality of publications. Also, we have created new virtual platforms and international networks to exchange our knowledge. We have as well transformed this social, economic and health crisis brought upon us by COVID-19, into a source of opportunities for the growth and promotion of research in Latin America.

Urologic patients, require researchers to work on favoring their goals. A collaborative network, the established and coordinated protocols, the safety of patients and researchers, assertive and constant communication, and effective technology use, are the essential tools to resume institutional investigation under these critical conditions.

Keywords:

COVID-19,
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Resumen

La pandemia del coronavirus (COVID-19), tipificada como tal en marzo de 2020 por la Organización Mundial de la Salud (OMS), ha superado la capacidad de los sistemas de salud para ayudar a las víctimas y ha desencadenado un cambio radical en la investigación médica y en el seguimiento de los registros para ensayos clínicos en campos urológicos de todo el mundo.

El año pasado, casi el 90 % de los sitios clínicos cerraron la inscripción de pacientes, mientras que, al mismo tiempo, investigadores de todo el mundo iniciaron casi 1000 ensayos clínicos de COVID-19. Esta pandemia catastrófica nos ha permitido ampliar exponencialmente nuestro conocimiento médico. La comunidad urológica mundial ha creado y publicado una infinidad de artículos científicos: estableciendo pautas de reacción para el diagnóstico, tratamiento y seguimiento de las diferentes condiciones urológicas en todas las áreas del campo, reportando las experiencias en los servicios de urología y proponiendo nuevas estrategias.

La Confederación Americana de Urología (CAU) ha impulsado proyectos de colaboración internacional que han permitido conocer cómo los Servicios de Urología de América Latina enfrentaron la pandemia, incluidos los desafíos, las fortalezas y las áreas de oportunidad para la atención urológica. También nos permitió aumentar el número y la calidad de las publicaciones. Además, hemos creado nuevas plataformas virtuales y redes internacionales para intercambiar nuestro conocimiento. También hemos transformado esta crisis social, económica y de salud que nos ha traído el COVID-19, en una fuente de oportunidades para el crecimiento y fomento de la investigación en América Latina.

Los pacientes urológicos, requieren que los investigadores trabajen en favor de sus objetivos. Una red colaborativa, los protocolos establecidos y coordinados, la seguridad de pacientes e investigadores, la comunicación asertiva y constante, y el uso efectivo de la tecnología, son las herramientas esenciales para retomar la investigación institucional en estas condiciones críticas.

Palabras clave:

COVID-19, coronavirus, investigación urológica, Confederación Americana de Urología

Introduction

The World Health Organization (WHO) declared the coronavirus (COVID-19) pandemic in March 2020, and since then, the pandemic has exceeded the capacity of health systems to aid

victims. It also has triggered a radical change in medical research as well as in the monitoring of the enrollment for clinical trials in urologic fields around the world. Last year almost 90%

of clinical sites closed patient enrollment, while at the same time, researchers around the world initiated almost 1000 COVID-19 clinical trials.^(1,2) While the suspension of oncologic clinical trials was justified by protecting the vulnerable population and preserving medical resources, there is a need to discuss the future consequences of the interruption of clinical trials in terms of oncologic patient's treatment, their potential benefit, and the delay of scientific answers and drug development.⁽³⁾ The impact this will have is far from being possible to quantify.

Nowadays, things are changing, and preventive measures are better understood, so clinical trials are back on, but only as research teams follow the recommendations issued by entities such as the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the National Institute of Health (NIH). These organizations make their recommendations mainly to sponsors, and are referred to Institutional Review Boards or Independent Ethics Committees (IRB/IEC). We are finally directed to preserve the health of patients and volunteers during the pandemic.⁽⁴⁻⁶⁾

We aimed to review how research has been made during the COVID-19 era. Components of research (i.e., visits, informed consent, standard procedures, tests) will be discussed separately for better understanding. We will also present a summary of the development of research in Latin America during the COVID-19 era.

What just happened?

As mentioned earlier, the most critical issue was the lack of resources (monetary and human). All those human and monetary budgets

went to aid COVID patients; as it was the needed course of action at that point. IRBs and medical organizations suspended all research activities, resulting in considerable delays in database input, document management, and sponsor meetings.⁽⁷⁾

When the situation was difficult; and we did not know anything about the virus, the protection tools, and the interventions to achieve low morbidity and mortality rates, governments prioritized COVID research. Studies were requested, regardless of the type: real-world data, clinical trials, and others. Money was not an issue as it was available for facing the emergency.⁽⁷⁾

Regulatory agencies released statements to resume research safely. These recommendations might lead to a significant change in the way clinical trials are conducted, changes that are likely to remain stable even in post-pandemic times.⁽⁸⁾ In this scenario, alternative ways of carrying on with clinical trials could include telemedicine and less frequent testing and follow-up. These strategies might improve the protection of patients and healthy volunteers who participate in different studies. These alternative methods are not likely to be face-to-face encounters; however, we lack too much information regarding this issue.⁽⁴⁾

Researchers need to inform the community that we are conducting trials, ensuring their protection, and fulfilling Good Clinical Practices (GCP) and the Helsinki Declaration. This situation might be seen as an opportunity to be creative in the involvement of patients, researchers, and sponsors.

Regarding clinical trials

About recruiting

The FDA and EMA recommendations (rules that almost all countries in the world have followed) stopped all trials around the globe. Nonetheless, during the second half of 2020, recruiting re-started, but only for life saving and essential trials, as only they were given new approval.⁽⁹⁾ Randomized controlled trials were affected because of a recruitment deficit in terms of time, patients, and reliable endpoints.

There are some crucial ways to solve this issue. Authors described methods like pooling data, combining information from multiple trials that were not initially configured as a network of sites. It might be possible to reach valid conclusions, once recruitment problems are sorted.⁽¹⁰⁾ Sponsors and researchers must balance the cost/risk of recruiting new patients or continuing a study in terms of safety for the participants and research team.

Protocol and Informed Consent Form (ICF)

Protocol amendments due to COVID-19 without an increase in patient safety risks can be done with the approval of the IRB/IEC. When alterations are necessary during a pandemic, such as modifications of procedures, it should be informed to the IRB/IEC. After its approval, it should be presented to the local Agency. Generally, in cases of research of new drugs under Phase I or II trials, and some Phase III trials, any amendment which affects the safety of the participants, the scope of the research, or the quality of the study, must be presented to the local Agency and the IRB/IEC. Also, all deci-

sions to adjust the way a clinical trial is conducted should be based on a risk assessment by the sponsor and discussed with every researcher.

⁽¹¹⁾Currently, there is some evidence that the pandemic led to more good research, leaving aside some requests and inquiries that were doubtfully reasonable but required as part of the protocol.⁽⁸⁾

In the case of the ICF, the FDA suggests the traditional paper signed copy (in cases of this being impossible, they accept electronic alternatives). The EMA clearly states (especially in re-sign cases) that "... it should be avoided that trial participants visit trial sites for the sole purpose of obtaining re-consent. Suppose re-consent is necessary to implement new urgent changes in trial conduct (mainly expected for reasons related to COVID-19 or important safety issues for other trials). In that case, alternative ways of obtaining such re-consent should be considered during the pandemic." These alternatives are verbal agreements, video calls, or email with confirmed reception.⁽⁶⁾ Again, electronic resources, including electronic consent, allow the wellness and safety of participants, minimizing loss or withdrawal.⁽¹²⁾

Visits

Standard protocols include follow-up visits where the patient is usually asked to answer questions about symptoms, or validated questionnaires to evaluate the clinical effectiveness, adverse effects, natural disease evolution, and other relevant aspects depending on the study's goal. The safety and well-being of trial participants and research team members are of the utmost importance. In this setting, every action is directed to maintain physical distancing,

including limited contact between participants, research team members, and the institution environment.⁽¹³⁾ As stated by the FDA and the EMA, "... sponsors should evaluate whether alternative methods for safety assessments could be implemented when necessary and feasible and would be sufficient to assure the safety of trial participants..." Also, phone contact or virtual visits, including telemedicine, should be preferred for health preservation. The sponsor is responsible for determining whenever a personal visit (either at home or the institution) is necessary and, in extreme cases, if the study can go on in these particular circumstances.^(4,6) As suggested by Nabhan et al., this "new normality" could represent an opportunity to improve patient follow-up, including remote tools to improve patient compliance with the trial. Virtual visits and telemedicine require patient access to a secured virtual platform, but solving this issue would lead not only to saving time and money but to elevating patients' adherence to trials.⁽⁸⁾

Laboratory and image studies

These tests are usually performed by the research team at an approved site. Usually, this place is where visits are made, and primary trial documents are stored. Of course, participants may have limitations to turn up to the institution that enrolled them because of the pandemic. Consequently, agencies encourage sponsors to accept, in case of the participant not being able to reach the institution, that laboratory, imaging, or other diagnostic tests be performed at a local authorized/certified laboratory or relevant clinical facility.^(4,6) However, these centers need to be monitored by the

sponsor. These measures also assure protective conditions such as social distancing and protective protocols. There would ideally be a major revision at the local institution in the case of core results (inclusion criteria or main result). Some patients might also receive tutorials with the complete instructions to undergo the required tests or even a virtual supervised test.

Standard Operating Procedures (SOP)

An SOP is a set of step-by-step instructions compiled by the sponsor to help researchers carry out routine operations. SOPs aim to achieve efficiency, quality output, and uniformity of performance, while reducing miscommunication and failure to comply with industry regulations. In clinical research, SOPs support the group's standard practices and daily conducted processes to ensure the execution of research tasks following institutional, state, and federal regulations. SOPs should contain adequate detail to guide research staff through a particular procedure and establish uniformity in everyday functions. All SOPs had to change during the pandemic, including items on how to prevent COVID-19 infection. In the case of COVID-19 infection, recommendations must be clear for the team to advise and create an unequivocal chain of command.⁽¹⁴⁾

Monitoring

As previously described, all agencies recommended alternative approaches to maintain trial participant safety and data quality.⁽¹⁵⁾ These included enhanced central monitoring, telephone contact, and online video calls. They

are always supported by a review and update of SOPs. Any protocol deviation in terms of GCP should be informed immediately. On-site audits should be postponed or avoided, and remote audits are strongly recommended, according to the EMA.(16)

Latin-American urologic research

This catastrophic pandemic allowed us to expand our medical knowledge exponentially. The entire world's urologic community has created and published an infinity of scientific articles: establishing Guideline reactions for diagnosis, treatment, and follow-up of the different urologic conditions across all areas of the Urology field, reporting the experiences at urology services, and putting new strategies forward. The *Confederación Americana de Urología* (CAU) has promoted international collaborative projects that have led to gaining insight on how the Latin American Urology Services faced the pandemic, the challenges, the strengths, and the areas of improvement for urologic care. It also allowed us to increase the number and quality of publications.

We have created new virtual platforms and international networks to exchange our knowledge. Also, we have transformed the social, economic and health crisis of COVID-19 into a source of opportunities for the growth and promotion of research in Latin America.

Some essential tips to share are: (15,16)

- It is possible to work at home. Get ready to do it and establish some rules to do it well. The information must be in the cloud, available for all, at any place and time, but according to data safety protocols.

- Communication with the sponsor is essential. Establish new due dates to accomplish the goals and inform of new plans.
- If it is imperative, modify the research and data analysis. This depends on the stage of the pandemic. As we previously stated: communication with the sponsor is vital. Remember that any modification must be informed to the Institutional Review Board (IRB).
- Use different ways to collect the information: remember that we are now digital. Nonetheless, remember that not all people are digital.
- The most crucial issue during research is to protect the research subjects. Therefore, make sure this critical topic is covered. Also, protect researchers and collaborators.
- Train different people to work in different areas. Remember that people might get sick, but the project still needs to go on.
- Schedule frequent meetings with the team but do not overdo it. Remember the importance of mental health.

Conclusions

Urologic patients, especially those with oncological conditions, require researchers to work on favoring their goals. A collaborative network, established and coordinated protocols, the safety of patients and researchers, assertive and constant communication, and effective technology use are the essential tools to resume institutional research under these critical conditions.

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