Commentary

Increased Vulnerability of Clinical Research Units During the COVID-19 Crisis and Their Protection

Maria de Miguel, PhD[1]; Bernard Doger, PhD[2]; Valentina Boni, PhD[1]; Tatiana Hernández-Guerrero, MD[2]; Irene Moreno, MD[1]; Daniel Morillo, MD[2]; Victor Moreno, PhD [2]; and Emiliano Calvo, PhD [1]

Lay Summary:

• Currently, the complexity of clinical trial development in oncology is being further complicated by the coronavirus disease 2019 (COVID-19) pandemic, which is reducing the resources needed to comply with protocol-specific procedures while putting patients in units, who are already vulnerable, at increased general risk not only for COVID-19 infection but also with respect to their baseline disease.

• Individualizing the management of patients while ensuring their safety and adherence to the study protocol, establishing specific staff contingency plans, and maintaining sponsor and contract research organization (CRO) alignment are some of the key issues for maintaining the continuity of cancer patients' investigational treatment and minimizing their infection risk as well as the risk to staff members of the unit, sponsors, and CROs while maintaining the integrity of data quality and compliance with good clinical practice.

KEYWORDS: COVID-19, clinical research units, clinical trials integrity, patients' safety, serological tests, vulnerability.

When in December 2019 a novel cluster of viral acute respiratory disease later known as coronavirus disease 2019 (COVID-19) turned up in Wuhan, China, the unprecedented global consequences that were coming a few months later were practically unpredictable. Despite the shocking news coming from China, which reached almost 10,000 new cases in the initial month,[1] Europe calmly watched these events unfold from a distance. Rapidly, the COVID-19 pandemic expanded to Europe, and the first uncontrolled continental focus was Italy, where the current number of deceased people exceeds by many thousands the number in China. The situation in Spain is also alarming, with almost 250,000 infected people and more than 25,000 deaths (May 4) as well as hospital saturation and early health care system collapse. The incidence started increasing rapidly in Italy by the end of February, whereas in Spain, we had a 2- to 3-week lag, which allowed for some anticipation time to implement contingency measures.[2]

Different factors contributed to this dramatic situation in our country, which presumably will become worse during the following weeks before we finally reach the peak of incidence. First, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) combines high transmissibility (effective reproductive number, 2.9)[3] with high mortality rates. Second, suppression policies were implemented late in our country despite the time-gap advantage in comparison with Italy and worldwide, and this further allowed the uncontrolled national spread of the virus. Finally, the acute, exponential increase in the number of new cases and the need for intensive care unit care by a high proportion of patients for a prolonged time are putting our already maximized health care system under exceptional strains. With this, Spain has been under an official state of alarm since March 13: except for medical care and basic services, people have been confined to their residences to slow down the rate of infection and allow our health care network to cope until herd immunity is established.

In this context in which urgent care is the priority, oncology patients receiving treatment are even more vulnerable because they might be seriously affected by COVID-19,[4] but they also need to come to the hospital and expose themselves to the infection to receive treatments for their life-threatening disease. Among these patients, those in clinical trials are especially defenseless and susceptible because they cannot receive investigational treatments outside their clinical research unit (CRU), with the treatments administered by specifically trained people in specifically approved facilities for the given clinical study. In Europe, 12,798 clinical trials were available during 2019, and Spain occupied the fifth position in recruitment with 14.4% of the total.[5] During the last decade, oncology clinical trials have significantly increased in complexity because of extensive pharmacokinetic and pharmacodynamic studies, strict radiological evaluations, the introduction of paired biopsies, and Bayesian modeling designs needing real-time

Corresponding Author: Emiliano Calvo, PhD, START Madrid–HM CIOCC Early-Phase Program, Centro Integral Oncológico Clara Campal, Hospital Universitario HM Sanchinarro, Calle Oña 10, 28050 Madrid, Spain (emiliano.calvo@startmadrid.com).

[1]START Madrid-HM Centro Integral Oncológico Clara Campal (CIOCC) Early Phase Program, HM Sanchinarro University Hospital, Madrid, Spain; [2]START Madrid-Fundación Jiménez Díaz (FJD) Early Phase Program, Fundación Jiménez Díaz Hospital, Madrid, Spain

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TABLE 1. Reasons and Challenges for Increased CRU Vulnerability During the COVID-19 Crisis

- Challenge for patients to comply with intense study protocol visits to the site
- Highly demanding, protocol-specific procedures of studies to follow without protocol violations or safety concerns
- Multidisciplinary and multidepartmental clinical trial complexity (ie, PK/PD, radiological images, and biopsies) that requires sophisticated organization
- Refinement of staff roles involved in clinical trials that are highly specialized and involve study-specific training (this makes unit employees difficult to replace and patients unable to be transferred to another CRU for treatment)
- Large variety of mandatory job positions required to achieve adequate clinical research development compliant with GCP: investigators; RNs; TNs; IND pharmacy; DM; scheduler; and regulatory, budget, and contract staff
- Need for fluid cooperation with and dependence on other hospital departments and specialties to comply with protocol procedures
- Study decision making that involves alignment with sponsors and CROs now sometimes threatened by a hyperdefensive general approach instead of a case-by-case assessment
- Upper management reorganization of hospital and medical spaces and staff to prioritize COVID-19–infected patients
- Decreased facility resources for clinical trial participants

Abbreviations: COVID-19, coronavirus disease 2019; CRO, contract research organization; CRU, clinical research unit; DM, data manager; GCP, good clinical practice; IND, investigational new drug; PD, pharmacodynamics; PK, pharmacokinetics; RN, research nurse; TN, treatment nurse.

data extraction. Therefore, clinical research involves the inner workings of many different pieces for its appropriate development, and it consequently acquires the fragility of these programs during a crisis such as the one that we are facing. This, together with good clinical practice requirements for conducting studies, makes it unfeasible to transfer patients from one highly affected CRU during this crisis to another one with better conditions regarding COVID-19 infection to allow patients to continue their investigational treatments, as we would do with conventional chemotherapy. In this situation, in a CRU, the strength of the chain is that of the weakest of its links; therefore, all links need to keep working well and to be well aligned (Table 1).

The COVID-19 pandemic could dramatically affect clinical trial development because of staff and patient quarantines, study closures, travel limitations, and interruptions in the supply of investigational products, among other things. On the other hand, for many patients, to be enrolled in a clinical trial is the best—and sometimes only—option for receiving antitumoral treatment, so our goal is not letting them down while accomplishing the Hippocratic precept of "primum non nocere" (ie, patients' safety, including clinical study integrity and performance as per protocol). We are an international corporation (Early-Phase Clinical Drug Development in Oncology) with complementary parallel research programs that have been developed in different countries (including 2 different sites in Madrid) in public and private health care systems and that collaborate together synergistically. We anticipated for several weeks the chaotic situation arriving Spain and elaborated a 360-degree strategic plan to face the different scenarios to come. To the best of our knowledge, these are novel plans elaborated under exceptional circumstances that might serve other researchers and CRUs of any medical area to allow the continuity of patients' investigational treatment while minimizing the risk of infection, keeping the integrity of data quality, and maintaining compliance with good clinical practice (Fig. 1).

As a result, during March and April 2020, the period with the highest incidence of COVID-19 infections and highest death rates in Spain (the country with the highest rate of COVID-19 deaths per million citizens for several weeks), all of our 183 active patients in investigational studies were able to continue receiving their treatments as per protocol. In addition, 56 new patients were recruited into our clinical studies, and they represented 73.7% of the new patients treated during the same period in 2019. This slight decrease in the accrual of new patients possibly reflects the fact that 26 of the 139 active clinical trials (18.7%) restricted the inclusion of patients because of the pandemic. Those studies that were put on hold responded to country-related general decisions made by sponsors' headquarters instead of making decisions related to the complexity of clinical trials because most of the ones with labor-intensive processes, such as extensive pharmacokinetics or sequential tumor biopsies, could continue normally. However, the studies involving cellular therapies had to be put on hold because of potential restrictions on preplanned intensive care unit admissions for T-cell infusions, as per protocol, to prioritize patients with COVID-19.

1. General measures. Just as for the rest of the hospital departments, basic protective actions have been implemented for all persons accessing the unit.[6] The use of face masks and regular hand washing with soap and hydroalcoholic solutions are reinforced. Staff and patients are instructed to maintain appropriate distances and to avoid contact with suspected or infected persons. In this regard, all staff members have been trained to rapidly communicate the start of any respiratory symptom that could suggest COVID-19 and stay at home and to self-quarantine if they are

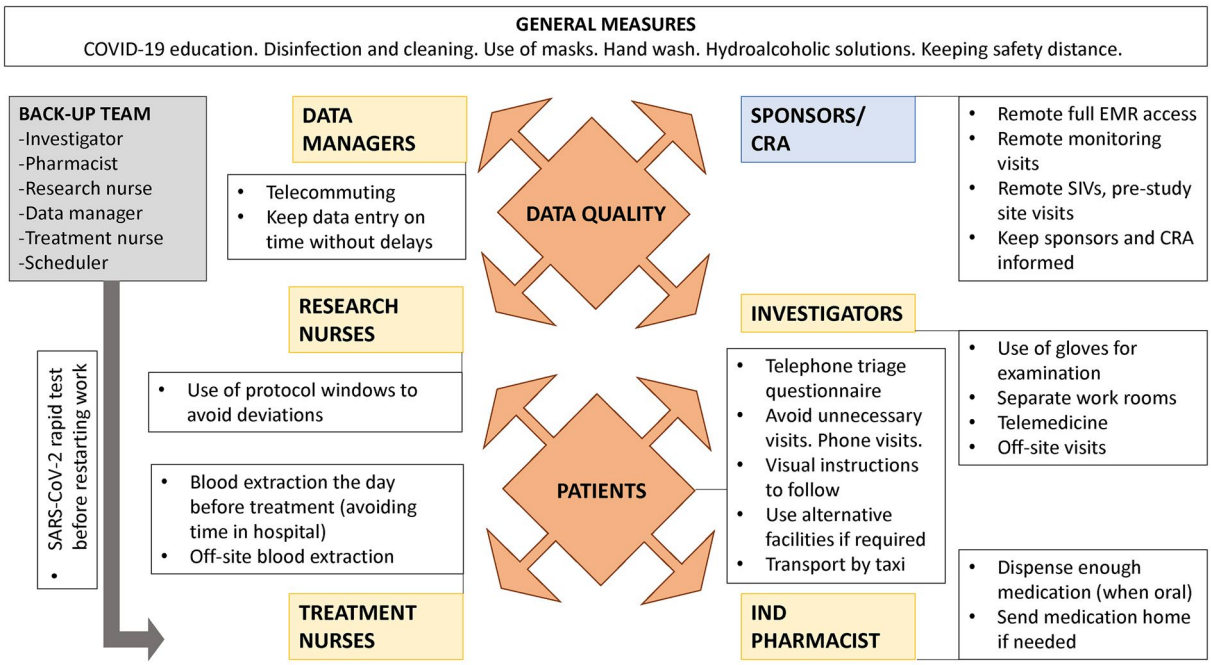

FIGURE 1. Representative diagram of the steps adopted to fight COVID-19 in a clinical research unit. COVID-19 indicates coronavirus disease 2019; CRA, clinical research associate; EMR, electronic medical report; IND, investigational new drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIV, site initiation visit.

in close contact with an infected person. Spaces have been optimized, physicians are not sharing working areas, and other staff members are having functional compartmentalization of their working spaces to avoid common exposure and intraprogram viral infection; all areas are being cleaned and disinfected twice daily by the cleaning services.

2. Patients. For patients coming to the clinic, telephone triage is being conducted the day before. When questioning about suspicious symptoms (eg, cough, dyspnea, fever, and anosmia) suggests an infection, patients are advised to stay home and ask for medical support or to go to the emergency room if needed to avoid spreading the virus among other patients or staff within the unit. Once they arrive, visual instructions are posted in key areas to instruct them about how to reduce risks, and a temperature check is performed immediately as a second previsit triage. All efforts are made to reduce their time at the hospital; therefore, protocol windows are being used to perform rapid blood tests the day before treatment in patient-free areas. In agreement with sponsors and study protocols, patients are being rescheduled to reduce their visits to the minimum extent, and transport by taxi instead of public options is being organized. Lastly, because trial participants may not be able to come to the investigational site for a protocol-specified visit because of logistics in the context of the national lockdown, alternative locations for assessments, including local laboratories and imaging centers, are being used if necessary and feasible after a sponsor's approval.
3. Clinical staff. Investigators have to ensure the safety of trial participants as well as the clinical study's integrity, so individualized decisions focusing on their potential impact need to be made. Patient examinations are performed with disposable gloves, and telemedicine or virtual visits are encouraged when possible for specific study visits that do not include treatment administration. Protocolled clinical follow-up visits and nurses' patient education visits are being made by teleconference or video conference when medication does not have to be administered. Moreover, we also suggest the possibility of organizing team groups composed of an investigator and a research nurse to perform domiciliary visits so that blood tests, pharmacokinetics, and medical examinations can be performed at the homes of patients if this is needed. In line with this and in collaboration with our investigational new drug pharmacists and sponsors, oral medications are being sent to patients when there are no other safety concerns.

4. Data management and sponsor cooperation. Changes in study visit schedules, missed visits, and patient delays may sometimes lead to missing information and safety challenges. In these cases, information is being captured to explain the reasons for missing data and the relationship with COVID-19 if this occurs. Remote-monitoring visits by sponsors and contract research organizations (CROs) should be promoted for the safety of sponsors and CRO workers. In particular, electronic medical record systems include comprehensive and complete software that permits offsite monitoring visits to obtain complete medical histories, including scanned source documents, to the same extent as on-site visits. In fact, in accordance with Spanish Medicines Agency recommendations, remote monitoring has been prioritized in agreement with sponsors and clinical research associates so that critical data entry is not delayed in this context. Similarly, data managers and data entry workers are eagerly encouraged to telecommute because their roles do not require them to be working in the same location as the patients are. Other visits, such as site initiation visits and prestudy site visits, are also arranged remotely, so we maintain the usual pace and quality of work during the crisis.
5. Backup teams. One of the major concerns is having enough active staff members in the different roles required for a CRU to ensure proper treatment delivery and study conduct as per study protocol. Thus, in the case of mandatory collective quarantine due to infectious exposure or close contact with a COVID-19–positive person, the establishment of an autonomous backup team to take over each role in the CRU, if needed, would secure continuity. Backup teams include the minimum personnel required to run the unit: a clinical researcher, a pharmacist, a research nurse or coordinator, a treatment nurse, a data manager, and a scheduler. Backup teams need to stay away from the hospital, be home-confined and work from home as feasible, and be replaced every 14 days (ie, the established quarantine period for this virus). Whether backup teams can be infected during their time away from the hospital or a rollover team can already be infected is a significant worry that is solved by the introduction of rapid anti–SARS-CoV-2 testing combined with clinical assessments of symptoms and signs of respiratory disease.
6. CRU staff COVID-19 diagnoses and decision-making implications. The Biopanda COVID-19 rapid test kit is a qualitative lateral flow immunochromatographic assay for the detection of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to SARS-CoV-2 in blood that has high relative sensitivity and specificity (88% and 96.7%, respectively, for IgM and 99.9% and 98.3%, respectively, for IgG [data not shown]). This cassette test allows for antibody detection within minutes on-site with high specificity and sensitivity and is cost-efficient. The use of this practical and convenient test, in combination with polymerase chain reaction (PCR) for uncertain results, allows the identification of those in an active, early phase of infection (IgM+ and IgG–) who need to be quarantined at home and those with a past infection (IgM– and IgG+) who are already immunized and, therefore, theoretically protected against the virus and are, so far, quarantine-free workers with additional value in this context of staff optimization.

The use of rapid tests for the CRU staff could have relevant consequences in different scenarios. The confirmation of an IgG+ status can allow staff members who are quarantined because of close contacts affected by COVID-19 to return to work. Also, when staff members have been confirmed to have immunity, backup teams can be discontinued, and work can continue normally. Finally, for staff members with symptoms, a rapid IgM+ diagnosis allows fast isolation (which decreases the risk of spreading) and replacement by the backup team. In this context, viral RNA testing might be performed by PCR for uncertain serologic results in symptomatic patients, but this testing is unable to detect a past infection, for which IgG testing is more informative; therefore, it is recommended to combine both types of tests, as needed, because the information that they provide is complementary.[7]

In our CRU, we have tested 58 of our workers (85%) with the rapid test. Fifteen of these workers (26%) had COVID-19–related symptoms such as fever, cough, myalgia, and anosmia. Within this subgroup, 11 staff members (73%) had serologic confirmation of exposure: 6 with a past infection (IgG+) and 5 with an active infection (IgM+ and IgG+). As for the asymptomatic employees, the majority (90.7%) had a negative test, however, 2 (4.7%) were IgM+ (...), and 2 more (4.7%) were IgG+ (Fig. 2).

The reliability of serologic testing, its sensitivity and specificity at different time points of the infection, and its cross-reactivity with other viral pathogens or antibody kinetics over time are not yet fully understood.[8] In general, the serologic test results for our staff members are plausible and agree with their symptoms, close contacts, and PCR results as well as the time frame, although follow-up rapid testing, which might provide further information,

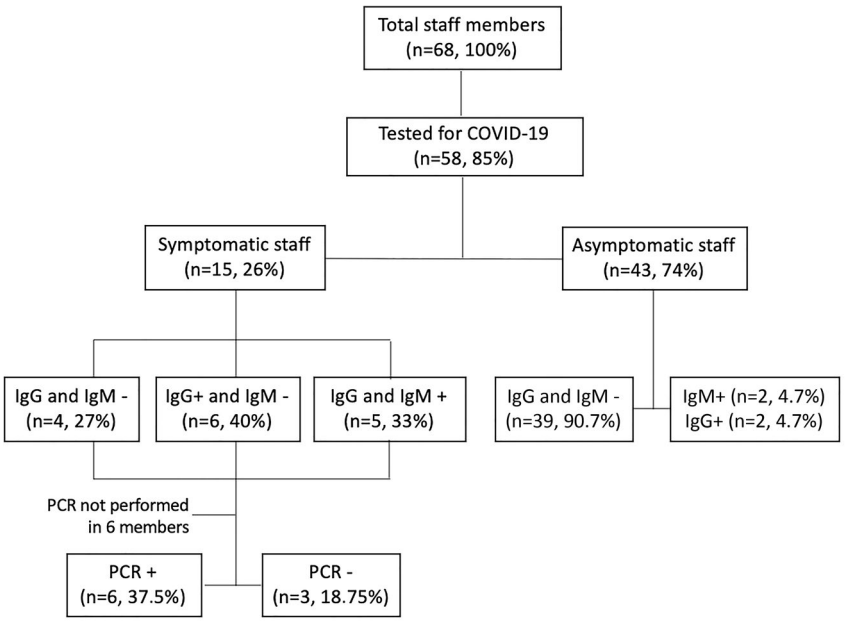

FIGURE 2. Flow diagram of COVID-19 detection results for staff members. COVID-19 indicates coronavirus disease 2019; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

is not being performed. In total, 15 members of our staff (22%) took a different practical approach in terms of safety and containment measures derived from these testing results.

With the implementation of all these measures (most of them feasible and reproductible), we have been able to treat patients and maintain active recruitment in our CRU while keeping safe our patients and staff members from our program as well as sponsors and CROs and ensuring the quality and good performance of the studies despite these current, very unfortunate circumstances.

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