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The Challenges of Urological Research in COVID-19 Era: Lessons Learned for Immediate Response to the Pandemic

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After being declared a worldwide pandemic by the World Health Organization (WHO) in March 2020, the "Coronavirus Disease 2019" (COVID-19) has had a significant impact on healthcare services in entire medical fields, including urology.[1,2] Despite development and widespread vaccine availability, COVID-19 and its emerging variants are still an evolving situation with more than 800,000 new cases per day in the United States at the time of this writing.[3] As part of the safety protocols, elective surgeries and in-person visits were restricted to decrease the chance of virus transmission and complication, and adapted guidelines released to minimize the risks for both patients and healthcare professionals delivering urological service.[4] The COVID-19 pandemic not only impacted the clinical practice but also other urological domains, including training and research.[5,6] COVID-19 transmission has interrupted the typical course of urological studies and trials such that numerous research projects have either been slowed down or come to a halt.

Along with the global impact of the pandemic on clinical research, we faced remarkable challenges in urological studies at our center, especially with conducting 2 large randomized surgical trials.[7,8] In this article, we aim to review some aspects of the global impact of COVID-19 on the research and share our experience at the University of Southern California (USC) with tackling COVID-19-related limitations in urological research.

GLOBAL EXPERIENCE

During the early phases of pandemic, numerous non-COVID-19 trials were suspended or stopped because of the difficulties in continuing under lockdown conditions.[9] The analysis of Medidata, including 5222 studies and 198,120 study-sites, showed a significant decline in the recruitment of clinical trials globally, with 65%, 79%, and 74% decrease in March, April, and May, 2020 compared to the same period a year prior to that.[6] This change was more prominent in oncology trials, with more than 80% decrease in number of recruited patients after the pandemic compared to the pre-COVID-19 era. In a study from Italy, complete or partial shutdown was reported in more than 80% of the oncology research activities during lockdown period.[10] This substantial interruption in cancer research was somewhat expected, given the immune system vulnerability of cancer patients that put them at significantly higher risk for COVID-19 infection and adverse outcomes.[11] The pandemic also generated significant challenges for surgeon-scientists conducting research. In a survey on the impact of COVID-19 on surgical research, the majority of the members from the Association for Academic Surgery and Society of University Surgeons have reported a decrease in research productivity, minimized personnel due to social distancing, and trial suspensions.[12]

In response to this public health emergency, several authorities tried to provide timely guidelines for healthcare providers and researchers. In March 2020, the Food and Drug Administration (FDA) issued a guidance, containing nonbinding recommendations on how to conduct clinical trials of medical products during COVID-19 pandemic. The goal of this guidance was to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency.[13] The last version of the FDA guideline, released in August 2021, provided more details in this regard, including answers to questions that FDA has received from stakeholders. The general recommendation was to re-assess clinical trials in a case-by-case basis to see if they should proceed using the pandemic-modified protocols or revert to pre-pandemic versions.

OUR EXPERIENCE AT USC

During the past almost 2 years, the "USC Office of Research" has announced COVID-19 research guidance,

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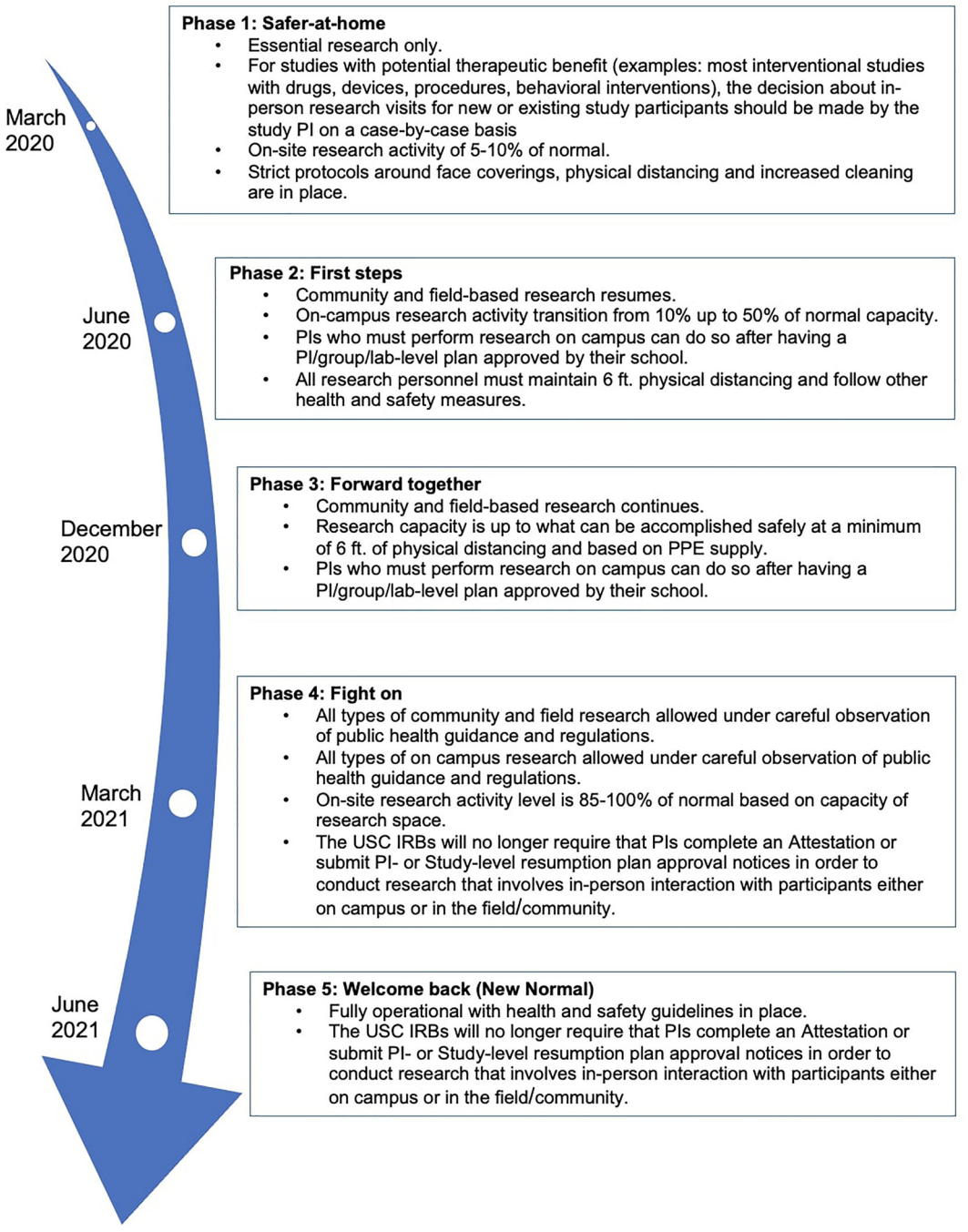

Figure 1. Summary of the USC guidelines for research ramp-up phases under COVID-19. PI: principal instigator; PPE: personal protective equipment. (Color version available online.)

describing different ramp-up phases based on existent conditions and public health guidelines (Fig. 1). This process initially started under very strict protocols, allowing for only therapeutic trials, yet eventually reached the point of returning to a "new normal" status. The aim of all these recommendations were to provide a safe environment for the researchers at USC in order to minimize the risk of infection or spreading the disease among the research team as well as study participants. Nevertheless, in this period of time, we have struggled with several challenges in performing our research studies and trials. Some of these challenges are still ongoing despite returning to the new normal. With the support of our research team and other colleagues, we tried to overcome each challenge through the following pathways.

1. Decreased number of procedures: During the COVID-19 pandemic, the number of elective procedures has been decreased significantly. Recommendation was set to prioritize the procedures by degree of urgency and postpone "non-essential" surgeries. Therefore, even some oncologic surgeries such as low-stage nephrectomies, low-risk cystectomies, and majority of radical prostatectomies were recommended to be postponed.[14,15] This resulted in a 68%-78% decrease in the procedures for benign

conditions, such as vasectomy, transurethral resection of the prostate and urodynamics as well as 43%-53% decrease in the oncological procedures, such as prostatectomy and radical cystectomy in the United States during the lockdown.[16]

To maintain our research productivity despite decrease in the number of surgical procedures, we swapped over the number of retrospective and data base-related projects, including multicenter studies (vs prospective studies and/or trials). Some of these studies were already published or presented at the regional and/or international meetings.[17-20]

2. Restrictions on the presence of staff, including research team, in the labs and/or office and/or operating room: During the first phase of research ramp-up, only 5%-10% of the normal on-site research activity was allowed (Fig. 1). Moreover, none of the research volunteers and undergrads did have the permission to attend in-person research activities. This caused several challenges in the process of study consenting, obtaining urine and/or blood and/or tissue specimens, and in-person data collection. To overcome this limitation, we asked the principal investigators, clinical fellows, and residents for further contribution in research projects. It is worth mentioning that we tried to maintain a balance in service over education and/or research to preclude burnout in urology team, especially in such a complex situation.[21]

3. Decreased number of in-person visits: Based on our institutional policy, there was a limit for in-person visits (either for clinical care, research interaction, etc.) while majority of visits converted to telemedicine (eg, video or phone calls), when possible. A retrospective analysis of urologic oncologic visits in our department from March to June 2020 (pandemic period) compared to the same weeks of 2019 showed a significant increase in the telemedicine visits (average weekly percentage change: +391.2%; P <.001), despite the significant decrease in the overall appointments (especially for new patients).[22]

Telemedicine has been implemented and adopted successfully in urology during the pandemic. According to the 2020 AUA Annual census data, 71.5% of urologists participated in telemedicine during the pandemic, with about 50% and 77% providing encounters for new and established patients, respectively.[23] A systematic review, including 45 urological studies has shown that telehealth can be implemented successfully in the management of some patients with prostate cancer, urinary incontinence, pelvic organ prolapses, uncomplicated urinary stones, and uncomplicated urinary tract infections.[24] We had a conventional experience with telemedicine, especially for patients who lived in long-distance or out of state regions. For the research purposes, telemedicine can significantly help with obtaining subjective information, including patient-reported outcomes (eg, quality of life, pad usage questionnaires) as well as para-clinical (laboratory and imaging) data. We found telemedicine as a feasible, effective, and cost-effective way for both initial counseling and follow-up visits, for both clinical and research purposes.

For the necessary in-person visits, all patients and/or research participants were asked to fill-out a COVID-19 screening questionnaire. During clinic visits or participation in research activities, all efforts were made to minimize the time that participants were exposed to other people. Participants in community- or field-based research activities were required to wear masks, stay a minimum of 6 feet apart, and use hand sanitizer prior to participating in research activities.

4. Prohibition of person-to-person consenting: Traditional paper-based consenting has been the most widely accepted form of authentication. Most of research studies, including majority of our trials, require in-person informed consenting. We believe that indirect consenting, such as electronic consent (e-Consent) or consenting through mail and fax could be considered as an appropriate alternative method.

Despite the known benefits of electronic consent (e-Consent) for research, there are still some concerns to adopt this method, including ethical, legal, and social issues as well as user interface/experience considerations.[25] Therefore, FDA has issued a guidance that provides recommendations on the use of e-Consent for human subject research.[26] In line with this, the "USC Office for the Protection of Research Subjects" states that "e-Consent and electronic signatures may be used if the procedures for obtaining them, and the vendor, are approved by the Institutional Review Board (IRB), and the risk of breach of confidentiality is minimized."[27] However, some consideration should be given when using e-Consent tool, including the ability of individuals to access and/or use the technology, the ability of the study team to verify the identity of the individual using the technology, the availability of the study team to answer questions, and security measures to ensure the privacy and confidentiality of information collected with the electronic technology.

During the pandemic, we included the option for e-Consenting in the protocol of our new projects. For our ongoing studies, we tried to obtain the consent in the clinic (ie, at the time of preoperative counseling) to avoid multiple in-person contacts and reduce the time of exposure to other people.

5. Decreased productivity: The final outcome of all aforementioned challenges is decreased productivity (eg, research proposals, obtaining grants, and publications) of the research team. We tried to maintain our research productivity through focusing on remote work (ie, manuscript and/or grant writing and data analysis), especially for those who were not able and/or not allowed to attend in-person studies.

REAL-WORLD EXAMPLE: FROM EXPERIENCE TO IMPLEMENTATION

In light of the national and institutional guidelines, all non-therapeutic trials (both oncologic and non-oncologic) were brought to a halt in our department after

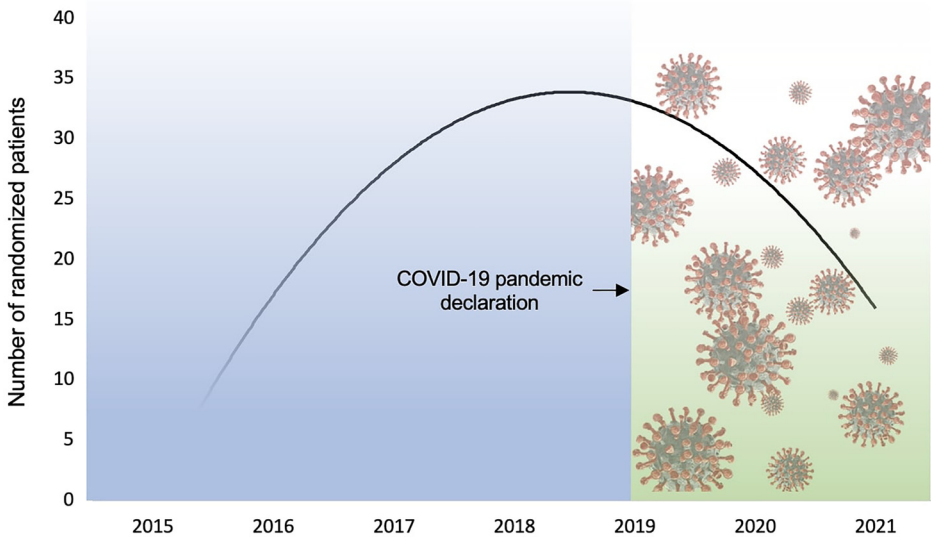

Figure 2. PUBMIC trial accrual trends in pre-covid and covid era. (Color version available online.)

declaration of COVID-19 pandemic. Even for the therapeutic trials, those that required in-person visits (for physical exam, blood sampling, etc.) were suspended. Nevertheless, we were able to continue our PUBMIC (Prophylactic Use of Biologic Mesh in Ileal Conduit) trial (ClinicalTrial.gov number, NCT02439060),[7] given the fact that it included bladder cancer patients undergoing radical cystectomy with curative intent. Yet, we faced major challenges in completing the recruitment and follow-ups of this trial. This trial started in early 2016, aiming to assess the efficacy of biological mesh to decrease the risk of parastomal hernia in patients undergoing cystectomy and ileal conduit. With regards to the recruitment, we witnessed a 50% reduction (24 vs 48) after the pandemic over the course of 12 months compared to the same period of time in pre-COVID-19 era (Fig. 2). In terms of follow-ups, however, we tried to replace the in-person visits with telemedicine. In addition, since the outcome of this trial was mainly focusing on "radiologic" parastomal hernia, we inquired the patients to perform imaging with their local facility and send them to our office for review. Despite the limitations, we were able to close the recruitment phase in May 2020 and achieve a more than 90% follow-up compliance rate.

We have leveraged our experiences in PUBMIC trial to mitigate the consequences of the COVID-19 pandemic on the participation and attrition rate for our other surgical trial at USC: "Robot-Assisted Radical Prostatectomy With or Without Vesicopexy in Patients With Prostate Cancer" (ClinicalTrial.gov number, NCT04981834).[8] We were able to capitalize on remote means to counsel patients, obtain informed consent, and collecting follow-up data. For the majority of our patients, we have tried to obtain informed consent by contacting them through telemedicine weeks in advance of their surgical appointment in order to properly counsel them on the nature of the trial and leave sufficient time to address their inquiries and concerns. Additionally, we have trained further medical staff to obtain consent from patients in clinic (when present) in order to take advantage of the minimal in-person presence for some of the patients in advance of their surgery. The modifications that we implemented in "vesicopexy" protocol helped us to have a satisfactory participation rate in this trial. In the initial 2 months of the trial, despite the new year's holidays and a surge in the COVID-19 cases, we were able to exceed 75% of the expected enrollment rate. Since the main outcomes of this trial are also "subjective" (ie, urinary continence and quality of life), we have been able to perform follow-ups thoroughly through telemedicine.

Table 1. Summary of our recommendations for urological research in the COVID era.

Recommendations
Renovate with retrospective and data base-related projects, including multicenter studies (vs prospective studies/trials).
Increase in the participation of PIs, clinical fellows, and residents in research projects
Use of Telemedicine (video and phone call visits)
Use of indirect consenting (ie, e-Consent, mail, fax)
Focus on remote work, meetings and brainstorming to keep up with manuscript writing, grant preparation, and data analysis

PI, Principal investigator.

CONCLUSION

COVID-19 pandemic has had significant impact on urological research studies and trials. Modifications in research process and study protocols can potentially help the researchers to overcome any unexpected obstacles throughout such challenging circumstances. Lessons learned and our recommendations to optimize urological research in the COVID-19 era is summarized in Table 1.

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