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Research during COVID-19

Rapid Adaptation of a Surgical Research Unit to Conduct Clinical Trials During the COVID-19 Pandemic

Juliet Emamaullee, MD, PhD, a,b,* Michael Bowdish, MD, MS, a,b
Pui Yuk Yan, MS, d Valentina Rodina, MD, MS, a and Linda S. Sher, MD a,b

a Department of Surgery, University of Southern California, Los Angeles, California
b Keck School of Medicine, University of Southern California, Los Angeles, California

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ABSTRACT
The coronavirus disease 2019 (COVID-19) pandemic has brought most ongoing clinical trials to a standstill, while at the same time emphasizing the need for new therapeutic treatments and strategies to mitigate the morbidity and mortality related to COVID-19. Recent publication of several observational studies has generated much discussion surrounding efficacy of drugs including hydroxychloroquine, azithromycin, and remdesivir, stressing the need for high-quality prospective, randomized control trials in patients with COVID-19. Ongoing "stay at home" orders and institutional policies mandating "work from home" for nonessential employees, which includes most research personnel, have impacted the ability to implement and conduct clinical studies. This article discusses the approach of an experienced clinical trials unit to make adjustments for ongoing studies and ensure the safety of study participants. At the same time, plans were implemented to continue collection of data to achieve endpoints, safely enroll and follow participants in studies offering potential benefit, and quickly implement new COVID-19 clinical trials. The existence of a Division of Clinical Research with regulatory, budgeting, contracting, and coordinating expertise within a department of surgery can successfully accommodate a crisis situation and rapidly adapt to new requirements for the safe, efficient, and effective conversion to a remote work force without compromising the research process.

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Background

Concerns over high transmissibility, an unknown burden of disease, variable clinical presentation, and mortality associated with coronavirus disease 2019 (COVID-19) have led to extensive, government-mandated "stay at home" orders since early March 2020, including all nonessential industries and employees. There has been a broad and dramatic reduction in clinical trial activity after implementation of these policies. Several factors have contributed to this acute decline in clinical research: avoidance of in-person encounters to promote study participant safety, efforts to reduce risk to research coordinator staff and comply with work-from-home orders, and strategies to minimize the unintended consequences of
COVID-19 infections on primary and secondary end points in ongoing studies. This has required a careful assessment of ongoing studies to determine if enrollment should be held or if enrollment should continue if there is a significant potential benefit to a participant. Furthermore, for studies with ongoing or newly enrolled participants, adjustments are required for safe follow-up for the participant and the study personnel.

In parallel, there has been a pressing need to develop and study new antiviral and anti-inflammatory medications and other interventions to treat the most serious clinical manifestation of COVID-19, severe acute respiratory syndrome of coronavirus-2. At the onset of the pandemic, there were no FDA-approved specific treatments for severe acute respiratory syndrome of coronavirus-2, and the subset of patients who develop this syndrome are highly contagious, require invasive ventilation, and experience significant mortality. With only a series of small observational studies reported, generating much discussion about efficacy, study design, and safety of medications including hydroxychloroquine, azithromycin, and remdesivir, among others, there was and remains an urgent need for infrastructure that allows for rapid implementation of high-quality, multicenter randomized control trials.

Recognizing the evolving challenges of the COVID-19 pandemic, the Division of Clinical Research in the University of Southern California Department of Surgery proactively implemented a strategic plan to address the needs of ongoing studies and redeploy our experienced clinical trials team toward COVID-related studies. In this article, we outline our approach to provide guidance to other institutions and promote timely and expanded efforts at implementation of COVID-19-related clinical trials and continue non-COVID studies in the setting of a pandemic.

Structure of a division of clinical research within a department of surgery

Clinical trials provide new drugs, devices, and treatment strategies with the ultimate goal of reducing the burden of disease. Regardless of the source of funding for clinical trials, specific resources are required to assure efficient and effective implementation and conduct of these studies. Depending on the investigator, sponsor, and/or institution, major limiting factors to participating in clinical trials include investigator experience, research staff expertise, institutional regulatory bodies, financial support, institutional resources, the available patient population, and cooperation among referring physicians and insurance companies.

The Division of Clinical Research in the surgery department was established in 2013 to provide a consistent foundation and support structure for the conduct of clinical trials within the department. Creation of the division involved pooling resources including existing coordinator staff from individual surgical investigators and required financial investment from the departmental leadership. By centralizing the clinical trials process within the department and under the guidance of an experienced chief and seasoned research team, the capacity for clinical studies has increased substantially while maintaining a stable number of study personnel (Fig. 1). The division was self-funded through industry and publicly funded study budgets within the first year of its creation. On average, the overall operational budget for the division is approximately $1,100,000/y.

The current team includes a physician division chief and associate chief, two regulatory and budget specialists, a 0.6 FTE biostatistician, a research nurse and eight study coordinators that each has expertise in specific clinical specialties and an ability to effectively provide coverage to other service lines, across a department that includes >100 surgical faculty. Importantly, the division offers 24 h/7 d a week coverage to guarantee that enrollment is efficient and that adverse event reporting can be completed according to federal, institutional, and sponsor requirements. The division has established and administered a general use tissue and blood biorepository for research endeavors.

The mission of the division is to provide infrastructure and oversight for the implementation and conduct of clinical trials in accordance with good clinical practice (GCP). The entire process is managed by the research team with oversight by the division chief and thus can accommodate less-experienced investigators willing to enhance their knowledge and activities in clinical research (Fig. 2). Goals include assuring the feasibility of each study before implementation through a thorough analysis of the patient population, participating physicians, institutional resources, and study budget. The team coordinates the site selection activities, institutional review board (IRB) application, budget preparations and negotiations, contract completion, purchasing agreements, committee approvals (biohazard, radiation therapy etc.), and coordination of various institutional departments (laboratory, radiology, operating room, etc.). Working closely with the IRB, contracting, and hospital-based approval committees and services has enabled the efficient implementation of clinical trials by surgery department investigators.

By the time of the site initiation visit, representatives of all areas of the hospital have been brought together to assure appropriate training. A primary and a backup coordinator are assigned to every study, and they work together to coordinate all details alongside the principal investigator (PI). Before the COVID-19 pandemic, twice-weekly team meetings were convened to review study progress, address any concerns, and discuss new amendments, reportable events, or regulatory issues to assure timely submission and resolution. A series of internal quality metrics have been monitored including time to activation, number of studies, number of PIs, patient enrollment, sponsor feedback, Food and Drug Administration audits, study reimbursement, and protocol adherence (i.e., number of deviations). We have also incorporated a biostatistician and established a relationship with our departmental data science group to further streamline data collection and analysis.

Adaptation to pandemic workflow and ongoing clinical trials

Work from home

Shortly after the first COVID-19-related death in Washington state in February 2020 and subsequent outbreak in the United...
States, the first COVID-19-related death in California was reported on March 4, 2020.6 Accepting that moving forward with ongoing clinical trial activity would be fraught with uncertainty, plans were immediately implemented on March 8 to prepare for social distancing before formal policy changes related the California stay-at-home order announced on March 16, 2020. Departmental administrators were requested to establish remote access to the electronic medical record, network drives, and virtual desktop environments for every team member on March 13, and all nonphysician personnel began working from home on March 16. These efforts were directed at the identification of the following areas that would require modification: minimization of direct patient care for routine study activities, logistics of research staff working

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**Fig. 1** – Annual growth of clinical trials activity and personnel in the Division of Clinical Research, Department of Surgery, USC. By integrating clinical trial activities into a single division, the capacity to take on additional trials increased substantially with a stable number of research personnel.

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**Fig. 2** – Structure and processes of the Division of Clinical Research, Department of Surgery, USC. In the COVID-19 pandemic, this infrastructure plan was harnessed to rapidly transition to COVID-19 clinical trials. (Color version of figure is available online.)
from home, and study-specific protocol deviations, enrollment pauses, and remote site monitoring visits (Fig. 3).

Communications

Before COVID-19, there were twice-weekly in-person meetings. Beginning on March 16, biweekly team meetings were changed to a daily virtual format, as a brainstorming and troubleshooting session to address issues in real time. To determine how to continue to follow ongoing study participants as well as to determine how to proceed with enrollment, each coordinator communicated with their study sponsors to obtain amendments outlining safe virtual follow-up, address potential protocol deviations, aspects of consent and enrollment criteria in the face of the COVID-19 pandemic. Research coordinators also contacted study participants to explain changes in study protocols and visits.

There was an urgent need from sponsors to accommodate remote monitoring of ongoing studies. Remote, HIPAA-compliant access to the electronic health records were provided to study monitors, and we provided instruction and oversight for remote electronic health records training capability for monitors who were not initially trained to use our system.

Management of study procedures in non-COVID-19 studies

PIs, sponsors, and the study team communicated to identify the subset of non-COVID-19 studies that would remain open to enrollment because of the potential benefit of access to investigational medications or devices for patient populations with serious or life-threatening conditions. The continuation of these types of studies was in accordance with institutional guidelines, which were reviewed frequently as plans evolved to gradually phase in more non-COVID-19 clinical studies. Divisional leadership participated in campus-wide task forces formed to develop and implement clinical research activity, and as a result, was able to communicate policy changes to the research staff during daily team meetings. Sponsors were highly responsive, providing amendments to allow for study adjustments, including suspension of enrollment when appropriate for a specific study, protocol modifications to allow for remote follow-up and designed for participant safety as well as to assure that data collection to achieve endpoints could be collected, and implementation of remote monitoring, etc. In response to the special needs for limiting contact, the IRB and Office for the Protection of Research Subjects implemented remote HIPAA-compliant consenting methods, which were included as amendments where appropriate. Over the last 2 wk of March, more than 50 protocol amendments were submitted to the IRB to address these issues. The IRB policy of rapid turnover of amendments related to COVID-19-related study adjustments resulted in expedited approvals and implementation of safety measures within days of submission.

Within our surgical research unit, high-priority studies were identified to continue or to start. These included provision of devices or drugs with a significant potential for participant benefit and new COVID-19 studies. Enrollment in many ongoing elective clinical trials was temporarily halted,
but participants already enrolled continue to be followed according to the individual study amendments. Furthermore, close contact has been maintained to assure the safety of the participants and timely reporting of any events. Organizational plans have been implemented for the continued enrollment and conduct of the studies managed by our team. These included the following measures:

1. Reallocation of study personnel on a voluntary basis to COVID-19 studies that might require occasional work at the hospital.
2. Study personnel asked to self-assess for risk factors to exclude themselves as volunteers for new COVID-19 studies.
3. Initially, nonphysician study personnel were not permitted to have direct patient contact and attendance in the hospital was only permitted in nonclinical offices adjacent to the hospital and not in patient care areas.
4. After proper education regarding of study staff pertaining to use of personal protective equipment and on a voluntary basis, study coordinators were permitted to enter the hospital and patient care areas but not to have direct contact with any patient diagnosed with COVID-19 or under investigation for COVID-19.
5. Use of personal protective equipment and daily screening of staff and participants has been in accordance with institutional policy and local regulations.

Communications were sent to the departmental faculty to notify them of the changes and to request that all new study patients be discussed with the division chief to determine the need for enrollment and to develop a plan for the safest conduct of the study.

Preparation and implementation of COVID-19 clinical trials

University of Southern California experience

The initial response of the clinical trials unit was designed to make appropriate safety adjustments for study personnel and study participants. Once a remote working process was enacted and found to continue to be efficient and effective, the additional and important benefits of our streamlined trial assessment and implementation process became apparent during discussions surrounding new COVID-19-related clinical trials.

The institution took prompt action in providing important recommendations and guidelines for research across the spectrum of clinical and laboratory-based research. A COVID-19 Scientific Merit Review Board, which included divisional leadership, was quickly instituted to guide investigators and coordinate COVID-19-related clinical trials. This was accompanied by institutional commitments for rapid IRB reviews of COVID-19-related amendments and studies and expedited contract completion with sponsors. Frequent and bidirectional communication with these entities has allowed for extremely effective collaboration.

The changes and adjustments that were made for the purpose of the departmental studies proved invaluable in preparing for and implementing COVID-19 trials. The organization described previously was also appropriate for these studies. In addition, the institution and IRB facilitated the ability to adjust the consenting process by permitting the following:

1. Implementing remote electronic and telephone consents for legally authorized representatives of incapacitated patients.
2. Developing nonpaper consents and HIPAA records to avoid maintaining potential fomites.

The potential impact on research personnel in the COVID-19 pandemic has created unique challenges. The PIs work closely with the study coordinators to assure that studies are conducted safely and in accordance with GCP. Direct patient contact only involves the caregivers already involved in the patient care who are educated in the administration of study drugs and sample collection. Study coordinators communicate throughout the process with all caregivers and have remote access to records to assure that all data are collected and that all serious adverse events are reported according to the sponsor, IRB, and Food and Drug Administration guidelines. The coordinators organize the various hospital services to conduct the study including but not exclusively, the pharmacy, laboratory, and imaging. All COVID-19 study-related activities are reviewed in the daily team meetings.

As an example of striving for efficiency, after receipt by the study team of documents for an NIH-funded randomized control trial, IRB approval was obtained within 1 wk. The team developed an organizational chart including remote tasks and on campus tasks and worked with various hospital services to prepare for the study. A safety plan was implemented for study personnel. All preparations were completed including contracting and site initiation within 4 wk of document receipt and screening began, with the first randomization occurring 2 d after study activation. Using this approach, our surgical research unit has enrolled >20 COVID + intensive care unit patients in studies over a 4-wk period.

Key considerations when conducting COVID-19 clinical research

Implementation of COVID-19 clinical trials in a pandemic setting presents many challenges and can overwhelm even an experienced study team. Based on our experience, the following are critical components to successful study implementation and enrollment:

1. Each institution should establish a mechanism of prioritization of studies as there may be studies that compete for a specific patient population. Some protocols may limit nonstudy protocol therapies and/or prevent future enrollment in new COVID-19 trials. We would recommend considering various cohorts based on the World Health Organization COVID-19 Ordinal Scale for Clinical
Improvement and creation of multidisciplinary teams to review these cohorts to determine study prioritization. 2.
2. The PI must be prepared to be engaged in study initiation, screening, enrollment, and conduct of the study including direct patient contact when required.
3. Mechanisms should be established for remote and electronic consents to prevent fomites related to paperwork.
4. Ancillary services including inpatient pharmacies, laboratory, and radiology must be engaged to assure that the study is feasible and to strategize implementation.
5. We do not permit our research coordinators to have direct patient contact. A study team with discrete roles for the PI and study coordinators allows for efficient enrollment and maintenance of data collection and event reporting. Specific roles and tasks should be designated for research staff as these are complicated and generate a great deal of paperwork.
6. The nurses in the various units should be educated so that they can work with the team to provide drugs and obtain data.
7. Plans for frequent troubleshooting and communication among divisional leadership and study staff should be implemented before activation.

**Moving forward with ongoing non-COVID clinical trials during a pandemic**

**Financial viability**

Although our division has been self-funded through ongoing activities, allowing for all salaries to be covered through the next academic year, the slow-down of “elective” research was expected to have an effect on our future financial viability. Several strategies will be required to maintain financial viability in the face of decreased enrollment, all aimed at preparing for the reopening of ongoing study activities, resuming enrollment, and activation of new studies. As part of our “work from home” team management, we have continued to set targets for IRB approvals, budgeting, and contracting that will allow new studies to start in a timely fashion when the institution has eased restrictions on research activities. At the same time, observational and registry studies that do not require close or frequent patient contact have continued with timely data entry into sponsor websites. Finally, research team members have been provided additional work from home activities, including data collection for investigator-initiated studies and pending grant proposals. To date, these adjustments have allowed for maintenance of financial viability and support for research staff. Over time, it will become more evident if and how this has been impacted.

Research staff were reassigned to accommodate the growing number of COVID-19 studies. In ongoing and new COVID-19 studies, PIs and divisional leadership have worked together to develop an organized approach to control coordinator exposures while assuring that studies continue in accordance with GCP. These studies are labor-intensive, and budgets should be designed to account for the increased time and effort required to complete them effectively. For departments and institutions that are unable to maintain financial viability, options include furlough, administrative leave, and even potential layoffs.

**Benefit of pandemic workflow modifications on future clinical research activities**

After nearly 3 mo of experience using our adapted organizational structure, several beneficial aspects of the modified workflow have emerged. Moving forward, we anticipate that personnel will maintain the option to work remotely when research activities do not require them to be on-site. Studies similar to the COVID-19 trials that involve rapid enrollment and time-intensive documentation will be assigned a coordinator team, rather than 1-2 individuals, to maintain enrollment capacity, data entry, and event reporting in a timely manner and avoid excessive overtime activity. Pandemic era study modifications including telehealth patient visits, screening of study participants for symptoms of infection before coming on site, and emphasis on hygiene and personal protective equipment, even in a post-COVID-19 world, will become routine.

**Conclusions**

The benefits of a dedicated clinical trials unit within a department of surgery include consistency, efficiency, timely study implementation, conduct in accordance with GCP, financial viability, and the ability to educate young investigators and encourage increased participation in clinical research. The value of this approach has been evident at our institution, as indicated by the increase in the number of studies, competitive enrollment, number of investigators, sponsor satisfaction, and financial solvency of the division. Most importantly, in a crisis situation, as we are experiencing with the COVID-19 pandemic, we have demonstrated that a dedicated clinical research team can quickly adjust to the new “normal”. Our approach has allowed surgical PIs to continue to efficiently manage study participants, enroll patients in beneficial studies, engage with sponsors, handle regulatory issues, and ultimately be prepared to swiftly implement new COVID-19 trials and continue ongoing clinical trials that predate the current pandemic.

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