Clinical Trials During a Pandemic

Alan Goldhammer, PhD[1]
Consultant in Drug Regulatory Affairs

The zoonotic coronavirus strain, SARS-CoV-2, has spread worldwide in just a few months after the December outbreak and detection in Wuhan, China. The World Health Organization declared this a pandemic and it is difficult to find a country that has not been affected. Presentation of this respiratory virus to a naïve population with no prior immunity is resulting in high levels of morbidity and mortality. Although mortality is markedly higher among the elderly who have ongoing health issues, no population segment has been spared.

Aside from traditional epidemiological approach of disease identification and isolation, two key medical interventions are a vaccine to immunize the population against the virus and/or development of new or repurposed FDA-approved drugs to treat the infection and consequent medical events brought about by disease progression when the person's immune system is inadequate. Vaccine development warrants a separate discussion. The focus here is on molecule identification and how rapid response clinical trials can be structured and run.

The SARS-CoV-2 genome was sequenced quickly and its entry into cells elucidated.[2] Early identification of potential drug targets include two targets from the host cell: angiotensin converting enzyme 2 and the host cell produced serine protease that primes the virus spike protein; and from the virus: the RNA-dependent RNA polymerase, the coronavirus main protease, and a papain-like protease. Other potential targets have also been identified through genomics and protein characterization

A variety of *in silico* tools[3] have been used to predict the structures of potential inhibitors and these have been used to screen the library of FDA-approved drugs and experimental drugs for which there is preliminary human safety data from Phase 1 trials. Well over 70 drugs have been identified from various *in* silico studies and they come from almost every therapeutic category. *In vitro* cell culture systems are being used to refine this target list and look for those molecules that inhibit viral replication at concentrations that are pharmaceutically acceptable.[4]

In a pandemic situation, promising therapies must enter clinical trials quickly. Prompt gathering and analysis of trial data will inform clinicians about what works and what does not. Within this system there also needs to be a mechanism that makes potentially useful therapies available on a compassionate use basis. These two issues were addressed in the early days of research on HIV antivirals. While that crisis did not have the large population impact in the United States as SARS-CoV-2[5], there were common issues of finding therapies that worked along with making such therapies available as clinical supplies permitted so that a broader population could be treated. The Department of Health and Human Services convened a working group consisting of patient activists, experts in clinical trial design, the Food and Drug Administration, NIH and industry who were developing the new drugs. There was broad agreement among all the parties that the clinical trial process should not be compromised as proven therapies for HIV infection were in everyone's interest. Compassionate use would be permitted broadly for drugs having Phase 1 safety data but could be curtailed if there was evidence that it limited the availability of patients for clinical trials.[6]

The situation that society is facing today with SARS-CoV-2 is similar, but it appears that some of the lessons learned from the HIV drug development experience have been lost.[7] A patchwork group of trial sites is highly inefficient, yet that is what is presently in place. From the early data in Wuhan, we know that SARS-CoV-2 differentially affects the population by age, sex, and co-morbidity. Older patients with other health complications are frequently hospitalized, develop pneumonia which may or may not be impacted by cytokine storm.[8] This requires a multi-pronged clinical trial approach; patients must be stratified by clinical symptom as therapies for associated SARS-CoV-2 pneumonia are unlikely to be the same as treatments of mild infections designed to prevent serious progression. An IV administered drug will not be optimal for treating community symptoms. The therapeutic approach to HIV treatment demonstrated that a combination of drugs may be required to successfully treat patients. SARS-CoV-2 may require the same approach. Registered clinical trials have used this approach judging by result pre-prints and registered trials currently enrolling.[9] Unfortunately, there appears to be an over-focus on hydroxychloroquine with and without azithromycin.[10] This may result in some valuable therapies either not being studied or their path towards complete evaluation slowed down from a lack of patients in the trial.[11] The long half-life of hydroxychloroquine means that prospective clinical trial patients for other therapies might be disqualified after taking a small multi-day dose of this medicine.[12]

A pandemic calls for urgent action with quick decision making. In particular, a priority would be identification of a prophylactic therapy for healthcare workers and other first responders. The recent announcement of a public-private partnership to speed COVID-19 vaccine and treatment options came out on April 17.[13]

The following schema is but one approach to accelerating the development of SARS-CoV-2 therapies.[14]

The operation of program should be high level and centralized with the ability to make quick science-based decisions. The program is flexible and can adapt to new findings of the pathophysiology of the virus.[15] There would still be opportunities for small individually conducted clinical trials as not every clinical trial site is expected to be part of the centralized approach.

1. Multi-center clinical trials are essential; this can be done by setting up a linked set of geographically separated pandemic trial sites. Multi-center sites have been used by the National Cancer Institute as well as the National Institute for Allergy and Infectious Diseases. The United States has many clinical research institutions that can be organized into a massive trial infrastructure. This increases the total pool of patients affected by SARS-CoV-2 allowing statistically relevant trials to be designed, promptly carried out and analyzed. This is especially valuable in early stages of the pandemic when no one site may have enough patients for a given drug trial.[16] Although a world-wide approach might be desirable, the time spent organizing such an effort may cause inadvertent delays.[17] Linkage to foreign trial sites is important but not at the expense of slowing down research.
2. Protection of research subjects cannot be compromised, but rather than increase bureaucratic complexity, a Central IRB should be constituted for this purpose.[18] Meetings via teleconference can substitute for in person and each drug trial might warrant its own ‘sub-central IRB’ depending on whether special issues are posed. It goes without saying that IRB decisions must be made quickly. The goal is to reduce bureaucracy and while individual institutions desire to use their own IRBs is understandable, it is not appropriate for time sensitive research in a pandemic. Existing FDA regulations permit the use of Central IRBs and should be used.

3. A central Data Safety Monitoring Board(s) shall be established for the trial of a respective drug or combination drug. Looking at the data across multiple trials sites for emerging safety and efficacy signals can be facilitated this way.
4. Data collection must be collected electronically and uploaded promptly so that it can be centrally aggregated and analyzed. This requires common case report forms and data fields used across all data sites. The pharmaceutical industry routinely sets up automated systems to accomplish this in a scalable manner.[19]
5. A policy needs to be in place to inform trial sites about discontinuation or expansion of specific trials. Well defined criteria for decision making should be established.
6. Repurposed drugs (e.g., those already approved by the FDA) or experimental for which there is Phase 1 safety data can be entered in clinical trials with ample evidence to support the rationale for treatment. It is recognized in a zoonotic viral outbreak, a suitable animal model(s) that mimics humans may not exits and reliance on appropriate *in vitro* tests will have to substitute.[20] *In silico* studies are not sufficient to support entry into clinical trials.
7. A plan to use observational medical data should be part of any pandemic plan. Observational studies can be useful in identifying drugs that may be protective against the virus or progression to more serious post infection illness.[21] A drug or combination therapy may have prophylaxis benefits but have less or even no utility when the virus is firmly entrenched in the host.[22]

---

[1] Dr. Goldhammer is retired from the Pharmaceutical Research and Manufacturers of America (PhRMA) where he was Vice President for Science and Regulatory Affairs. While at PhRMA he managed the organizations drug safety and regulatory affairs activities. In 2005 he started on the planning committee and was the project manager for Observational Medical Outcomes Partnership (OMOP). After several years of productive research OMOP activities reorganized into the Observational Health Data Sciences and Informatics (or OHDSI, pronounced "Odyssey"). This program is a multi-stakeholder, interdisciplinary collaborative whose goal is to bring out the value of health data through large-scale analytics (https://ohdsi.org/).
Financial Disclosure: Dr. Goldhammer has equity investments in Johnson & Johnson and Merck.

[2] There have been numerous papers on mechanisms of viral docking and entry. A good general article on illness progression is here: https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes# and a more specific paper on receptor binding by Yan and colleagues is here: https://science.sciencemag.org/content/367/6485/1444

[3] *In silico* refers to computer modeling to examine the binding of molecules to various viral proteins. There are a number of software approaches and they yield slightly different results depending on the assumptions that are used to measure binding. One of the more extensive efforts was by Gordon and colleagues who developed a protein-protein interaction map revealing potential drug targets for FDA approved drugs and investigational compounds that have early stage human safety data:
https://www.biorxiv.org/content/10.1101/2020.03.22.002386v3

[4] The combination of *in silico* and *in vitro* studies is elegantly described by this large multidisciplinary group: https://www.biorxiv.org/content/10.1101/2020.04.16.044016v1 Importantly, they found a number of compounds demonstrating good *in vitro* activity at pharmacologically reasonable doses.

[5] Early on there was uncertainty about the mode of transmission of HIV that caused public concern. HIV infection remains a public health problem in a number of developing countries.

[6] Dr. Goldhammer had the privilege of serving on this work group as one of the industry representatives. The policy was announced in April 1992, "Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and Other HIV-Related Diseases." 57 Federal Register 13250.

[7] Treatment guidelines from the National Institutes of Health were not issued until April 21. This was an important document as it reinforced that there are no proven therapies for SARS-CoV-2 and that unproven drugs should not

be given for either pre- or post-exposure prophylaxis. Whenever possible drugs for treatment should only be given as part of a clinical trial so that data on effectiveness and safety can be collected.

[8] There have been numerous preprints from China and Italy on the breakdown of morbidity and mortality by age, sex, blood type, and co-morbidities. Experience from two New York City hospitals mirrors this: https://www.nejm.org/doi/full/10.1056/NEJMc2010419?query=featured_home

[9] It is difficult to provide synopses for much of this effort. Dr. Goldhammer has been reviewing select clinical trials and results for a daily newsletter. Those reports are archived at: https://agoldhammer.com/covid_19/

[10] A survey of registered clinical trials, points to 145 trials of hydroxychloroquine with and without azithromycin (there are a small number of other pharmaceuticals that are being looked at in combination with hydroxychloroquine) out of 750 total trials. Data was gathered from https://clinicaltrials.gov/ on April 22. A number of these trials are at foreign locations and the total number of patients enrolled is not fully known.

[11] China have closed two remdesivir trials because of lack of patients.

[12] Following a single 200 mg oral dose of PLAQUENIL to healthy males, the mean peak blood concentration of hydroxychloroquine was 129.6 ng/mL, reached in 3.26 hours with a half-life of 537 hours (22.4 days). In the same study, the plasma peak concentration was 50.3 ng/mL reached in 3.74 hours with a half-life of 2963 hours (123.5 days). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf FDA's issuance of an Emergency Use Authorization for chloroquine and hydroxychloroquine may have had the undesired effect of making these drugs standard of care in community settings: https://www.biocentury.com/article/304779

[13] Foundation for the National Institutes of Health (FNIH) press release: https://fnih.org/news/press-releases/nih-launches-partnership-to-speed-covid19-vaccines-treatments PhRMA brought two projects to the FNIH: a consortium on biomarkers and OMOP (cited in footnote 1). Both projects were initially planned by industry representatives within PhRMA and then brought to other stakeholders for further input and refinement. FNIH served as a third party that could involve multiple stakeholders from industry, academia and the FDA. Startup time for each project was lengthy and perhaps not a good model for this new FNIH effort to follow.

[14] This schema addresses the recently published critique by London and Kimmelman who argue against pandemic research exceptionalism: https://science.sciencemag.org/content/early/2020/04/22/science.abc1731

[15] The observation of large vessel strokes in young adults coupled with abnormal clotting in older patients suggests a role for anti-thrombolytic therapy in certain patients: https://www.medscape.com/viewarticle/929345

[16] It is also a potential difficulty as infections rise and a variety of different drugs need to be tried. Current examples are trials on losartan and valsartan that may have protective properties. There are only a small number of sites conducting these trials and whether there is sufficient patient enrollment to gather data in a timely manner is unclear.

[17] There needs to be a linkage to other nations affected by the pandemic with mechanisms to share information.

[18] PhRMA worked with FDA in the early 2000s to create a workable model for how Central IRBs might be employed. FDA Guidance on this matter is at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/using-centralized-irb-review-process-multicenter-clinical-trials

[19] In 2002, a PhRMA committee hosted a presentation from Pfizer clinical IT staff members who demonstrated the companies electronic clinical trial platform. Everything from case report forms on was automated and electronically filed. They had research groups in England, the US and Australia so that critical drug development analyses could be done in 24-hour cycles rather than just during US work hours. There is ample industry experience in conducting and automating clinical trial data acquisition and analysis.

[20] It Is only recently that investigators described an animal model suitable for SARS-CoV-2 research: https://science.sciencemag.org/content/early/2020/04/16/science.abb7314

[21] OHDSI (referred to in Note 1 above) is in the process of setting up a population-level effect estimation study to examine the comparative effects of COVID-19 treatments called Project Sc(y)lla: SARS-Cov-2 Large-scale Longitudinal Analyses. April 23 note at: https://www.ohdsi.org/covid-19-updates/

[22] Two HIV combination drugs: emtricitabine/tenofovir or lopinavir/ritonavir were identified as early candidates for SARS-CoV-2 therapy. Cao and colleagues showed that lopinavir/ritonavir did not provide a treatment benefit in adults hospitalized with severe COVID-19. New England Journal of Medicine: https://www.nejm.org/doi/full/10.1056/NEJMoa2001282 Looking across data sets of patients diagnosed with SARS-CoV-2 in New York City may provide an ample enough patient population to detect possible prophylaxis protection of this and other drugs (losartan and valsartan which are already in clinical trials) that may have utility. Clearly, such usefulness will have to be tracked in a trial study to confirm the observational finding.