Perspective

CLINICAL TRIALS

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Clinical trials in the time of a pandemic

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Abstract

The first rumblings about a new coronavirus spreading in China were heard in January 2020. By the end of that month, the World Health Organization, recognizing the severity of the disease and the potential for global spread, had declared a public health emergency. By February 2020, cases had been identified in multiple countries, clinical trials of treatments with some biological plausibility had begun in China, and the initial steps of vaccine development were underway. In mid-March, by which time countries around the world were experiencing rapidly increasing numbers of cases and deaths, the World Health Organization categorized the outbreak as a pandemic. This new coronavirus was designated SARS-COV-2 in recognition of its similarity to the coronavirus responsible for the severe acute respiratory syndrome outbreak in 2002–2003. The race is on to develop treatments that can mitigate the severe consequences of infection and vaccines that can prevent infection and/or diminish the severity of disease in those who do get infected. Many challenges face these development efforts. Some are similar to those faced in the past; others are new. The urgency of finding ways to treat, and ultimately prevent, the consequences of this new and potentially deadly infection has led to unprecedented focus on clinical trials.

Keywords

Clinical trials, COVID-19, pandemic, treatment, vaccines

Writing about the evaluation of treatments and vaccines for an infectious disease in the midst of a pandemic is dangerous—things change from day to day. This is especially true when the infectious agent is new, one we are experiencing for the first time.

We have faced a number of frightening outbreaks in recent years: HIV (1981–now), severe acute respiratory syndrome (SARS; 2002–2004), H1N1 influenza (2009–2010), and Ebola (2014–2015, 2018–2019). The COVID-19 pandemic is different from each of these in different ways. Unlike HIV, it is highly contagious and does not require sexual contact or contact with infected blood. Unlike SARS, infection may be transmitted by individuals who are asymptomatic, who may comprise a large proportion of those infected. Unlike H1N1 influenza, COVID-19 is more serious in older people and those with co-morbidities and has a higher mortality rate. And unlike Ebola Virus Disease, COVID-19 has become a global menace, not confined to a limited geographical region.

The clinical trials effort for COVID-19 got off the ground very quickly. Awareness of a potential pandemic did not arise until February 2020; by mid-April, over 70 agents had been registered with the Food and Drug Administration (FDA) for trials of potential treatments, and another 200 + agents were under discussion with the FDA. Nearly 1700 clinical trials (randomized as well as single-arm) had been registered on clinicaltrials.gov as of 23 May 2020.

Clinical trials face special challenges when the affected population is at high risk of death or a major morbid event. In contexts without proven, approved treatments, the challenges are particularly intense. Patients and their families often demand access to any treatment that shows promise of benefit and vigorously protest the concept of placebo-controlled trials. We have faced these challenges in the settings of advanced cancer, amyotrophic lateral sclerosis, and Duchenne muscular dystrophy, among others.[1]

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Infectious disease outbreaks create similar challenges when the disease caused by infection is serious and associated with substantial mortality. In the early days of the AIDS epidemic, AIDS activists protested the implementation of placebo-controlled trials, with particular ire directed toward trials of a drug intended to prevent AIDS-related blindness (ganciclovir),[2,3] but leaders of the activist movements soon recognized that well-designed, controlled trials would be the fastest way to determine what treatments actually worked.[4] During the West African Ebola outbreak of 2014–2015, it was not the patients as much as the humanitarian medical groups that resisted placebo-controlled trials of potential treatments, despite the fact that no treatment had been shown effective for this disease.[5] The desire to try something—anything—to save people who were horribly sick was understandable, but the result was that a number of inconclusive uncontrolled trials were done; one randomized treatment trial was initiated, but so delayed due to debates over the ethics and logistics that the outbreak waned, preventing that trial from yielding conclusive results.[6] It was not until the later outbreak in the Democratic Republic of Congo in 2018 that trials were able to be initiated early enough in the course of the outbreak to produce definitive (and thankfully positive) findings for two drugs.[7] (One vaccine trial using a novel ring cluster design did complete successfully[8].)

The COVID-19 pandemic is similar in some ways to the Ebola outbreak, but different in many others. Similarities include the lack of any known treatments or vaccines, the urgency felt by everyone involved to find effective treatments and vaccines, and the feeling on the part of many medical personnel that everyone must get a treatment, even if none had been proven to be safe and effective. These issues have undoubtedly created challenges for dealing with COVID-19. But there are many important differences. First, COVID-19 is a global threat, something that was feared with Ebola but fortunately did not materialize. Second, those countries initially hit hardest were in the "first world," meaning they have modern health care systems allowing for optimal supportive care, and modern communication systems, allowing information to be effectively transmitted. Third, because the coronavirus causing the pandemic is quite similar to those responsible for earlier outbreaks, a number of vaccine developers were able to quickly modify vaccine candidates for these earlier infections to fit the emerging SARS-COV-2 virus. Finally, the rates of serious infection and death for Ebola were much higher than those for COVID-19, with increasing recognition that many of those infected with this new coronavirus may not develop disease at all; this will complicate the effort to identify infected individuals, something that will of course be essential in evaluating vaccine candidates.

Evaluation of potential treatments

Clinical trials were initiated in China by February 2020. The trials were of varying designs and sizes; some were uncontrolled, some were controlled but open-label, and some were placebo-controlled. None of those reported trials have yielded definitive conclusions. By March, clinical trials were being initiated in the United States and other countries. Many of these trials were taking place at single institutions, but the NIH and the World Health Organization moved quickly to design and enroll into larger multisite trials.

Study designs

As in prior outbreak settings, there was some initial resistance to placebo-controlled designs, especially for the sickest patients. Drugs with some theoretical basis for having an effect on the virus were used; anecdotal reports of benefits fueled further interest. The most notable of these was hydroxychloroquine, a drug originally developed to treat malaria, currently used primarily for rheumatoid arthritis and lupus, but which was known to have some antiviral activity. Other drugs tried included the combination of lopinavir-ritonavir, a regimen used for HIV; plasma obtained from survivors of COVID-19; and high-dose vitamin C, all of which could be obtained without having received regulatory approval for treatment of COVID-19. Drugs with known antiviral activity and those with potential capability to prevent or diminish the "cytokine storm" that leads to some of the most serious sequelae of infection have been of greatest interest.

Randomized trials, however, were in fact initiated quickly. Some involved head-to-head comparisons of as-yet unproven treatments or compared different dose levels of an unproven treatment. For example, one study compared a 5-day versus a 10-day course of remdesivir and observed no difference in outcomes.[9] Unfortunately, similar outcomes in this type of design can only suggest that the regimens were equally effective or equally ineffective. Many trials undertaken by academic institutions have compared an investigational treatment in an open-label fashion to those receiving standard of care, with trials undertaken by pharmaceutical companies mostly incorporating a placebo control group.

Many trial sponsors have recognized the need to adapt to emerging findings. Because the disease is acute, and both recovery and death due to disease occur relatively soon after diagnosis, a follow-up period of 1–2 months is adequate to assess the clinical outcome of almost all individuals diagnosed with COVID-19. Additionally, because of the rapid spread of disease and the corresponding large number of individuals

being hospitalized, the potential population for clinical trials is quite large. Therefore, trials may be completed quickly, and positive results may suggest changes in other ongoing trials, such as modifying their control group to include the treatment newly identified as effective. Because of the ability to accrue quickly, some trials are evaluating multiple agents simultaneously, using designs that allow for dropping unpromising treatments and including newly emerging candidates.

Selection of endpoints

The mortality among people who are diagnosed with infection (who represent a subset of all infected, as it appears that many who are infected remain asymptomatic) is low enough that researchers have looked to earlier endpoints to evaluate treatment effects, especially in the less severely ill. Some studies have considered endpoints based on resolution of fever, resolution of or increased need for supplemental oxygen, or other markers of the disease. An ordinal scale approach, looking at outcomes ranging from full recovery to death, with intermediate categories based on outcomes like need for supplementary oxygen and need for mechanical ventilation, has been considered.[10] Because this type of endpoint requires a certain amount of clinical judgment and because many trials, especially those testing multiple regimens that may be delivered by different routes, are not conducted in a double-blind manner, other investigators have advocated using simpler outcomes that can be determined with less subjectivity. For example, an NIH-sponsored trial of remdesivir began with an ordinal endpoint, but partway through the trial changed to the endpoint "time to recovery," defined as the time the first of any of the following: not hospitalized; with no activity limitation; not hospitalized, some limitation and/or requiring home oxygen; and hospitalized but not requiring supplemental oxygen.[11] A large global trial mounted by the World Health Organization established mortality as its primary endpoint.[12]

Control groups

Unlike in the AIDS and Ebola outbreaks, there has been relatively little pushback on the use of placebo controls, probably because the vast majority of COVID-19 patients eventually recover—in the early days of AIDS the infection was anticipated to be uniformly fatal, and mortality due to infection with the Ebola virus was substantial. Some trials, particularly those in single centers, are being conducted with a "standard of care" control arm, typically when matching placebos cannot be readily obtained. Some trials are designed to adapt to early findings such that a treatment found effective would replace placebo or standard care as the control. In late April 2020, a large multicenter, multi-arm placebo-controlled trial sponsored by the National Institute of Allergy and Infectious Diseases announced that remdesivir had shown benefit on its primary endpoint of time to recovery (with suggestive but not definitive reduction in mortality) and that treatment became the control arm as the trial continued to study other treatments. Two other trials of remdesivir, one being carried out by its manufacturer Gilead and the other as part of a multicenter global collaboration sponsored by the World Health Organization, remain ongoing and may ultimately provide definitive evidence regarding remdesivir's effect on mortality.

Evaluation of potential vaccines

There is great interest in identifying a vaccine against SARS-COV-2. Many companies are studying candidate vaccines, some of which are being developed using novel manufacturing approaches that have not been used for any currently licensed vaccine. Because SARS-COV-2 is very similar in its molecular structure to other coronavirus such as SARS-COV-1 (responsible for the SARS outbreak in the early 2000s) and MERS (Middle East Respiratory Virus) for which some vaccine development work had already been done, vaccine researchers had a head start in looking for approaches to combat SARS-COV-2.

Vaccine developers face many important challenges, both scientific and logistical. First, we do not know whether people who have recovered from COVID-19 are protected against re-infection and future illness—and if they are, for how long. Most researchers speculate that there will be a period of protection, perhaps at least a year or two, but this is not known for certain at present. Second, we do not know what antibody level offers protection. Although it is clear that infected individuals do develop antibodies against the virus, these levels can vary substantially[13] and it is not clear whether there is some threshold that defines protection. Third, with multiple candidates possibly ready to go into field testing by late summer or early fall 2020, and given the continued emphasis on social distancing, wearing of masks, and so on even as stores and service providers begin to re-open, it is not clear that enough infections will occur to allow adequate efficacy assessment of all the vaccine candidates going into trials. Fourth, enough cases will need to be observed to assess safety, including the potential of the vaccines to enhance the disease symptoms, an issue that has been seen before with some vaccine candidates in other disease contexts[14] and which has been raised as a potential concern. Given that the proportion of those infected who ultimately die or suffer irreversible morbidity appears to be around 1%[15] (although it may be still lower since many of those infected remain asymptomatic and may never be

identified as having been infected), assurance of safety is particularly important.

Finally, once a vaccine candidate is shown to be safe and effective in phase 3 trials, there are two more hurdles. One aspect of vaccine development relevant to all new vaccines but of special relevance to vaccines manufactured using novel technologies is the need to demonstrate that the vaccine can be manufactured consistently from batch to batch. The FDA oversees the manufacturing process with meticulous care; stringent oversight of vaccine manufacture was put in place following the disaster with early polio vaccines whose flawed manufacturing processes resulted in many children contracting polio from the vaccine.[16] And once the manufacturing process is deemed satisfactory, there will be the challenge of producing enough vaccine to meet the demand, requiring not just the vaccine itself but the vials and syringes, at a time when the supply chain is under severe duress.

An alternative approach to evaluating a new vaccine is a "challenge trial," in which volunteers are vaccinated and then deliberately exposed to the virus to assess whether the vaccine is protective. Such trials have been done in other settings, including malaria, but never in a context in which the disease has potentially severe consequences and there is no known cure. While some have advocated for such an approach as a way to speed evaluation of efficacy,[17,18] others have questioned the ethics of such a trial and have argued that it would not necessarily accelerate the availability of a proven safe and effective vaccine.[19]

Some general issues

As of this writing, it is not clear how long this virus will continue to threaten global health. A possibility is that the infection rate will wane, possibly to the extent that ongoing trials (particularly the vaccine trials, as noted above) may not be able to complete successfully in the projected time frame. Such an experience during the West African Ebola outbreak in 2014–2015 has led to a proposal that for intermittent but regularly occurring outbreaks, a clinical trial that falls short of its projected sample size and/or primary events by the time the outbreak wanes should put the trial "on pause," and restart when infections begin to re-appear, rather than publishing a report with inconclusive data.[20] The World Health Organization's global trials of treatment and vaccine candidates have been designed under this model, which may be quite relevant currently since many expect recurrent waves of infections.

Another issue all trials will face is determining criteria for early termination, should emerging results appear either extraordinarily positive, highly unlikely to yield positive findings, or strongly suggestive of harm. The global urgency to identify effective treatments and vaccines has the potential to put a lot of pressure on data monitoring committees, trying to balance between making sure the data are reliable, and wanting to get potentially life-saving treatments to patients as soon as possible. Trial designers will need to give careful consideration to the criteria for early termination, to provide clear guidance to these committees as they review emerging results.

Final thoughts

The urgency to identify effective treatments and vaccines for COVID-19 has led to extraordinary efforts to design and mount clinical trials over an extremely short period of time, and to unprecedented levels of collaboration among governments, pharmaceutical companies, non-governmental organizations, and academic institutions worldwide. If the ongoing battle with COVID-19 has any silver lining, it may be to identify ways to make the process of drug and vaccine development more efficient and to be better prepared for the next global infectious disease pandemic.

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References

1. Blake V. The terminally ill, access to investigational drugs, and FDA rules. *Virtual Mentor* 2013; 15(8): 687–691.
2. Delaney M. The case for patient access to experimental therapy. *J Infect Dis* 1989; 159: 416–419.
3. Byar DP, Schoenfeld DA, Green SB, et al. Design considerations for AIDS trials. *N Engl J Med* 1990; 323: 1343–1348.
4. Ellenberg SS, Finkelstein DM and Schoenfeld DA. Statistical issues arising in AIDS clinical trials. *J Am Stat Assoc* 1992; 87: 562–569.
5. National Academies of Sciences, Engineering, and Medicine. *Integrating clinical research into epidemic response: the Ebola experience*. Washington, DC: The National Academies Press, 2017.

6. Ellenberg SS, Keusch GT, Babiker AG, et al. Rigorous clinical trial design in public health emergencies is essential. *Clin Infect Dis* 2018; 66(9): 1467–1469.
7. Mulangu S, Dodd LE, Davey RT, et al. A randomized, controlled trial of Ebola Virus Disease therapeutics. *N Engl J Med* 2019; 381(24): 2293–2303.
8. Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola Virus Disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet* 2017; 389(10068): 505–518.
9. Goldlman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Eng J Med*. Epub ahead of print 27 May 2020. DOI: 10.1056/NEJMoa2015301.
10. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020; 382(19): 1787–1799.
11. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19: preliminary report. *N Eng J Med*. Epub ahead of print 22 May 2020. DOI: 10.1056/NEJMoa2007764.
12. World Health Organization. "Solidarity" clinical trial for COVID-19 treatments, www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments (2020, accessed 24 May 2020).
13. Ni L, Ye F, Cheng M-L, et al. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. *Immunity* 2020; 52: 971–977.e3.
14. Smatti MK, Al Thani AA and Yassine HM. Viral-induced enhanced disease illness. *Front Microbiol* 2018; 9: 2991.
15. Basu A. Estimating the infection fatality rate among symptomatic COVID-19 cases in the United States. *Health Aff (Millwood)*. Epub ahead of print 7 May 2020. DOI: 10.1377/hlthaff.2020.00455.
16. Offitt PA. *The cutter incident: how America's first polio vaccine led to the growing vaccine crisis*. New Haven, CT: Yale University Press, 2005.
17. Eyal N, Lipsitch M and Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. *J Infect Dis* 2020; 221(11): 1752–1756.
18. Plotkin SA and Caplan A. Extraordinary diseases require extraordinary solutions. *Vaccine* 2020; 38(24): 3987–3988.
19. Branswell H. Infect volunteers with Covid-19 in the name of research? A proposal lays bare a minefield of issues. *STAT*, 1 May, https://www.statnews.com/2020/05/01/infect-volunteers-with-covid-19-in-the-name-of-research-a-proposal-lays-bare-a-minefield-of-issues/ (2020, accessed 31 May 2020).
20. Dean NE, Gsell PS, Brookmeyer R, et al. Creating a framework for conducting randomized clinical trials during disease outbreaks. *N Engl J Med* 2020; 382(14): 1366–1369.