COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES
SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT

HEARING CHARTER

Repurposing Therapeutic Drugs for COVID-19: Research Challenges and Opportunities

Friday, June 19, 2020
1:30 p.m. ET
Cisco WebEx

PURPOSE

The purpose of the hearing is to explore the scientific foundations behind repurposing existing drugs for the treatment of COVID-19. The Subcommittee will discuss how researchers identify and test approved drugs—developed for other uses—that could lessen the severity of COVID-19 symptoms and the regulatory approval process for the use of these drugs among infected patients. The Subcommittee will also explore how the Federal government conducts oversight and supports research in this area and how these processes have been affected by the current pandemic.

WITNESSES

- **Dr. Peter Lurie**, President, Center for Science in the Public Interest
- **Dr. James Finigan**, Director of the Respiratory Centers of Excellence, National Jewish Health
- **Dr. Rick Stevens**, Associate Laboratory Director for Computing, Environment and Life Sciences, Argonne National Laboratory
- **Dr. Benjamin Rome**, Associate Physician, Brigham and Women's Hospital; Postdoctoral Research Fellow, Harvard Medical School

KEY QUESTIONS

- How can existing FDA-approved drugs be used to treat COVID-19?
- How does the approval process for repurposed therapeutics differ from the traditional drug approval process?
- How should existing research and approval mechanisms be altered to meet the urgent need created by the ongoing pandemic?
- How can the Federal government support research into repurposing existing drugs that might not be profitable for industry?
- How have the Emergency Use Authorizations issued over the course of the pandemic adhered to best practices and the principles of scientific integrity?
- What are the challenges of conducting clinical trials during a pandemic?
- How can the Federal government incorporate clinical trial research into its broader pandemic planning and preparedness efforts?
- What opportunities exist for conducting low-cost outpatient trials of repurposed drugs that patients could take immediately after testing positive but prior to developing symptoms?

Background

There is no single drug or treatment plan that is reliably effective in combatting COVID-19.[1] There are many research efforts attempting to address this need, including the development of new drugs and CRISPR-based therapeutics, the use of convalescent plasma, and the repurposing of drugs that have been previously approved by the Food and Drug Administration (FDA) to treat other diseases. This hearing will primarily focus on the potential to repurpose drugs that have been deemed safe and effective for other diseases.

More than 2,000 studies addressing various aspects of COVID-19 are registered on ClinicalTrials.gov, including almost 50 federally funded clinical studies.[2] Many of these trials are directed at treatment, and the results of numerous trials involving therapies will be reported over the next few weeks and months.[3] It is vitally important that these study results are interpreted and presented clearly, and appropriately communicated to clinicians, the public, and policymakers.

Conducting Clinical Trials for COVID-19 Therapeutics

Large randomized, placebo-controlled trials are the ideal way to determine whether a drug is safe and effective at treating COVID-19. These are prospective studies that reduce bias and provide a rigorous tool to examine cause-effect relationships between an intervention and a health outcome.[4] Unfortunately, these types of trials are expensive, and private industry tends to fund clinical trials that promise to reap financial rewards. Shrinking Federal funding has made industry an important source of research; however, companies with financial interests in studies have more control over what doctors and patients learn about new treatments.[5]

During COVID-19, it seems that numerous, small stand-alone trials and observational studies of single treatments or interventions have grown, in part due to uncoordinated clinical research.[6] Some fear that so many trials have launched in response to COVID-19 that this could actually prevent studies from producing useful results — either because some may be potentially redundant or because each study does not involve enough patients to reach accurate conclusions.[7]

Clinical trials are much more difficult to conduct during pandemics. Researchers, institutional review boards, and regulators are accustomed to developing trial plans over months, not weeks.[8] Healthcare workers and trial coordinators must collect detailed data at regular intervals; this is

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[1] "Treatments for COVID-19," Harvard Health Publishing, Updated June 5, 2020, accessed here: https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19

[2] See https://clinicaltrials.gov/ct2/results/details?cond=COVID-19.

[3] Howard Bauchner and Phil Fontanarosa, "Randomized Clinical Trials and COVID-19: Managing Expectations," *JAMA*, May 4, 2020, accessed here: https://jamanetwork.com/journals/jama/fullarticle/2765696.

4 Eduardo Hariton and Joseph J. Locascio, "Randomized controlled trials—the gold standard for effectiveness research: Study design: randomized control trials," *BJOG*, Vol. 125(13):1716, DOI: 10.1111/1471-0528.15199, December 2018, accessed here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6235704/.

[5] Meredith Cohn, "Industry funds six times more clinical trials than feds, research shows," *Baltimore Sun*, December 15, 2015, accessed here: https://www.baltimoresun.com/health/bs-hs-trial-funding-20151214-story.html.

[6] Hans-Georg Eichler, et al, "Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?" *Clinical Pharmacology & Therapeutics*, DOI: https://doi.org/10.1002/cpt.1891, May 14, 2020, accessed here: https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1891.

[7] Zachary Brennan, "The latest obstacle in the search for a coronavirus treatment: Too many drug trials," *Politico*, April 30, 2020, accessed here: https://www.politico.com/news/2020/04/30/coronavirus-drug-treatment-trials-227508.

[8] R. Kiplin Guy, et al, "Rapid repurposing of drugs for COVID-19," *Science*, Vol. 368, Issue 6493, pp.829-830, DOI: 10.1126/science.abb9332, May 22, 2020, accessed here: https://science.sciencemag.org/content/368/6493/829.

harder when they lack adequate personal protective equipment and their workloads are already stretched thin.

Recruiting patients can also be challenging; even under ideal settings, trials can fail due to a lack of patient enrollment. An early explosion of cases followed by a steady decrease means that the recruitment window remains open only for a small amount of time. During the 2014-2016 Ebola outbreak in West Africa, for instance, the National Institutes of Health (NIH) was forced to cancel a trial of a promising therapeutic after the outbreak's decline made it impossible to find enough participants.[9]

In addition, physicians at trial sites that evaluated Gilead's remdesivir in Boston, New York, and Atlanta faced barriers to recruiting minority patients in clinical trials. Some of the sites working on the NIH-funded trial said that they did not receive consent forms for the study in Spanish.[10] To avoid wasting personal protective equipment, physicians working with translators had to call into the COVID-19 patients' rooms instead of being at the bedside. Some of the researchers said that explaining the study and getting consent took up to four hours, per patient.[11]

Researchers argue that *"for every week that trials do not deliver, more and more patients are exposed to the wrong treatments, which well-designed and rapidly run clinical trials could have taken off the table, making space to pursue, other, and ultimately more meaningful, therapeutic options."*[12] Without coordinated clinical research, well-funded scientific infrastructure, and reasonable regulatory flexibility and oversight, our efforts to find treatments for COVID-19 will be delayed.

Larger "platform" trials, like the World Health Organization's Solidarity clinical trial, facilitate the comparison of multiple treatments and approaches within a trial and across trials.[13] The FDA could encourage researchers to leverage "master protocols" that allow them to test multiple potential COVID-19 therapies at once.[14] However, the FDA does not have the power to coordinate trials—only to approve their design based on safety and efficacy criteria.[15]

FDA Approval for Repurposed Therapeutics

Developing COVID-19 therapeutics by repurposing approved drugs used for other illnesses takes advantage of existing information to enable rapid clinical trials and regulatory review.[16] Researchers can screen numerous drugs at one time, testing whether they may have an

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[9] During a subsequent Ebola outbreak in 2019, the NIH was able to generate enough clinical evidence to show that the therapeutic was ineffective. Zachary Brennan, "The latest obstacle in the search for a coronavirus treatment: Too many drug trials," *Politico*, April 30, 2020, accessed here: https://www.politico.com/news/2020/04/30/coronavirus-drug-treatment-trials-227508.

[10] Zachary Brennan, "Hit hard by the coronavirus, minorities find access to potential COVID-19 drugs via hospitalizations," *Politico*, May 20, 2020.

[11] *Id.*

[12] Hans-Georg Eichler, et al, "Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?" *Clinical Pharmacology & Therapeutics*, DOI: https://doi.org/10.1002/cpt.1891, May 14, 2020, accessed here: https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1891.

[13] *Id.*

[14] Stephen Hahn, Peter Marks, and Janet Woodcock, "The Path Forward: Coronavirus Treatment Acceleration Program," FDA, April 20, 2020, accessed here: https://www.fda.gov/news-events/fda-voices/path-forward-coronavirus-treatment-acceleration-program.

[15] Zachary Brennan, "The latest obstacle in the search for a coronavirus treatment: Too many drug trials," *Politico*, April 30, 2020, accessed here: https://www.politico.com/news/2020/04/30/coronavirus-drug-treatment-trials-227508.

[16] R. Kiplin Guy, et al, "Rapid repurposing of drugs for COVID-19," *Science*, Vol. 368, Issue 6493, pp.829-830, DOI: 10.1126/science.abb9332, May 22, 2020, accessed here: https://science.sciencemag.org/content/368/6493/829.

unexpected potential to fight the SARS-CoV-2 virus, and then narrow down a list of the most promising candidates.[17] Preclinical testing can move faster since scientists already have a general understanding of these drugs' toxicity, efficacy, and safety information.

When the FDA approves a drug for a particular purpose, it allows the company selling the drug to label and market it for that purpose. These approvals are made after the company submits sufficient evidence that the drug is safe and effective. *In vitro*, or "test tube" tests, and animal studies provide mechanistic information, giving preliminary evidence that the drug has the intended effect on the virus being studied. Companies then use this information to apply for FDA approval to move into clinical trials. These consist of three phases of testing, where controlled experiments are done on increasingly larger populations to determine the safety and efficacy of the drug.[18] The FDA's Center for Drug Evaluation and Research (CDER) then reviews the information submitted by pharmaceutical companies and determines whether the demonstrated benefits of the drug outweigh any demonstrated risks.

When a drug is finally granted FDA approval, a company has received permission to market it for the specific indications that were tested and reviewed by the FDA. However, physicians are legally permitted to prescribe drugs for off-label purposes that have not been studied by the company or approved by FDA.[19] In order for an approved drug to be labeled and marketed for another purpose, the same clinical trial process must occur. Safety trials can typically be expedited, due to the drug's prior clinical trials, but key questions must still be answered. The population taking the drug for its labelled use might be entirely different than the population that would take it for COVID-19 treatment. For example, there exists a wealth of information in the FDA's safety database on the benefits and risks of taking hydroxychloroquine for lupus or arthritis. However, patients sick with COVID-19 may be older and sicker, and the disease may have compromised organs that tend to be healthy in the typical lupus or arthritis patient. Thus, CDER's risk-benefit calculation – the determining factor for FDA approval – is fundamentally different when the drug is applied to a different disease in a different population. For example, a higher level of risk might be acceptable for a deadlier disease; or, if a drug is less effective on COVID-19 than it is for its approved use, its toxicity levels may be deemed unacceptable given the only marginal benefit.

Numerous drugs are currently being tested for their effectiveness against COVID-19. Most notable are hydroxychloroquine and chloroquine, which have been FDA-approved as anti-malarials[20] and have scientific support for several off-label uses; remdesivir, an antiviral that currently has no FDA-approved uses;[21] and famotidine, an over-the-counter heartburn

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[17] Carl Zimmer, "Old Drugs May Find a New Purpose: Fighting the Coronavirus," *New York Times*, May 1, 2020, accessed here: https://www.nytimes.com/2020/04/30/health/coronavirus-antiviral-drugs.html.
[18] "Development and Approval Process | Drugs," U.S. Food and Drug Administration, accessed here: https://www.fda.gov/drugs/development-approval-process-drugs
[19] Rebecca Dresser and Joel Frader, "Off-Label Prescribing: A Call for Heightened Professional and Government Oversight," The Journal of Law, Medicine, and Ethics, Fall 2009, accessed here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2836889/
[20] "Plaquenil," U.S. Food and Drug Administration, accessed here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf
[21] Andrew Joseph, "As the coronavirus spreads, a drug that once raised the world's hopes is given a second shot," Stat News, March 16, 2020, accessed here: https://www.statnews.com/2020/03/16/remdesivir-surges-ahead-against-coronavirus/

medication.[22] Remdesivir has been granted an Emergency Use Authorization (EUA) for the treatment of COVID-19, based on preliminary clinical trial results.[23]

Emergency Use Authorizations

The Secretary of Health and Human Services (HHS) has the authority to grant EUAs to facilitate the availability of medical products during public health emergencies. This allows the Federal government to provide state and local governments with medical supplies through the Strategic National Stockpile. HHS can grant EUAs to unapproved drugs, or to off-label uses for drugs. A public health emergency must be declared in order for HHS to issue EUAs, and the EUA elapses once the public health crisis has concluded.[24]

The standards for granting an EUA are much lower than the standards for FDA approval of a drug. The FDA may issue an EUA if "it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition."[25] There are no public hearings held to solicit comment as there would be in a drug approval process, and only a few senior FDA officials might review the EUA, rather than a number of FDA staff and scientists.[26]

Hydroxychloroquine

On March 28, the FDA issued an EUA for hydroxychloroquine and chloroquine, anti-malarial medications that have been approved for use in lupus and arthritis cases. Chloroquine has shown anti-viral properties in various *in vitro* tests, and it has been proposed as a treatment for numerous diseases, including SARS, Ebola, dengue, Zika, and chikungunya. However, in animal studies, chloroquine was not effective in combatting these viruses, and in some cases exacerbated the diseases.[27] Hydroxychloroquine and chloroquine entered the COVID-19 conversation in March, when various media outlets began reporting on the drugs' potential antiviral properties, and a French paper was published suggesting that a combination of hydroxychloroquine and an antibiotic had been effective in a small number of COVID-19 patients. President Trump then began publicly advocating for use of the drugs on his Twitter account and at White House press briefings.[28] On March 23, he announced, "At my direction, the

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[22] Elizabeth Cohen, "Common heartburn drug may have helped 10 patients at home with Covid-19," *CNN*, June 5, 2020, accessed here: https://www.cnn.com/2020/06/04/health/famotidine-covid-19-case-series-study/index.html
[23] "Emergency Use Authorization," U.S. Food and Drug Administration, Updated June 13, 2020, accessed here: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
[24] "FAQs on Emergency Use Authorizations (EUAs) for Medical Devices During the COVID-19 Pandemic," U.S. Food and Drug Administration, April 29, 2020, accessed here: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-emergency-use-authorizations-euas-medical-devices-during-covid-19-pandemic
[25] "Emergency Use Authorization," U.S. Food and Drug Administration | Public Health Emergency, September 5, 2019, accessed here: https://www.phe.gov/Preparedness/planning/authority/Pages/eua.aspx
[26] Nicholas Florko, "Why was an obscure federal bureaucrat involved in Trump's emergency hydroxychloroquine authorization?," *Stat News*, April 24, 2020, accessed here: https://www.statnews.com/2020/04/24/why-rick-bright-involved-hydroxychloroquine/
[27] Franck Tournet and Xavier de Lamballerie, "Of chloroquine and COVID-19," *Antiviral Research*, Vol. 177, May 2020, accessed here: https://www.sciencedirect.com/science/article/pii/S0166354220301145?via%3Dihub
[28] Philip Bump, "The rise and fall of Trump's obsession with hydroxychloroquine," *Washington Post*, April 24, 2020, accessed here: https://www.washingtonpost.com/politics/2020/04/24/rise-fall-trumps-obsession-with-hydroxychloroquine/

federal government is working to help obtain large quantities of chloroquine."[29] The FDA issued an EUA for chloroquine and hydroxychloroquine on March 28.[30]

The decision to issue an EUA came under fire from scientists, including a number of former FDA officials. While FDA has the flexibility to extend EUAs to drugs that do not meet the threshold for FDA approval – and while this flexibility is important – experts were concerned that the lack of any clinical evidence for hydroxychloroquine's and chloroquine's effectiveness would send a confusing, and potentially harmful, message. Furthermore, widespread use of the drugs would potentially interfere with researchers' ability to collect meaningful data.[31]

On June 15, the FDA revoked the EUA for hydroxychloroquine and chloroquine after concluding that it is "no longer reasonable to believe that oral formulations of [hydroxychloroquine] and [chloroquine] may be effective in treating COVID-19, nor is it reasonable to believe that the known and potential benefits of these products outweigh their known and potential risks."[32] The notice of revocation noted that previous findings regarding the drugs' effect on viral shedding have not been replicated in controlled experiments, and that no experiments have shown decreased mortality or other positive outcomes due to use of the drugs.[33]

[29] *Id*.
[30] Letter from Denise M. Hinton to Rick Bright, "Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease," U.S. Food and Drug Administration, March 28, 2020, accessed here: https://www.fda.gov/media/136534/download
[31] Charles Piller, "Former FDA leaders decry emergency authorization of malaria drugs for coronavirus," *Science*, April 7, 2020, accessed here: https://www.sciencemag.org/news/2020/04/former-fda-leaders-decry-emergency-authorization-malaria-drugs-coronavirus
[32] Letter from Denise M. Hinton to Gary L. Disbrow, U.S. Food and Drug Administration, June 15, 2020, accessed here: https://www.fda.gov/media/138945/download
[33] *Id*.