

VIEWPOINT

Finding Effective Treatments for COVID-19 Scientific Integrity and Public Confidence in a Time of Crisis

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Everyone wants new treatments and vaccines to address the devastation of coronavirus disease 2019 (COVID-19). But, currently, under intense pressure and based on hope and limited data from poorly conducted clinical trials and observational data, many clinicians are embarking on ill-advised and uncontrolled human experimentation with unproven treatments.¹ This approach cannot provide answers about what treatments are effective, and it poses undue risk to patients. In this light, decisions to seek and invoke Emergency Use Authorization (EUA) authorities from the US Food and Drug Administration (FDA), such as the recent EUA for chloroquine and hydroxychloroquine,² which will further increase use of these drugs for treating individuals with COVID-19, are noteworthy and deserve careful attention. Not only are there potential negative consequences from uncontrolled use of these drugs based on currently unconvincing data but, equally concerning, the integrity of governmental decision-making is increasingly coming under pressure, risking harm to both patients and to the public confidence needed to respond effectively to this pandemic.

In 2014, Ebola virus disease, then believed to be fatal to most infected individuals, was widespread in West Africa. Early doses of “secret serum,” the triple monoclonal antibody combination (ZMapp), were given

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to 2 US citizens. Both survived, generating intense global pressure to use this product and other unproven treatments. At the time, it was argued³ that even promising therapies most often prove ineffective or harmful and that, even in an emergency, the fastest route to learning whether experimental products work was with randomized clinical trials (RCTs). At the same time, it was noted that, provided adequate supplies, access for patients who could not enroll in clinical trials could be facilitated through FDA “compassionate use” (or “expanded access”) provisions. Such provisions, unlike EUA, require consent and provide enhanced clarity to physicians and patients that the product is experimental and not necessarily endorsed by the government.

However, there was extreme resistance to conducting RCTs, and by the time a study that compared the monoclonal antibody combination therapy with standard care was underway, the epidemic was waning and the trial terminated before it could reach definitive conclusions. It took 4 years and another outbreak to learn

that any potential benefit afforded by this triple antibody product was less than that of 2 similar treatments. Furthermore, because of the deficit of RCTs, it is still not known whether other experimental Ebola treatments are of value or may be injurious. As a result of these experiences, a consensus emerged that sound research can and should be done during emergencies and that RCTs are the most ethical and reliable approach to quickly identify effective treatments and ensure that the most people benefit.⁴

In this context, the recent issuance of the chloroquine/hydroxychloroquine EUA, in the midst of political pressure and with scant and conflicting supporting evidence, should be of serious concern. Although everyone hopes these drugs will be found to work, the weakness of currently existing efficacy data and safety concerns are significant.^{1,5} Furthermore, growing enthusiasm about the drugs has resulted in unintended consequences, including anecdotal reports of fatal ingestions as well as hoarding that puts patients who need the drugs for proven indications at risk. Resulting shortages also risk promoting production and use of substandard or counterfeit substitutes.

Why the concern about EUAs? An EUA is intended to allow use of select experimental products or of approved products for unproven indications with

exceptions to FDA requirements that may not be feasible to meet during some emergencies (eg, good manufacturing practices, institutional review boards, written informed consent).

EUA issuance requires the FDA's scientific review, an independent process of high integrity, to conclude that it is reasonable to believe that “the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product.”⁶ Although this standard is short of requirements for full drug or biologic approvals, it still depends on careful weighing of available evidence and represents a de facto government judgment in support of a specific use in a specific emergency. Although unintended, it is not infrequent to see an EUA portrayed as akin to an FDA approval, including now for chloroquine/hydroxychloroquine.⁷

EUAs that have been requested and granted in the past, such as during the anthrax attacks of 2001 and the 2009 pandemic influenza A(H1N1), have all been underpinned by substantive evidence supporting the standard of known and potential benefits being likely to exceed risks, particularly as compared with the recent chloroquine/hydroxychloroquine EUA. For example, oseltamivir, a drug of known safety and

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effectiveness approved for children and adults, was made available for use in infants under an EUA based on science-based dosing guidance during the 2009 pandemic influenza A(H1N1). In addition, peramivir, an unapproved drug, was authorized for patients who required intravenous therapy, with the decision supported by safety and effectiveness data from nearly 2000 patients in prior trials for seasonal influenza.

Given the unique powers, role, and circumstances of EUAs, if scientific independence and objectivity in requesting and making EUA determinations are not rigorously upheld, not only will such EUA-related decisions risk being compromised or erroneously made, but, particularly if harm occurs, public confidence in the FDA may also be eroded. Confidence in the FDA and the government as a whole will be critical to the success of future steps needed to contain this pandemic, including vaccination, which is likely to be initially feasible only under EUA provisions and must not be undermined.

When EUA status is sought or granted seemingly under pressure, it may also open a floodgate of efforts to promote unfounded use of other unproven treatments, risking a perception that special interests can influence FDA decisions. Just days after the issuance of the chloroquine/hydroxychloroquine EUA, there were reports of high-level advocacy on behalf of experimental products with even less well-defined risk/benefit ratios, including favipiravir⁸ (a Japanese anti-influenza drug that is unapproved in the US and has been associated with birth defects in animals) and an unproven natural killer cell therapy derived from placentas.⁹ Such pressure, even when well intended, can endanger the intent and inherent protections of the EUA provisions to allow an agile emergency response and regulatory flexibility and ensure that the

FDA plays a key role as a trusted, independent scientific reviewer of the facts that protects people in the US when decisions must be made in a time of crisis and based on limited data.

With so much at stake, what should be done? First, the regulatory and research communities owe it to patients, families, and clinicians to quickly learn what treatments are effective. RCTs led by the National Institutes of Health, the World Health Organization, Inserm, and others to evaluate a number of investigational drugs, including hydroxychloroquine, are already underway. Enrollment is proceeding rapidly; the more effective a drug, the sooner the results will become apparent. However, it is of concern that there are no clear answers yet from China. A recent review¹⁰ suggests that scientists in China planned at least 87 drug studies, including 10 studies of chloroquine or hydroxychloroquine, but studies reported to date have been small and have provided conflicting results.

Second, it is important to optimize treatments that already exist, including supportive critical care. As learned from the Ebola outbreak, mortality can be reduced through identifying best practices. Even the most promising new drugs should work best when supportive care is optimized. Efforts are underway to share emerging knowledge about care of patients with COVID-19 (such as through Project ECHO) and can help lead to rapid definition of the most important questions and studies to answer them.

Third, and most important, it is critical to protect the integrity of and resulting public trust in the scientific and regulatory agencies and their advice and decisions. That trust will be needed once vaccines against COVID-19 become available and in future public health emergencies.

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