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VIEWPOINTS

Therapeutic Emergency Use Authorizations (EUAs) During Pandemics: Double-edged Swords

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Given the urgent need for treatments during the coronavirus disease 2019 pandemic, the US Food and Drug Administration issued emergency use authorizations (EUAs) for multiple therapies. In several instances, however, these EUAs were issued before sufficient evidence of a given therapy's efficacy and safety were available, potentially promoting ineffective or even harmful therapies and undermining the generation of definitive evidence. We describe the strengths and weaknesses of the different therapeutic EUAs issued during this pandemic. We also contrast them to the vaccine EUAs and suggest a framework and criteria for an evidence-based, trustworthy, and publicly transparent therapeutic EUA process for future pandemics.

Keywords. COVID-19; emergency use authorization; treatment.

During the coronavirus disease 2019 (COVID-19) pandemic, there has been an intensified sense of urgency in identifying effective treatments. This therapeutic challenge is unprecedented, not just for scientists, manufacturers, or clinicians, but also for regulatory bodies such as the US Food and Drug Administration (FDA). The rapidity with which trials are being performed and the results disseminated has been unparalleled. However, the practice of authorizing widespread use of drugs based on limited early evidence through emergency use authorizations (EUAs) can have unintended and potentially deleterious consequences.

The EUA pathway is a way for the FDA to facilitate the availability and use of medical countermeasures during public health emergencies, such as the current COVID-19 pandemic [1]. It was developed in 2004 as part of Project Bioshield as a response to terrorism threats that emerged with and after the September 11, 2001, attacks in the United States. It was modified in 2013 to give the FDA the ability to prepare for biothreats in advance. A key feature of the EUA is that it directs the FDA to consider the known and potential benefits and risks of medical products used for urgent unmet needs during a public health emergency. The EUA mechanism, by definition, will lead to authorizations based on more limited evidence than a full approval. In granting EUAs, the FDA is permitted flexibility with regard to the level of evidence used to form the basis for authorization.

During the COVID-19 pandemic, the FDA has issued EUAs for multiple therapies, including hydroxychloroquine, convalescent plasma, remdesivir, bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, and baricitinib administered with remdesivir. In several instances, however, these EUAs were issued before definitive evidence supported the routine use of these drugs. A potential danger of making an experimental therapeutic agent available through an EUA during a pandemic is that the authorized agents become quickly and widely used, only to discover that they are ineffective in some cases. In addition to potentially promoting ineffective or even harmful therapies and eroding public trust, issuance of an EUA has a direct impact on the public's and clinicians' perception of candidate therapies, sometimes clouding clinical equipoise. This may, in turn, lead to difficulties in recruitment for ongoing trials and hindering the generation of the definitive evidence needed to develop safe and effective therapies. The FDA, in collaboration with manufacturers and the clinical research community, needs to ensure the collection of definitive data to allow rapid access to promising therapy, while ultimately licensing both safe and effective products.

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EUAS FOR COVID-19 THERAPEUTICS

The first FDA EUA for COVID-19 therapy was issued in March 2020 for hydroxychloroquine. At that time, the clinical evidence in support of hydroxychloroquine was derived from small studies of low methodological quality, based on surrogate outcomes. Widespread use of hydroxychloroquine occurred, but ongoing cohort studies showed equivocal results [2]. Eventually, randomized controlled trials (RCTs) did not show any benefit and suggested potential harm [3–7], and the FDA withdrew the EUA. By this time, however, thousands of patients had received hydroxychloroquine and were unnecessarily exposed to potential adverse events. These patients were also not eligible for other therapeutic studies, slowing enrollment and potentially delaying development of new and more effective treatments.

Access to convalescent plasma as an investigational treatment was provided early in the pandemic under a different mechanism from EUAs through an FDA-authorized Expanded Access Program, which allows broader availability of an experimental treatment having potential for benefit to patients providing informed consent and collects limited safety and outcomes information. Convalescent plasma was since authorized for use under an EUA, and has since been used to treat > 100 000 patients in the United States [8]. These programs have provided physicians and patients access to potentially beneficial but unproven therapy in many locations where clinical trials are not being performed. However, there are legitimate concerns that this EUA has impeded recruitment into RCTs needed to definitively assess the efficacy of other treatments. A recent meta-analysis of 10 RCTs for the treatment of COVID-19, which included the preliminary results from the largest trial Randomised Evaluation of COVID-19 Therapy, did not find any association of convalescent plasma with improved survival or other positive clinical outcomes. Yet, these studies did not adequately assess the role of high-titer plasma in early mild to moderate COVID-19 or in patients who are not already on corticosteroids, which may impede passive immunotherapy [9]. A large single-arm observational study [10] did establish convalescent plasma as a generally well-tolerated therapy, and in February 2021, the FDA issued a revision to the earlier convalescent plasma EUA to "limit the authorization to the use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients early in the disease course" [11]. This revision was supported by uncontrolled observational data showing that mortality was lower in patients transfused early compared with those who were transfused later, and in those who received high-titer plasma rather than who received medium- or low-titer plasma [12]. These results have not been verified in RCTs. Thus, we are still in need of results from RCTs of high methodological quality to determine if there is a specific population, clinical phenotype, or time in the disease course that convalescent plasma may be beneficial. The EUA experience with plasma illustrates the challenges of meeting a demand to provide access to potentially helpful therapies for COVID-19 in the midst of efforts to discover which patients would benefit from them. Adding to the complexity are the challenges of developing and interpreting high-quality studies of therapeutic agents that are not well characterized in a disease state that is incompletely understood.

The remdesivir EUA issued in May 2020 was based on an interim analysis of the National Institutes of Health (NIH)-conducted Adaptive COVID-19 Treatment Trial (ACTT-1) [13] before the final results of the study were available, leaving clinicians with no clear actionable evidence-based guidance for use of a drug with limited availability. It took weeks after the EUA for the complete study results to be published. Fortunately, remdesivir RCTs have since been reported, but most still have methodological limitations assessing clinical outcomes other than mortality, for which we have low certainty of meaningful benefit. ACTT-1 found the drug resulted in a clinically meaningful reduction in time to recovery—a finding that ultimately led to approval of this medication. However, at the time the EUA was issued, in addition to ACTT-1, studies by the manufacturer and other investigators were ongoing. Additionally, while studies in nonpregnant adults have now been largely completed, trials in vulnerable populations such as pregnant women and young children have not been completed, and the broad application of this EUA (and subsequent EUAs for other drugs) to other populations was made with limited data on efficacy and few or no data on safety.

In November 2020, 2 EUAs were issued for severe acute respiratory syndrome coronavirus 2–neutralizing antibody therapies. The first one authorized the use of the monoclonal antibody bamlanivimab for the treatment of outpatients with mild-to-moderate COVID-19. It was based on an interim analysis of a phase 2 trial, which suggested a benefit in the composite outcome of number of emergency department visits and/or hospitalizations. The low number of patients developing this composite outcome in both arms (5/309 receiving bamlanivimab vs 9/143 receiving placebo) indicated the fragility of the result, meaning that a small change in these numbers (eg, just a few less events in the placebo arm) might change the conclusion to a lack of benefit. The second EUA was issued later in November 2020 for the antibody combination of casirivimab and imdevimab for treatment of mild-to-moderate disease in ambulatory settings [14]. Data supporting this EUA were based on a phase 2 trial that reported fewer medically attended visits or hospitalizations in patients with high risk of disease progression (4/151 in the combined treatment arms compared with 7/78 in the placebo arm) [15]. Similar to the results of the bamlanivimab trial, the low event rate indicated fragility. Although the use of any intravenous antibody therapy with limited supply comes with economical, logistic, infection prevention, and equity challenges, the

fragility—and therefore uncertainty—of the evidence raised additional concerns. A third and most recent EUA for neutralizing monoclonal antibodies was issued for the combination of bamlanivimab and etesevimab in February 2021. The fact sheet developed for healthcare providers at the time of the EUA did not have adequate data on patient important outcomes to critically appraise the evidence for efficacy [16]. Moreover, the study results from the trials that led to the EUA are still not published or available as preprints, making it difficult to judge its therapeutic benefits.

The COVID-19 treatment EUA issued in November 19, 2020, was for the combination of baricitinib with the antiviral remdesivir. The EUA was based on then-unpublished data from the NIH-conducted ACCT-2 trial [17]. The manuscript was published after the EUA and demonstrated that the median time to recovery from COVID-19 was 1 day shorter in the baricitinib plus remdesivir arm (7 days) compared with placebo plus remdesivir alone (8 days) [18]. However, the majority of the patients in the trial did not receive corticosteroids, which have been shown to reduce mortality in severe COVID-19 [19].

Thus, the potential additional benefits of adding baricitinib and remdesivir to corticosteroids for the treatment of severe COVID-19 are unknown, and it is hoped that future studies address this more clinically relevant question.

IMPLICATIONS AND CONSEQUENCES

Philosophers have characterized ethics as a discourse between what is good and what is right [20]. The ethical dilemma is well illustrated by these EUAs, which prioritize the potential benefits of experimental interventions on recipients (the "good") on the one hand with clinical research, which emphasizes the duty to pursue the correct answer to a question (the "right") on the other. These are urgent times. Although the FDA has done remarkable work under considerable political and public pressure to satisfy the "good," it must also satisfy the "right" by considering the full implications of issuing an EUA on scientific progress and the clinical practice community, working with manufacturers and investigators to collect additional relevant data to confirm the anticipated benefits the EUAs hope to provide. Many promising therapies are showing only modest or borderline benefits in the limited populations studied. There are likely subgroups that would show more benefit and some that may show less, but without more robust trial data, precision treatments are being wielded as blunt instruments. Continued data collection and comparative studies are the only way to answer the critical questions of which treatments are the best for which patients. It is also important to include vulnerable populations such and immunocompromised hosts, children, and pregnant and lactating women in clinical trials earlier so that broad EUAs can be supported by some interim data on these populations.

Even with the difficulties of the present pandemic setting, COVID-19 treatment trials that provide high-quality evidence on important patient outcomes have been performed expeditiously. The combination of a high incidence of infection and acuity of illness allow for rapid patient accrual and outcome assessment. The pivotal Randomised Evaluation of COVID-19 Therapy and Solidarity studies are examples of swiftly conducted, massive, open-label useful RCTs performed in practical ways that served to both demonstrate effective therapies to current patients while also collecting clinical evidence that inform decision making for future patients. Although there are many barriers to doing so, completion of high-quality clinical trials during a pandemic can and must be accomplished [21].

The EUA process is challenging because it attempts to overcome systemic deficiencies that limit the speed of rapid innovation in times of need. The clinical trial infrastructure of the United States is not facile. Attempting to introduce experimental treatments outside of tertiary care academic medical settings and systematically study them is nearly impossible. As a case in point, for all the deficiencies noted in the single-arm structure of the convalescent plasma Expanded Access Program, it represented a serious attempt to provide clinical trial infrastructure to sites that otherwise would not have access. To address this challenge, a holistic approach will be needed. This approach should include establishing clinical trial consortia and clinical trial infrastructure, funding mechanisms, and better analytical tools so that the EUA mechanism can be based on stronger data and the trials can be performed on larger populations in more diverse settings to increase access to treatments and the ability to gather generalizable data. An example of such a consortium is the NIH ACTIV collaboration, which has implemented several master protocols of multiple candidate therapeutic agents using existing NIH-funded clinical trials networks for other infectious diseases [22]. With effective vaccines available and hopefully the end of the pandemic in sight, it is time to consider how we might restructure the clinical therapeutic trial infrastructure for the rapid evaluation of therapies during future pandemics.

The issuance of EUAs for drugs and therapeutics stands in contrast to those issued for vaccines. The FDA EUA vaccine guidance document [23] precisely addressed the outcomes, sample size requirements for clinical trials, duration of follow-up for adverse events, and the levels of efficacy before the EUA will be issued. Independent review by the Vaccine and Related Biologic Products Advisory Committee provides a level of transparency for vaccine EUAs. Establishing a similar benchmark process for EUAs for therapeutics for pandemic agents would serve us well.

We understand the EUA process for therapeutic agents is different from vaccines and has unique challenges, in large part because of the heterogeneity of therapeutic approaches, patient populations, and illness severities. We also acknowledge

the inherent uncertainty, especially early in an epidemic, about which populations and clinical outcomes are important to study. However, EUAs during epidemics such as the COVID-19 pandemic should be issued based on explicit evidence-based criteria that are publicly transparent (Table 1). These criteria can also be used as nonbinding guidance for investigators conducting studies with an intent to apply for an EUA. Such a process can be done in an expeditious manner even in pandemic settings, and adapted to evolving evidence. The efficacy and safety outcomes need to be tailored to each type of therapeutic agent and the context of its use. Clinical endpoints should always be reported and, whenever possible, should be standardized based on well-defined clinical syndromes or degree of severity of illness (Table 2). Where putative surrogate endpoints or biomarkers are used based on intended biologic activity, they should be validated to predict clinical outcomes. Standardizing endpoints across trials will facilitate comparative evaluation of therapeutic agents. Setting these benchmarks should be a transparent, evolving, collaborative, and iterative process that engages all the stakeholders and is based on the best available scientific evidence.

Table 1. Suggested Process and Criteria for Evidence-based and Trustworthy EUAs During Epidemics

- Establish predetermined clinical efficacy and safety outcomes that should be reported. These should be tailored to therapeutic agent class (eg, antiviral, immune-modulatory), novel or known drug class, clinical setting (eg, ambulatory, hospitalized), severity (eg, mild-moderate, severe, critical), and clinical phenotype (eg, early or late in the infection, with inflammatory parameters and hypoxemic respiratory failure or with inflammatory parameters and shock).
- Establish predetermined subpopulations to be included in studies, inclusive of diverse races, ethnicities, patients at high risk for severe disease or complications from the therapies (eg, elderly, individuals with a high body mass index, immunocompromised individuals) and special populations (eg, children, individuals who are pregnant or breast feeding).
- Established criteria for outcomes and populations to be studied should be adapted to evolving knowledge and understanding of the disease and therapies.
- Establish predetermined criteria for minimum "level of evidence" to issue an EUA. The criteria do not have to be based on type of trial design (eg, phase 3 RCT), but rather on principles such as the inclusion of patient-important outcomes or the presence of minimal threats to validity. For example, a phase 2 trial with a large effect size, with very little bias, statistical imprecision or fragility can be considered acceptable.
- Establish and follow explicit criteria for appraisal of the evidence from the studies. The rationale and judgments that lead from evidence to the issuance of the EUA should be clearly stated. The EUA fact sheet for healthcare providers should include a critical appraisal of the studies and also judgments about the balance between benefit vs harm, cost, accessibility, feasibility, and equity. An already established and trusted methodology like GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) or another similar method could be used.
- If feasible, establish an independent advisory group to conduct an independent review of the evidence using these criteria, as is being done for vaccine EUAs by the Vaccine and Related Biologic Products Advisory Committee.
- Establish a process to facilitate and encourage peer review publication of the results of the study or studies that led to the EUA in an expedited time frame.
- If possible, encourage sharing of data from RCTs to facilitate patient-level meta-analyses of subgroups across trials.

Abbreviations: EUA, emergency use authorization; RCT, randomized controlled trial.

Table 2. Minimum Clinical Outcomes for COVID-19 Therapy Studies Based on Clinical Context/Severity of Illness

Clinical context/severity of illness	Clinical outcome(s)
Prophylactic trials	Rates of defined symptomatic disease with laboratory-confirmed SARS-CoV-2 PCR positivity
Treatment trials in ambulatory patients with mild symptoms	Defined measures of symptom improvement and rates of hospitalization
Treatment trials in hospitalized patients with moderate disease	Rates of progression to severe disease, critical disease, and defined measures of symptom improvement
Treatment trials in hospitalized patients with severe disease requiring supplemental oxygen	Mortality, rates of progression to needing noninvasive and invasive mechanical ventilation, and defined measures of symptom improvement
Treatment trials in hospitalized patients with critical illness (ventilator support or shock needing vasopressors)	Mortality, ventilator free days, ICU free days and defined measures of symptom improvement

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Note

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References

1. Emergency use authorization. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization. Accessed 29 March 2021.
2. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA **2020**; 323:2052-9.
3. Recovery Collaborative Group, Horby P, Mafham M, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med **2020**; 383: 2030-40.
4. Cavalcanti AB, Zampieri FG, Rosa RG, et al; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med **2020**; 383:2041-52.
5. Pan H, Peto R, Henao-Restrepo AM, et al; WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Engl J Med **2021**; 384:497-511.
6. Self WH, Semler MW, Leither LM, et al; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. JAMA **2020**; 324:2165-76.
7. Ulrich RJ, Troxel AB, Carmody E, et al. Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind randomized controlled trial in hospitalized patients. Open Forum Infect Dis **2020**. doi: 10.1093/ofid/ofaa446.
8. FDA issues emergency use authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in administration's fight against pandemic. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment. Accessed 29 March 2021.
9. Janiaud P, Axfors C, Schmitt AM, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. JAMA **2021**; 325:1185-95.
10. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc **2020**; 95:1888-97.
11. FDA in brief: FDA updates emergency use authorization for COVID-19 convalescent plasma to reflect new data. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-updates-emergency-use-authorization-covid-19-convalescent-plasma-reflect-new-data. Accessed 29 March 2021.
12. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. MedRxiv doi:10.1101/2020.08.12.20169359.
13. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med **2020**; 383:1813-26.
14. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19. Accessed 29 March 2021.
15. Fact sheet for health care providers emergency use authorization (EUA) of casirivimab and imdevimab. https://www.fda.gov/media/143892/download. Accessed 29 March 2021.
16. Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab and etesevimab. https://www.fda.gov/media/145802/download. Accessed 29 March 2021.
17. Coronavirus (COVID-19) update: FDA authorizes drug combination for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19. Accessed 29 March 2021.
18. Kalil AC, Patterson TF, Mehta AK, et al; ACTT-2 Study Group Members. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med **2021**; 384:795-807.
19. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA **2020**; 324:1330-41.
20. Meacham W. The Good and the right. **2011**. https://www.bmeacham.com/whatswhat/PDF/GoodAndRight_v2_3.pdf.
21. Kalil AC. Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA **2020**; 323:1897-8.
22. COVID-19 therapeutics prioritized for testing in clinical trials. https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials. Accessed 22 April 2021.
23. Development and licensure of vaccines to prevent COVID-19- guidance for industry. https://www.fda.gov/media/139638/download. Accessed 29 March 2021.