Emergency Approvals for COVID-19: Evolving Impact on Obligations to Patients in Clinical Care and Research

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The U.S. Food and Drug Administration (FDA) recently granted an emergency use authorization (EUA) for convalescent plasma to treat patients with coronavirus disease 2019 (COVID-19) (1). Recognizing substantial evidentiary gaps, several institutions are considering steps to advance controlled trials, including either "avoiding or minimizing" legally permissible nontrial use of convalescent plasma (2). Especially with additional EUAs anticipated for COVID-19 therapeutics and vaccines, this approach raises urgent questions about whether institutions and clinicians may restrict clinical access to EUA products, including to facilitate the conduct of trials.

Convalescent Plasma EUA

To issue an EUA, the FDA must conclude that a product "may be" effective and that its known and potential benefits outweigh known and potential risks (1). Given this low bar, supporting evidence may be insufficient to change the standard of care. Indeed, the FDA acknowledged the weakness of available evidence on convalescent plasma, noting in its EUA that convalescent plasma "should not be considered a new standard of care" and ongoing trials should not be altered (1). The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel and the Infectious Diseases Society of America (IDSA) echoed these conclusions, stating that "[t]here are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19" (3) and recommending convalescent plasma only within a clinical trial (4).

Discretion Regarding Unproven Interventions

A central question for institutions and clinicians is whether their obligations to patients require them to offer EUA products. These obligations depend not on a product's legal availability, but rather on the weight of the evidence supporting it.

Traditional FDA approval typically supports clinical adoption of new standards of care because approval reflects a determination that a product's benefits outweigh its risks on the basis of a demonstration of safety and substantial evidence of effectiveness, a higher threshold than that required for an EUA. In contrast, an EUA should lead clinicians to shift the standard of care only if sufficient evidence exists to convince them that providing the intervention is in their patients' best interests. Short of this, institutions can choose whether to offer the EUA product to patients outside the standard of care, as can clinicians when permitted to do so by their institution's policy. Although EUA provisions allow the FDA to lower its evidentiary standards temporarily, they do not compel others to do so.

Emergency use authorizations based on strong evidence can support a shift in the standard of care, even if important questions remain unanswered. For example, remdesivir's EUA was based in part on topline data from the double-blind, randomized, placebo-controlled ACTT-1 (Adaptive COVID-19 Treatment Trial) demonstrating a shortened time to recovery for severely ill patients with COVID-19 (5), a benefit confirmed upon final analysis (6). Results from the World Health Organization's Solidarity trial subsequently called the drug's efficacy into question (7), demonstrating the evolving nature of these issues, although the FDA ultimately granted remdesivir traditional marketing approval. Despite concerns about whether that approval was warranted, given the data existing when the EUA was granted and consensus guidelines recommending remdesivir's use, failing to offer the drug (when available) might have been viewed as improperly withholding an intervention from which severely ill patients could expect to benefit.

In contrast, if an EUA is based on weak evidence, such as observational data or uncontrolled trials—as in the case of convalescent plasma—institutions and clinicians can reasonably decline to offer the product without wronging eligible patients (8). Although malpractice litigation may follow, a successful claim requires that patients demonstrate a breached duty of care. The FDA, NIH, and IDSA statements about convalescent plasma make that demonstration unlikely. Litigation always carries some uncertainty, and even failed attempts are unpleasant and expensive, but treatment decisions should be guided by evidence, not fear of lawsuits.

Offering Unproven EUA Products Exclusively Through Trials

Institutions and clinicians choosing not to offer authorized but unproven interventions may nevertheless wish to pursue trials of those interventions to develop critical evidence. Limiting access to EUA products exclusively to patients in trials may be justified on 2 grounds: first, uncertainty about whether the product's benefit–risk balance is truly favorable, and second, a desire to minimize recruitment problems stemming from nontrial access. Although resolving uncertainty rapidly is critical for patients facing serious and life-threatening conditions, such as COVID-19, the trials-only approach may prompt concerns about both voluntariness and fairness (9).

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Restricting an EUA product to trials clearly limits patients' choices and, when imposed by institutions, clinicians' discretion. This limitation is especially pronounced when transfer between institutions is difficult or impossible. If an EUA is based on weak evidence, however, restricting access to trial participants is not coercive because patients are not threatened with the withholding of a standard-of-care intervention to which they are entitled. To the contrary, this approach is analogous to restricting off-label use of drugs being studied for new, as yet unproven indications, as well as to regulations restricting "expanded access" to patients who cannot enroll in a trial (9). Although patients may prefer nontrial access, restricting it in these circumstances is commonly viewed as a reasonable limitation while the necessary data are gathered.

A more compelling concern about the trials-only approach is the potential for unjust disparities in access, especially given valid reasons for patients to distrust both research and medical institutions, including racism and other concerns. However, there is no guarantee that unproven interventions will be distributed more fairly outside of trials. Moreover, especially in a public health emergency, it is reasonable to prioritize efforts to expeditiously resolve questions about the safety and efficacy of unproven products because this is what has the greatest potential to promote patient benefit (10). Institutions that restrict EUA products to trials should inform surrounding communities and newly admitted patients of these constraints, although this is an imperfect solution. Finally, to avoid injustice, institutions adopting such policies must not disproportionately be those serving disadvantaged communities and must not make exceptions for privileged patients.

CONCLUSION

The authority to make drugs rapidly available may be useful in an emergency, but it entails important tradeoffs. Emergency use authorizations expand treatment options, but only evidence should shift the standard of care. Regardless of whether an EUA has been granted, institutions and clinicians are not obligated to offer unproven interventions; rather, they must assess available evidence and treat patients accordingly. The decision to offer unproven EUA products exclusively through clinical trials is therefore ethically permissible—and may be critical to enabling evidence-based treatment decisions.

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