Developing Therapeutics During the Coronavirus Pandemic and Future Public Health Emergencies

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This document was developed by IDSA and HIVMA to provide recommendations for Congress and federal agencies to optimize clinical trial design and to strengthen the emergency use authorization (EUA) process for therapeutics for COVID-19 and future novel infections. The recommendations are intended to better balance the need for the rapid development and deployment of new therapeutics, while ensuring sufficient clinical trial data to support safe and optimal use. The recommendations also address the need to ensure equitable access to clinical trials and EUA therapeutics for Black, Indigenous and other people of color; Latinx communities; immigrants and others who are underserved or live on low incomes.

Strengthening the Emergency Use Authorization Process

Issues:

To provide timely access to potentially beneficial treatments, the U.S. Food and Drug Administration (FDA) has issued EUAs for therapeutics before sufficient evidence is available to support the standard approval process and the routine use of the therapeutic agent as part of the standard of care.[1,2] Authorizing therapeutics through EUAs can expedite access to potentially helpful treatments. However, by potentially allowing widespread use of ineffective or even harmful therapies, issuance of an EUA potentially undermines the ability to complete placebo-controlled clinical trials, thereby compromising the collection of necessary data to evaluate the safety and effectiveness of therapies and determine their optimal clinical use.[3] This also serves to undermine public confidence in the EUA process and the therapeutics that are granted EUAs.

IDSA and HIVMA recommend that the FDA:

- Establish and publicly communicate benchmarks for COVID-19 therapeutics to receive an EUA, as the agency did for COVID-19 vaccines, and requirements for receiving licensure after an EUA is granted.
- Require the public release of clinical trial data both before a therapy receives an EUA and before it receives subsequent routine approval.

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[1] Roy Guharoy, Edward P Krenzelok, US Food and Drug Administration (FDA) Emergency Use Authorization: Glass Half Full or Glass Half Empty?, Clin Inf Dis, 2020; ciaa1653, https://doi.org/10.1093/cid/ciaa1653

[2] Mike Z Zhai, Carolyn T Lye, Aaron S Kesselheim, Need for Transparency and Reliable Evidence in Emergency Use Authorizations for COVID-19 Therapies, JAMA Intern Med, May 19 2020 https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2766372

[3] Benjamin N. Rome, Jerry Avorn, Drug Evaluation during the COVID-19 Pandemic, N Engl J Med June 11 2020 https://www.nejm.org/doi/full/10.1056/NEJMp2009457

- Require the sponsor to have a plan for completing and publishing data from definitive clinical trials post-EUA and to articulate a plan for pursuing licensure once granted an EUA.
- Require the sponsor to include plans for recruiting children, individuals who are pregnant and breastfeeding, and other who are immunocompromised, including people with HIV. In addition, require inclusion of populations heavily impacted by the pandemic, including Black, Indigenous and other people of color, Latinx communities and other underserved populations.
- For products available through an EUA, collaborate with manufacturers, health care facilities, private and federal payers and other federal agencies to collect additional evidence to monitor utilization and outcomes by adapting existing COVID-19 registries and data platforms and, if necessary, create new data collection mechanisms.

Optimizing the Clinical Trial Infrastructure

Issues:

Outpatient clinical trials for therapeutics can be more challenging because they require large numbers of participants and a complex infrastructure to ensure participant follow-up and safety monitoring. Similar to the issues regarding safety considerations for vaccines, the risk-benefit calculus is more complicated in treatments for individuals with mild-to-moderate disease, who generally recover without intervention, as compared with therapies for patients hospitalized with severe COVID-19. The risk of SARS-CoV-2 transmission to staff in the outpatient setting is another important consideration. Treatment for outpatients with mild disease must demonstrate meaningful clinical improvements and must be safe with few adverse effects, easy to store and administer, and scalable to both provide equitable access and demonstrate a population-level benefit for preventing disease progression. The current infrastructure of clinical trials limits the speed of innovation and makes the study of experimental treatments extremely difficult even in tertiary care academic medical centers. Safety precautions for staff add expense and complexity. In particular, therapies such as blood products that may not have much profit potential rely on federal or other non-commercial funders for development and study.

IDSA and HIVMA recommend:

- Increased federal investment in research to study and develop COVID-19 outpatient treatment options, to address barriers to timely identification of infected patients for trials and to support clinical trial engagement and outreach to those most vulnerable to COVID-19, including older individuals; Black, Indigenous and other people of color; Latinx communities; immigrants and other populations that are underserved and most heavily impacted by COVID-19 and other infectious diseases.
- Collaborations between the FDA, the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC) and the clinical research community to strengthen and improve the clinical trial infrastructure, expand funding mechanisms, and develop better analytical and predictive tools. Federally supported infrastructure should provide an integrated framework to link individuals diagnosed with COVID-19 to appropriate trials and encourage large-scale collaboration across many different types of facilities. Such an approach will increase the reach of trials of promising therapeutics to populations that are typically omitted from studies. This goal is best accomplished by performing studies on larger, more diverse populations, including

settings outside the traditional urban tertiary care academic centers, thereby increasing access to treatments for patients and the ability to gather data across a broader range of participants more rapidly.

Health Equity and Access

Issues:

Historically, enrollment of communities of color and other underserved populations has been low in clinical trials due to multiple factors including medical mistrust, access limitations, concentration of studies in tertiary care academic centers, racism and other forms of discrimination, and stigma. These are the populations most heavily impacted by COVID-19 and other infectious diseases epidemics and therefore must be prioritized for promising investigational therapeutics. Steps must be taken to ensure equitable access to outpatient treatment options that are available through an EUA or through approval for commercial use by FDA.

Successful efforts should build on the progress of programs like the NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities, which expands existing community outreach by NIH-funded COVID-19 clinical trial networks, and the Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP) initiative, which focuses on hard-hit populations and aims to understand and alleviate barriers to access.

IDSA and HIVMA recommend:

- The FDA identify appropriate benchmarks for enrollment of populations disproportionately impacted by the respective condition for which an EUA or standard approval is being sought.

- Congress increase funding for targeted biomedical research initiatives, adopt actionable diversity policies and strategies for awardees of NIH funding, and direct NIH to provide training and technical assistance to help funding recipients achieve diversity goals. This new funding should supplement, not supplant, existing appropriations and create sustainable and predictable funding for research agencies. Diversity policies that Congress and NIH promote for funding should ensure that:

    - Federal and private industry clinical trial sponsors prioritize a diverse research workforce, including Black, Indigenous and people of color in addition to including safety-net hospitals as clinical trial sites;
    - Clinical trial sponsors ensure that research practices, trial designs and enrollment processes directly address the history of racism in clinical research by engaging Black, Indigenous and other people of color, Latinx communities and other underserved populations throughout the research process;
    - Clinical trial sponsors engage with community leaders, including community-based participatory research groups, to support education about enrollment in research studies;

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- Clinical trial sponsors ensure that study enrollment processes include comprehensive information about clinical trials and research studies with a transparent informed consent process;
- Clinical trials sponsors promote and expand access to the appropriate training on Good Clinical Research Practice (GCP), including medical ethics for medical and medical support staff;
- Clinical trial sponsors are encouraged to open outside of business hours and on weekends to broaden access to people whose jobs or family responsibilities do not permit weekday participation;
- Federal clinical trial sponsors be allowed to cover trial participants' expenses related to participation, including transportation costs.

Improving the Allocation and Distribution of EUA Products

Issues:

The U.S. Department of Health and Human Services (HHS) Assistant Secretary for Preparedness and Response (ASPR) plays an important role in overseeing the distribution of EUA products to states. During the coronavirus pandemic, in addition to maintaining dedicated web pages for therapies available under EUA, ASPR has held weekly stakeholder calls and office hours to provide updates on the allocations, respond to questions and learn about frontline issues. These offerings have been helpful and should be maintained, but additional steps are needed to improve transparency and the distribution process. In addition, guidance is needed to assist states and facilities with ensuring equitable access to EUA products for the populations most heavily impacted by COVID-19.

IDSA and HIVMA recommend that:

- ASPR maintain a high level of transparency and outreach in its role in coordinating the allocations and distributions of therapeutics available under an EUA through regular stakeholder virtual meetings and outreach to heavily impacted communities to assess access and other mechanisms.
- ASPR publicly disclose on a dedicated webpage details on state allocations and distributions and the data used to inform them.
- ASPR predict allocation decisions further in advance than the current one-week time frame to allow health care facilities to assess their inventory and to prepare the delivery systems, e.g., the monoclonal antibody products available under EUA are administered by infusion and require intensive facility and staffing preparation and protocols.
- HHS develop and regularly update guidance and best practices for states and facilities to ensure access to outpatient COVID-19 treatment for older Americans, communities of color and other populations most heavily impacted by COVID-19.
- CMS increase payments to providers to better reflect the costs of administering COVID-19 therapeutics (particularly those requiring infusion) and to support data collection, including information on whether medications are being used equitably among disproportionately affected communities.

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