VIEWPOINT

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

An Unprecedented Partnership for Unprecedented Times

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Viewpoint

It has been more than a century since the world has encountered a pandemic like coronavirus disease 2019 (COVID-19), and the rate of spread of COVID-19 around the globe and the associated morbidity and mortality have been staggering.[1] To address what may be the greatest public health crisis of this generation, it is imperative that all sectors of society work together in unprecedented ways, with unprecedented speed. In this Viewpoint, we describe such a partnership.

First reported in Wuhan, China, in December 2019, COVID-19 is caused by a highly transmissible novel coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). By March 2020, as COVID-19 moved rapidly throughout Europe and the US, most researchers and regulators from around the world agreed that it would be necessary to go beyond "business as usual" to contain this formidable infectious agent. The biomedical research enterprise was more than willing to respond to the challenge of COVID-19, but it soon became apparent that much-needed coordination among important constituencies was lacking.

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Clinical trials of investigational vaccines began as early as January, but with the earliest possible distribution predicted to be 12 to 18 months away. Clinical trials of experimental therapies had also been initiated, but most, except for a trial testing the antiviral drug remdesivir,[2] were small and not randomized. In the US, there was no true overarching national process in either the public or private sector to prioritize candidate therapeutic agents or vaccines, and no efforts were underway to develop a clear inventory of clinical trial capacity that could be brought to bear on this public health emergency. Many key factors had to change if COVID-19 was to be addressed effectively in a relatively short time frame.

On April 3, leaders of the National Institutes of Health (NIH), with coordination by the Foundation for the National Institutes of Health (FNIH), met with multiple leaders of research and development from biopharmaceutical firms, along with leaders of the US Food and Drug Administration (FDA), the Biomedical Advanced Research and Development Authority (BARDA), the European Medicines Agency (EMA), and academic experts. Participants sought urgently to identify research gaps and to discuss opportunities to collaborate in an accelerated fashion to address the complex challenges of COVID-19.

These critical discussions culminated in a decision to form a public-private partnership to focus on speeding the development and deployment of therapeutics and vaccines for COVID-19. The group assembled 4 working groups to focus on preclinical therapeutics, clinical therapeutics, clinical trial capacity, and vaccines (**Figure**). In addition to the founding members, the working groups' membership consisted of senior scientists from each company or agency, the Centers for Disease Control and Prevention (CDC), the Department of Veterans Affairs (VA), and the Department of Defense.

On April 17, the NIH-led Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership was formally announced.[3] Demonstrating unprecedented commitment, ACTIV's industry partners agreed to support a prioritization of therapeutic and vaccine candidates, no matter who has developed them. Industry partners indicated their willingness to contribute their respective clinical trial capacities, irrespective of the agent to be studied. For their part, the public partners resolved to work at unprecedented speed on research and regulatory issues to drive expedited evaluation and rapid scale-up and manufacturing of candidate therapies with predicted successful outcomes.

The main goals of ACTIV are to establish a collaborative framework for prioritizing vaccine and therapeutic candidates, to streamline clinical trials and tap into existing clinical trial networks, and to coordinate regulatory processes and leverage assets among all partners. In the short time since the public announcement, ACTIV has continued to expand and attract additional involvement from academia, industry (now 18 biopharmaceutical companies), and government agencies. ACTIV has also taken steps to ensure that the NIH-coordinated initiative is closely interconnected and complementary with other COVID-19 efforts, including those led by the FDA and BARDA's Medical Countermeasures Task Force, as well as international initiatives led by the Bill & Melinda Gates Foundation, the Wellcome Trust, the European Commission, the UK government, and the World Health Organization.

ACTIV's 4 working groups, each with one cochair from NIH and one from industry, have made rapid progress in establishing goals, setting timetables, and forming subgroups focused on specific issues (Figure).

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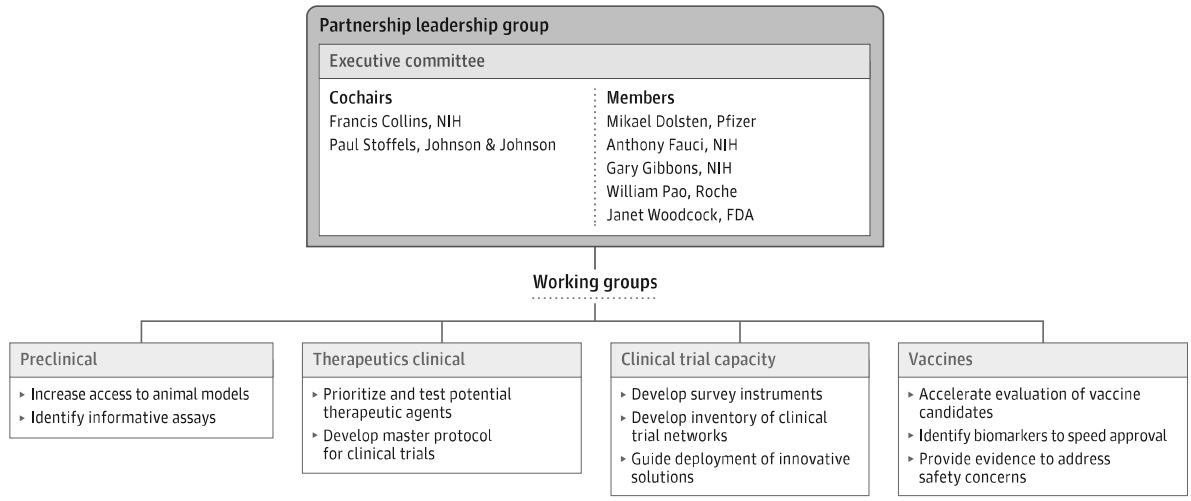
Figure. The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership



COVID-19 indicates coronavirus disease 2019; FDA, Food and Drug Administration; and NIH, National Institutes of Health.

The goals of the working group, along with a few examples of their accomplishments to date, include the following.

The Preclinical Working Group was charged to standardize and share preclinical evaluation resources and methods and accelerate testing of candidate therapies and vaccines to support entry into clinical trials. The aim is to increase access to validated animal models and to enhance comparison of approaches to identify informative assays. For example, through the ACTIV partnership, this group aims to extend preclinical researchers' access to high-throughput screening systems, especially those located in the Biosafety Level 3 (BSL3) facilities currently required for many SARS-CoV-2 studies. This group also is defining a prioritization approach for animal use, assay selection and staging of testing, as well as completing an inventory of animal models, assays, and BSL 3/4 facilities.

The Therapeutics Clinical Working Group has been charged to prioritize and accelerate clinical evaluation of a long list of therapeutic candidates for COVID-19 with near-term potential. The goals have been to prioritize and test potential therapeutic agents for COVID-19 that have already been in human clinical trials. These may include agents with either direct-acting or host-directed antiviral activity, including immunomodulators, severe symptom modulators, neutralizing antibodies, or vaccines. To help achieve these goals, the group has established a steering committee with relevant expertise and objectivity to set criteria for evaluating and ranking potential candidate therapies submitted by industry partners. Following a rigorous scientific review, the prioritization subgroup has developed a complete inventory of approximately 170 already identified therapeutic candidates that have acceptable safety profiles and different mechanisms of action. On May 6, the group presented its first list of repurposed agents recommended for inclusion in ACTIV's master protocol for adaptive clinical trials. Of the 39 agents that underwent final prioritization review, the group identified 6 agents—including immunomodulators and supportive therapies—that it proposes to move forward into the master protocol clinical trial(s) expected to begin later in May.

The Clinical Trial Capacity Working Group is charged with assembling and coordinating existing networks of clinical trials to increase efficiency and build capacity. This will include developing an inventory of clinical trial networks supported by NIH and other funders in the public and private sectors, including contract research organizations. For each network, the working group seeks to identify their specialization in different populations and disease stages to leverage infrastructure and expertise from across multiple networks, and establish a coordination mechanism across networks to expedite trials, track incidence across sites, and project future capacity. The clinical trials inventory subgroup has already identified 44 networks, with access to adult populations and within domestic reach, for potential inclusion in COVID-19 trials. Meanwhile, the survey subgroup has developed 2 survey instruments to assess the capabilities and capacities of those networks, and its innovation subgroup has developed a matrix to guide deployment of innovative solutions throughout the trial life cycle.

The Vaccines Working Group has been charged to accelerate evaluation of vaccine candidates to enable rapid authorization or approval.[4] This includes development of a harmonized master protocol for adaptive trials of multiple vaccines, as well as development of a trial network that could enroll as many as 100 000 volunteers in areas where COVID-19 is actively circulating. The group also aims to identify biomarkers to speed authorization or approval and to provide evidence to address cross-cutting safety concerns, such as immune enhancement. Multiple vaccine candidates will be evaluated, and the most promising will move to a phase 2/3 adaptive trial platform utilizing large geographic networks in the US and globally.[5] Because time is of the essence, ACTIV will aim to have the next vaccine candidates ready to enter clinical trials by July 1, 2020.

While the activities of ACTIV remain a work in rapid progress, one main element is evident: a public-private biomedical research partnership of this scope and scale has never before come together in such a short time frame.[6] For a point of comparison, the NIH's highly successful partnership with industry on common diseases, the Accelerating Medicines Partnership (AMP), took about 2 years from concept to launch.[7]

What has made the difference? Aside from the unquestionable urgency and enormous public health need posed by the

COVID-19 pandemic, one key factor that helped to speed the formation of this partnership was having the US and European government regulatory agencies directly involved from the outset. In addition, all participants, including the expert program managers from FNIH, were actively involved in coordinating and organizing the elements necessary to turn this mandate for research acceleration into reality in record time.

Indeed, with the important contributions of their time, their expertise, and their ingenuity, ACTIV's partners have embraced the spirit of a principle attributed to President Harry S. Truman: "It is amazing what you can accomplish if you do not care who gets the credit." Such an unprecedented partnership will be necessary to mount an effective and sustained response in these unprecedented times.

ARTICLE INFORMATION

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