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BUILDING THE CRITICAL PATH FOR COVID-19 THERAPEUTICS

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for COVID-19 Therapeutics

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This Duke-Margolis resource on COVID-19 response policies is intended to inform and help guide policy makers addressing the evolving COVID-19 pandemic in the United States and around the globe, and will be updated as the pandemic and response capabilities change over time.

It contains recommendations for a U.S. Federal response as well as steps and resources for stakeholders across the health care ecosystem. We will add further resources to address a range of related, critical policy challenges.

We thank our many collaborators, co-authors, and reviewers who have contributed significant expertise and guidance on these rapidly evolving issues. Please reach out to us with additional suggestions for resources and effective policies at dukemargolis@duke.edu - we welcome your input.

Executive Summary

Hundreds of therapeutics are in preclinical or clinical development for treating COVID-19 patients. But as of May 2020, so far none have demonstrated effectiveness sufficient to warrant approval for general use, although one antiviral drug (remdesivir) has shown sufficient impact in ongoing clinical trials to support an authorization for emergency use. This is a reflection of the complexity, time, costs, and uncertainties associated with developing therapeutics – a process that not only encompasses preclinical evaluation and clinical trials to demonstrate safety and effectiveness, but also manufacturing at pandemic scale, and sufficient payment to enable appropriate and effective access. Recent major initiatives including the Administration's announcement of Operation Warp Speed, building on over $10 billion in Congressional support for research and development on vaccines and other COVID-19 therapeutics, reflect the unprecedented policy attention and financial support being directed to mitigate the health and economic impact of the pandemic.

Policy attention has understandably focused on the development of vaccines as the path to recovery. But even with these unprecedented actions, the widespread availability of effective vaccines remains many months away, if not longer. To reduce the impact of the pandemic in the

meantime, intensive effort is also needed to accelerate therapeutics development to help prevent infections, reduce their severity, and mitigate or prevent further outbreak waves.

Building on recent initiatives, we propose a comprehensive set of critical path steps to substantially shorten the time and increase the capacity for bringing safe and effective treatments to market at scale. Figure 1 on page 3 summarizes the overall approach, which does not relax the standards on safety and effectiveness of COVID-19 treatments. Rather, it lays out a hyper parallel path for promising therapeutics that replaces and augments the usual highly sequential development process. This critical path develops needed evidence in less time through more powerful and efficient clinical studies, while simultaneously preparing the manufacturing capacity needed to make the treatment available quickly to all patients who may benefit. It also recognizes that there are unprecedented opportunities to use electronic data systems, artificial intelligence, and other emerging analytic tools to learn more about COVID-19 treatments after they reach the market, enabling better clinical and policy choices to maximize their impact. Action on these reforms now would lead to much faster progress on clinical testing and achieving access to safe and effective therapies months before a vaccine is available.

Key steps on the critical path for new therapeutics include:

Create a clear pathway for promising therapeutics *(page 7)*
- Identify promising therapies early for additional support
- Track and share key nonproprietary information for better investment decisions and planning
- Create clear pathway all the way to widespread access, to help product developers plan effectively and execute quickly

Increase clinical trial effectiveness and capacity *(page 9)*
- Develop COVID-19 master protocols
- Encourage broad use and transparency of master protocols by publishing protocols and tools to facilitate their implementation
- Support broad COVID-19 trial networks, testing multiple treatments efficiently
- Share nonproprietary data using common data models, for use as control populations and to guide further clinical studies
- Implement expanded access programs with mechanisms for reliably collecting key data on patients and outcomes

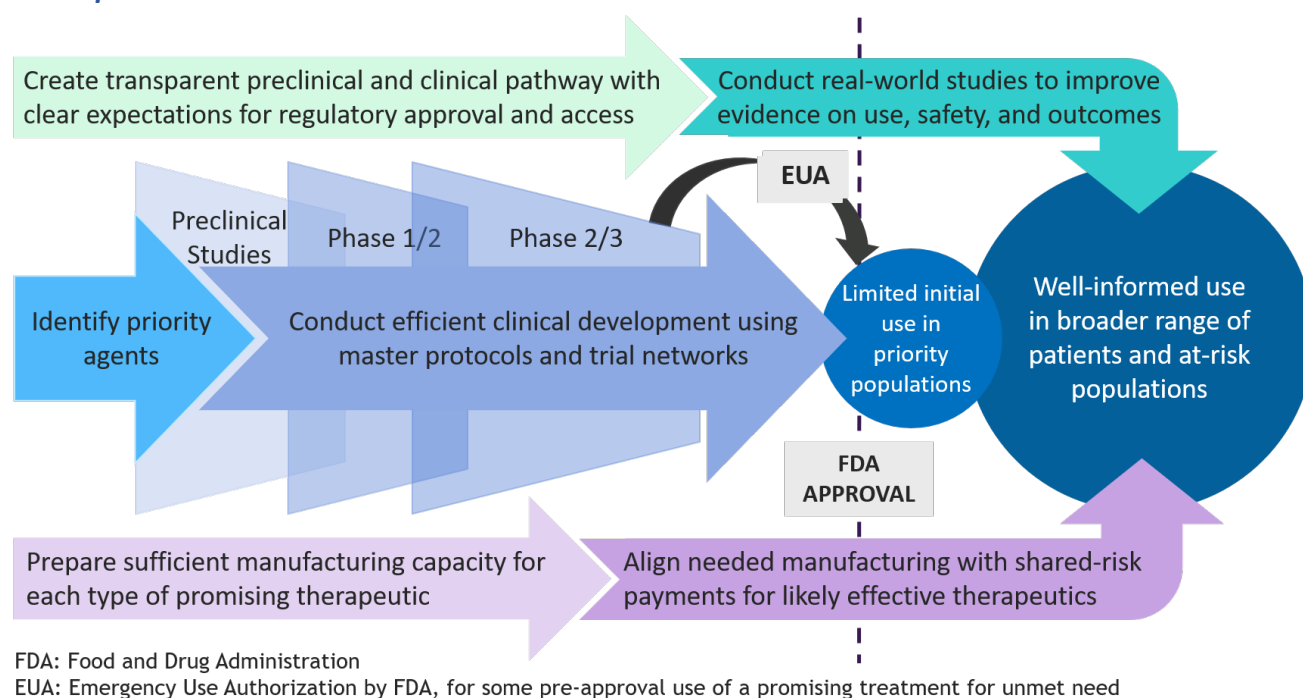**Anticipate capacity for rapid access without shortages** *(page 14)*
- Use product tracking to anticipate capacity needs to avoid delays in access
- Avoid potential shortages by redirecting capacity and developing new capacity, with shared risk financing if necessary
- Develop advance purchasing models that pre-commit sufficient volume for population access

Conduct effective real-world data collection and studies after emergency use authorizations and approvals *(page 18)*
- Plan for augmenting evidence at product approval or in emergency use authorization by building on existing common data models and electronic data networks
- Provide Federal funding to assure broad participation in key postmarket studies that meet benchmarks for speed and quality
- Link payment to implementing virtual postmarket registries and aligned studies

Most of these steps can be accomplished without further legislation, using some of the $10 billion appropriated by Congress through the CARES Act and other supplemental funding to support therapeutic development. In conjunction with the administrative steps and the private-sector actions we propose, further appropriations to accomplish these aims would enable more support for therapeutics development and could be linked to accomplishing some of the benchmarks we describe. A clear and comprehensive path from early development through effective widespread access to therapeutics is critical for reducing the enormous ongoing health and economic impact of the pandemic.

Figure 1: Parallel actions on the critical path for development and access to COVID-19 therapeutics

FDA: Food and Drug Administration
EUA: Emergency Use Authorization by FDA, for some pre-approval use of a promising treatment for unmet need

Introduction

The Federal government, researchers, industry, charitable foundations and the entire global community are mobilizing an intensive effort to develop treatments and vaccines for COVID-19. Much of this effort is appropriately directed toward developing vaccines capable of preventing infections of the novel SARS-CoV-2 virus.

While a focus on safe and effective vaccines is critical to our long-term ability to overcome the pandemic, other prophylactics and therapeutics are needed as quickly as possible to reduce the health impact of COVID-19 – and could be available much sooner than a vaccine. An effective prophylactic could potentially be used as a bridge to a vaccine for certain high-risk groups. Even after we develop and deploy successful vaccines, we will still need therapeutics that can help treat people for whom a vaccine may not be effective or those for whom it may not be an option.

To more efficiently advance these opportunities, we need to adopt a hyper parallel framework for discovery, development, manufacturing, and effective use – a process in which the usually highly sequential process for developing therapeutics is compressed, and activities are done in an overlapping fashion. Seamless trial designs can allow rapid transition from the early evaluation of a product's safety in small series to the large-scale evaluation of its efficacy in pivotal trials, while commercial scale manufacturing can be developed to avoid delays in broad availability as soon as safety and effectiveness is demonstrated. And as these treatments reach the market more quickly, we can use new analytic capabilities to assess large-scale real-world data to learn much more about how to use them effectively in particular patients and contexts – maximizing their real-world impact.

This new critical path for COVID-19 therapeutics will require us to engage in broader information sharing around early and later stage clinical development to maximize the chances of success and allow parallel planning where development and manufacturing challenges can be anticipated early. We need broader sharing of resources for pre-market assessment through standardized models and approaches, and more collaboration around clinical trial access through protocols that can be shared by multiple product developers. This requires collaboration around clinical trial access, manufacturing, and post market data collection to build in efficiencies that are needed to rapidly advance promising therapies.

Importantly, this critical path could be built for all four types of therapeutics that hold the potential to reduce the transmission and intensity of COVID-19 infections in the coming months:

- **Antivirals**: Drugs initially developed to treat other viral infections by interfering with viral replication are in clinical testing for COVID-19. Remdesivir was recently authorized for emergency use based on promising clinical trial results. Many more drugs, developed specifically for their ability to target this virus, are in preclinical testing. In addition, large-scale programs to screen a wide number of existing, pre-clinical compounds for potential activity against SARS-CoV2 are underway. Preliminary results from these studies have identified compounds that show promise, though more definitive trials are needed. While

the first generation of drugs that successfully target SARS-CoV-2 may have modest effect, the pattern for developing antivirals teaches us that the second and third generation drugs should offer greater benefits. In other conditions such as HIV and hepatitis C, early antiviral therapies had some impact on the course of infection, but also provided a foundation for the development of more effective next-generation therapies.

- **Immune modulators**: Most SARS-CoV2 infections do not have serious health consequences. However, severe complications in the minority of patients who are hospitalized – particularly elderly patients and those with comorbid conditions – have led to hundreds of thousands of deaths and to health care systems being pushed to or beyond crisis capacity worldwide. Studies have indicated that intense immune reactions, with "cytokine storm" and the release of other compounds involved in inflammatory response, may be important contributors to poor outcomes in these patients. Consequently, immune modulator drugs may be able to reduce the incidence of severe complications, critical illness and mortality in certain patients, as well as reduce the strain on health system capacity from COVID-19 in the months ahead. Because some COVID-19 patients also have serious complications from blood clotting, studies of anticoagulants and thrombolytic drugs are also getting underway.

- **Antibody-based treatments**: Serum from convalescent patients and hyperimmune globulins from the pooled antibodies of such patients have proven to be effective therapies and prophylactics in other viral conditions. Clinical studies using such antibody treatments in COVID-19 settings are underway. While supplies of such immune globulins will likely be limited, advances in monoclonal antibody technology permit large-scale synthesis of antibodies that could be effective against the virus. Through such an approach, the most potent antibodies that the body would normally produce to target the virus can be produced at large scale using biotechnology processes. These can be delivered as treatments in early infection, as well as used as post-exposure prophylaxis to prevent infection in those exposed to the virus. They may also be used as a prophylaxis in high risk populations. Some monoclonal antibodies can be engineered to have a prolonged half-life, perhaps requiring only monthly, bi-monthly, or even semi-annual infusions. Used in this way, the antibody drugs can serve as a bridge to a vaccine for certain patients. Promising monoclonal antibody compounds are expected to enter clinical testing soon, with results expected later in the summer.

- **Other drugs and biologics**: Hundreds of other compounds or approaches are in preclinical or clinical testing, ranging from cell-based therapies to treatments based on CRISPR technology. As evidence accumulates related to these diverse pathways of treating COVID-19, additional scientific and regulatory steps like those we propose for the other categories should be developed.

Supplemental Table 1 illustrates some of the promising treatments in the first three categories that are in advanced preclinical or clinical development.

Many efforts are underway to further advance the development of these treatments. **To accelerate this progress, we focus on four steps on the critical path of turning promising drug and biologic candidates into safe, effective, and widely available therapies:**

- **Create a clear pathway for promising therapeutic candidates**, including not only additional financial support from government programs designed to invest in promising therapeutics but also additional early support from regulators. Such supports cannot be provided to every product developer and must be prioritized. Prioritization starting with preclinical assessment should be based on publicly-available criteria that can be shared across industry and refined to enable more effective early assessment, including better informed funding decisions by foundations and private investors. Moreover, all priority products should have information made available – to the extent feasible – on each product's expected development milestones, including expectations about the start and duration of clinical testing and manufacturing needs. A shared understanding of key product development needs will avoid delays and shortages later.
- **Increase clinical trial effectiveness and capacity**, by using clear regulatory guidance on trial design to leverage master protocols that reduce the cost and increase the impact of expanding clinical trial sites, and to facilitate the development of networks capable of contributing to well-designed trials. The selection and enrollment of products into existing master protocols needs to be made highly efficient, so product developers don't undergo delays owing to the governance features of the master protocols. The master protocols should be designed and governed in a way to ensure that candidates are matched rapidly, trials enroll quickly and are conducted effectively, yielding meaningful results no matter where COVID-19 outbreaks are occurring.
- **Anticipate capacity for rapid access without shortages**, by planning ahead for each type of manufacturing capacity that may be needed, improving and reallocating existing capacity, and developing additional capacity that could be rapidly directed to particular treatments that show effectiveness. This may involve additional public investments in domestic manufacturing capacity, and contracts between manufacturers and public and private payers that commit to adequate supplies for covered populations rather than fee-for-service contracts.
- **Conduct effective real-world data collection and studies after emergency use authorizations and approvals**, by developing and then promoting the use of tools and resources to address key further questions about safety and effectiveness. A shared approach can answer many questions that cannot be fully addressed in pre-approval studies of reasonable duration and size, and can be done in collaboration with payers and real-world evidence networks.

These steps can be taken in conjunction with Federal actions and public-private collaborations that are already underway. The National Institutes of Health (NIH) and Foundation of the National Institutes of Health's (FNIH's) Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership, for example, has been established to prioritize candidates, help promising ones move forward, and expand streamlined trials including through NIH's trial networks. The Adaptive COVID-19 Treatment Trial (ACTT), supported by the National Institute of Allergy and Infectious Disease (NIAID) is already conducting randomized trials of prioritized agents at over 60 sites in the United States, Europe, and Asia. Other research and trial infrastructure efforts like I-SPY 2, an adaptive trial network for breast cancer therapies, have implemented their own

processes to prioritize studies of promising COVID-19 therapies. Robust coordination between these prioritization activities will help advance the most promising agents to clinical testing.

At the same time, the U.S. Food and Drug Administration (FDA) has established the Coronavirus Treatment Acceleration Project (CTAP) to support more the implementation of rapid and efficient development programs for sponsors entering human testing of COVID-19 treatments. A range of additional public and private collaborations and initiatives are also addressing various aspects of the broader critical path to COVID-19 therapeutics. Many of the organizations leading these efforts, like the Clinical Trials Transformation Initiative (CTTI), are working to apply concepts like quality by design to ensure that COVID-19 trials make use of the best and most efficient approaches to rapidly generating the evidence that FDA will need for approval.

The Administration's recently announced Operation Warp Speed seeks to bring Federally-supported efforts together in a national program to accelerate the development of therapeutics, as well as vaccines and better diagnostic technologies. In addition to supporting development of new therapeutics, Operation Warp Speed intends to focus on building adequate manufacturing and supply chain support and assuring widespread and timely distribution of affordable therapies.

Our report describes steps to build on this progress – steps that the Administration, Congress, and the private sector can take to make sure the nation can overcome the key challenges and rapidly advance the development of treatments and prophylactics that will help fulfill therapeutic needs and help patients until an effective vaccine is available. It addresses both treatments already available and being repurposed for potential use against COVID-19, as well as new treatments that are or will launch clinical studies in the coming months. The recommendations are relevant to all potential types of therapeutics, and we believe they should be considered and enacted in collaboration with world health authorities to ensure global coordination of critical development efforts. We believe these efforts to promote an efficient development path for therapeutics will complement the promising work of NIH, FDA, the World Health Organization (WHO), and others to advance a parallel development track for a vaccine.

Create a clear pathway for promising therapeutic candidates

Governmental agencies are taking unprecedented steps to support preclinical and clinical development of new products to treat COVID-19. NIAID, Biomedical Advanced Research and Development Authority (BARDA), the Department of Defense (DoD), and private entities are committing substantial funding and streamlined pathways to support product development. FDA is providing extra assistance to COVID-19 product developers through its expedited review and approval tools, like its Fast Track and Breakthrough designations, and its ability to grant Emergency Use Authorization (EUA). The agency has achieved rapid response times on study protocol reviews and other regulatory actions.

However, with hundreds of products at various stages of development, it is possible that promising new therapies – especially from smaller, less experienced developers – may not be

well connected to these resources. As such, they may benefit from additional assistance. The ACTIV public-private collaboration through NIH and FNIH aims to identify promising candidates that may face challenges in obtaining adequate funding for development, or in progressing to clinical testing and standing up timely, well-designed clinical trials. To speed development, ACTIV will also promote the use of shared protocols across clinical trial networks, starting with NIH's networks, to increase the capacity for clinical development of these prioritized products.

Improve tracking and support for rapid progress on promising treatments

To make informed decisions that accelerate product development and to anticipate challenges in subsequent stages of development, criteria for accelerated assistance and key information on priority candidates should be publicly available. Some of the product information shared with FDA, NIH, BARDA and other relevant government officials is proprietary, and so cannot be made publicly available to protect its confidential nature without permission by the product sponsor. In 2014, in response to the Ebola outbreaks, NIH and FDA convened clinical researchers to prioritize products for development in a common protocol. Legal guidance for this process enabled some commercial confidential information to be shared to help identify priorities. Along with similar steps, ACTIV should develop and encourage public awareness and input on the considerations and criteria that it takes into account in identifying promising treatments, and should provide non-identifiable summary information on ACTIV findings and actions to support development. Other funders have different approaches and perspectives that they will use to drive their investment decisions. But a better shared understanding of opportunities and challenges, how products are being assessed, and the kinds of approaches that are being considered in ACTIV's work can make allocation of capital to these efforts potentially more efficient and help product developers maximize their chances of success.

ACTIV or collaborating organizations should also facilitate reporting, where feasible, on milestones for products that receive public support through its initiatives. This may include non-proprietary information that helps product developers avoid delays in later phases of development, such as identification of manufacturing capacity so that shared decisions can be made around the proper allocation of limited domestic manufacturing resources. Such information can also help provide milestones of success to gauge progress on different potential therapies, and to inform private efforts to support therapeutics development. This would help private foundations, industry, venture capital, and other potential funders allocate resources to the most promising candidates and help less experienced companies with innovative products plan for development more effectively.

Alongside ACTIV-led efforts to track and report on candidates receiving enhanced resources and support from the public sector, companies and industry organizations could work with organizations like FasterCures and the CTTI to publicly collect and report a limited number of other critical nonproprietary features of promising products in development. **Key nonproprietary information that should be publicly available include:**

- For earlier-stage products: type of product, key milestones in preclinical development, expected initiation of Phase I testing
- For products in clinical testing: study design, start date, endpoints, use of a master protocol, expected size and power, expected readout dates, significant updates on enrollment and retention; planned manufacturing capacity
- For approved products: randomized and observational postmarket studies being supported by the manufacturer or other bodies, including information on key design features, (e.g., use of standard protocols for data collection and analysis, manufacturing capacity and plans for expansion)

Such key information is not consistently available today. Some of these key data points and other relevant information are already included in trial reporting to clinicaltrials.gov, in announcements of new Federal actions to support therapeutics, and in public releases by individual product developers. Further steps to make such information reliably available could improve our ability to assess whether a clinical development plan is likely to succeed, to plan ahead for adequate manufacturing capacity, and to anticipate and collect postmarket evidence needed to augment what is learned in premarket clinical trials. Such a reporting tool would also assist potential trial sites in assessing where they should focus their efforts, and would help with alignment on effective protocols and tools for integrating data and findings across studies.

Increase clinical trial effectiveness and capacity

Clinical development, especially the conduct of well-designed clinical trials that provide meaningful evidence on the effectiveness and safety of new treatments, can be time consuming and costly. In the setting of a public health emergency, every effort must be made to identify which of the many promising therapies are effective, so that resources to provide rapid access can be concentrated on therapies that truly impact patient health. Steps to reduce time and cost of development are consequently important but must be done in a way that does not compromise safety or significantly impede our ability to develop rigorous evidence about the scope of a product's effectiveness.

The number of trials underway for COVID-19 therapies is increasing rapidly, but many do not randomize patients using widely-accepted and thus comparable treatment protocols, are too small to provide definitive answers about a product's safety and effectiveness, or are planned using individual protocols that are hard to align with other studies underway. In addition, distancing and other measures are having a significant impact on the spread of the virus, meaning benefits from mitigation could inadvertently hinder clinical trial progress. There are concerns that a significant number of promising drugs and biologics currently in preclinical testing could progress to human testing at the same time as clinical trial sites have diminishing patients with active infections.

Sponsors and policymakers should prepare now for a surge in promising therapeutics that will need access to clinical trial sites to determine their safety and effectiveness, particularly using efficient Phase 2/3 study designs that may be in limited supply relative to the demand for

clinical studies. As we describe in more detail below, foundational steps are already underway to substantially enhance the availability of effective clinical trial capacity COVID-19 products.

FDA's Center for Drug Evaluation and Research has taken important steps to enable rapid progress. In particular, FDA's [recent regulatory guidance on clinical studies for COVID-19 therapeutics](#) includes clear and specific approaches for designing pivotal trials to provide substantial evidence on effectiveness and safety, with a set of clinical trial endpoints that can be observed in a limited period of time. For treatments used for severely ill patients, these include mortality, respiratory failure (e.g., use of noninvasive or invasive ventilation), need for intensive care, and time to discharge and recovery, all measured from time of randomization. For treatments used in less severe, ambulatory patients, endpoints include hospitalization and time to sustained recovery. For prophylactic treatments, outcomes include occurrence of a lab-confirmed COVID-19 diagnosis (with or without symptoms), and severity of infection (e.g., duration or need for hospitalization).

The guidance also outlines the range of patients that should be part of the trial design, including elderly individuals and individuals from communities with relatively high shares of low-income and minority patients, which have been disproportionately affected. It outlines how clinical investigators can implement pre-specified approaches to move quickly to expand evaluations that show promising results into pivotal trials, how to determine more quickly whether agents are ineffective, and how to adjust enrollment in a "multi-arm" trial to make those decisions as quickly as possible.

The guidance indicates that it should generally be possible to complete well-designed trials very quickly – within 28 days for treatments in more severe patients, and in no more than a few months for other less severe study populations. However, this pace is only likely to be achieved through well-powered studies, particularly those that use consistent, straightforward master protocols aligned with the FDA guidance and that are designed in advance to use multiple arms including a "standard of care" control arm that can evolve over time. As we describe below, most COVID-19 clinical trials do not have these features – but timely action can change that, enabling substantially more rapid progress in the clinical evaluation of a much larger number of potential therapeutics.

Implement master protocols

Potential bottlenecks in trial initiation and patient recruitment can be alleviated with further development and use of master protocols for COVID-19 studies. Master protocols are utilized in specific instances where a sponsor wishes to have one single protocol across multiple, parallel sub-studies that are being conducted at the same time. They can be designed to facilitate the study of multiple diseases, multiple candidates, or both, and typically have a set of core data elements, measures, and endpoints that are collected in each sub-study. They can evaluate, in parallel, different drugs compared to their respective controls or to a single common control. These trials can be updated to incorporate new scientific information, like novel biomarkers, as medical science advances. The infrastructure for these trials can last for many years. This reduces

administrative costs and time associated with standing up new trial sites for each drug candidate. It allows more efficient coordination around the rapid recruitment of patients with COVID-19 in the setting of a public health emergency, where clinical resources are likely to be strained and providers have limited time to devote to the implementation of clinical studies.

Leading institutions have announced major collaborations to develop and implement master protocols, including NIH's Adaptive COVID-19 Treatment Trial (ACTT), WHO's Solidarity Trial, the University of Oxford's RECOVERY and PRINCIPLE Trials, and an addition of COVID-specific arms to UCSF and Quantum Leap Health's ongoing I-SPY-2, among others. Supplemental Table 2 highlights several of these promising initiatives and their key characteristics.

Additional master protocols are likely needed for a range of study types in different clinical settings, including: hospitalized patients with serious COVID-19 complications (endpoints related to mortality, vent use, time in hospital, etc.), patients with significant COVID-19 complications being managed on an outpatient basis (endpoints related to hospitalization with complications), patients with milder disease in outpatient setting especially those with higher risk of progression (endpoints related to progression to serious complications or hospitalization), and individuals at high risk of contracting COVID-19 who would benefit from effective prophylaxis (endpoints related to infection or complications from COVID-19). Studies might also focus on particular subgroups of these populations.

In each situation, we should accelerate use of a specific master protocol that would be focused on enrolling patients in this particular care setting and disease stage. The goal should be to pursue coordination around recognized master protocols that can be widely adopted across many different institutions to support well-powered studies that can be completed rapidly.

As these and other master protocols begin trial initiation and are considered for additional study sites and treatment modalities, protocol developers should publish their work and identify ways to encourage alignment. The RECOVERY trial, for example, has published their master protocol publicly as a resource for other researchers and for sponsors of additional studies, as has REMAP-CAP-COVID. All such master protocols should be published to facilitate efforts to harmonize them where appropriate and encourage their wider adoption.

Tools linked to these leading protocols are needed to help potential sites and patients better understand how they can participate and the potential benefits of doing so, thereby increasing the opportunities for patient enrollment in well-powered, well-designed trials. Such templates and associated tools for using them would describe key data on patient characteristics, treatment conditions, and primary and secondary endpoints. Such resources could be useful to many sponsors in planning their studies, leading to more efficient design choices. They would help additional trial sites, such as individual hospitals around the country, accomplish the key features of well-designed clinical trials by leveraging the trial network resources: feasible patient consent; appropriate randomization; data and endpoint collection, generally using electronic methods; and the capacity to provide alternative treatments to participating patients.

These tools would aim to be helpful for particular sites, but potentially could be adopted by health care systems, payers, or consumer- and patient-facing organizations that can assist individual sites or participants in developing the critical capacities needed for trial participation. CTTI is developing a set of tools and resources to provide a roadmap to more rapid adoption of COVID-19 master protocols that could serve as a basis for setting goals and accelerating the use of master protocols more broadly. These should be used to identify promising additional participants from interested research networks created for other purposes, health care systems, payers, and other organizations. As we discuss below, clinical research organizations can also assist with the adoption and use of the protocols and support expansion of networks.

These tools should also be used by NIH and other funders to set clear guidance and expectations about study design and performance. There are reasons why particular trials may decide to use different endpoints or designs, but the urgency of developing meaningful clinical evidence on COVID-19 treatments means that funders should have clear reasons for supporting alternative approaches. All COVID-19 clinical trials should be well designed reflecting best practices on endpoints and statistical methods, and powered to support rapid enrollment and execution within a several-month time frame. Variants from the design suggested by these best practices may be appropriate but should be justified.

Support enhanced COVID-19 trial networks

Well-developed master protocols provide the foundation for developing larger COVID-19 clinical trial networks by enabling existing networks, clinical research organizations, and additional potential trial sites to enroll more patients in more places in well-designed trials. This will allow clinical trials to respond to likely shifting geographic distribution of patients with COVID-19 as the management of the pandemic advances. The existence of widely accessible master protocols will reduce the time needed to ramp up and complete trials, and can make clinical trials more accessible to sites that may not have the resources or infrastructure to participate in trials without the that provided by a formulated master protocol. Governance of the master protocols has to ensure that the evaluation and entry of drugs into the protocol is done efficiently, so that there are not long delays while decisions are made about which therapies to admit. Such a framework will make experimental drugs and clinical trials more accessible to more patients.

Similar trial networks have facilitated collaboration and reduced the cost and time of clinical trials in other disease areas, such as cancer, Alzheimer's disease, and antimicrobial-resistant pneumonia. **The COVID-19 networks should be fast, flexible, and well-organized enough that clinical development programs can quickly use them rather than having to invest time and development costs in a "one-off" clinical development program with FDA.** Using master protocols, these networks should be able to implement multi-arm trials that can compare multiple treatment alternatives or combinations, and to shift over time as evidence on particular treatments accumulates, with new arms added and others removed.

The goal of the COVID-19 trial networks is to have treatments that don't work fail as quickly as possible, and to enhance the pace of accumulating evidence necessary for approval for treatments that do work. Because the effectiveness of candidate products is unknown, this work should be guided by a statistical assessment of optimal treatment selection and removal, based on statistical designs that limit errors in missing products that do really work, and that use prespecified methods to incorporate preliminary evidence on the treatment. Greater use of such adaptive approaches can also give sponsors the flexibility to react to clinical evidence as it's being collected, and modify the design and enrollment in trials by including more patients with characteristics that predict they are more likely to derive a benefit from a particular treatment. It can also allow providers to exclude patients from clinical trials who possess characteristics that suggest that a patient is more likely to suffer a side effect from a particular experimental treatment.

By enriching the enrollment in the trial for patients with characteristics that are likely to predict clinical successful outcomes, these approaches have the potential to make the development process more efficient and patient benefit more likely. This approach also allows providers and sponsors to potentially learn much more about the characteristics that can inform safer prescribing. Those that demonstrate significant likelihood of effectiveness should be shifted to larger-scale evaluation, that is, a rapid or seamless shift from Phase 2 into Phase 3 evaluation within the same trial network. The greater the capacity of the trial networks for conducting such studies, the more treatments can be screened and then moved through late-stage development.

Using this approach, clinical research organizations or network sponsors could assist with recruiting additional providers, sites, and patients, expanding their reach into diverse populations and regions. Better network tools would also assure that the trial subjects' time and effort to participate in a study would be likely to lead to meaningful new evidence; that is less likely to be the case in a small, standalone, underpowered trial. CROs and existing research networks, such as PCORnet and cancer clinical trial networks such as I-SPY, can be key contributors to building this enhanced trial capability.

ACTIV is encouraging the development of such clinical trial networks using master protocols, starting with the adaptation of existing NIH trial networks to conduct effective COVID-19 studies. These activities can be augmented to extend to other potential trial sites and clinical research activities, with benchmark goals for clinical trial capacity to stay ahead of the need for promising trial sites. **Efforts to implement new trial networks at scale should be global – particularly as waves or outbreaks of COVID-19 ebb and flow geographically over time.** Trial networks since GUSTO have for decades shown that it is possible to get large-scale participation built around simple, straightforward templates based on master protocols that can be adopted in multiple centers; this should be easier with the digital technologies used to support the emerging COVID-19 master protocols. RECOVERY is providing strong early evidence that simple, effective protocols can drive widespread participation; over the course of 8 weeks it has already enrolled 10,000 eligible hospitalized patients in the UK.

To support these efforts, ACTIV and other research support programs should track and publicly report on progress made toward the goal of large-scale trial capacity, and on the pace of conducting clinical evaluations of COVID-19 treatments, ideally as part of tracking and reporting on the clinical trials themselves that are underway. Key measures include the capacity and throughput of the trial networks.

Implement effective expanded access programs

While rapid completion of clinical trials of promising treatments is a critical priority, it is likely that many patients who are not able to enroll in such trials will want access to the therapy before approval – particularly patients with serious COVID-19 complications. **FDA should support the timely implementation of a model expanded access program for COVID-19 patients in cases where manufacturers have additional treatment capacity available – which is likely if the sponsor is ramping up production as described below.** This model COVID-19 expanded access program should include guidance and tools for setting up a registry to track the characteristics and outcomes of patients who receive treatments under the expanded access program, and to support the critical postmarket evidence development steps also outlined below. Coupled with standard data protocols, the widespread availability of electronic data systems should facilitate registry implementation, at least for hospitalized patients.

Anticipate capacity for rapid access without shortages

Ensuring that new COVID-19 treatments can be available at scale with minimal delay following FDA's EUA or approval requires advance planning and investment. As evidence on effectiveness of a therapeutic accumulates rapidly, planning for manufacturing capacity with supporting supply chains is needed in advance to have adequate quantities of the therapeutic available, including for the possibility of further COVID-19 pandemic waves. For repurposed drugs, this supply must be sufficient to continue to meet the needs of patients who already depend on the treatment.

Assess future COVID-19 treatment capacity gaps

The diversity of potential therapies for COVID-19 requires a range of manufacturing platforms, including for small-molecule parenterals, monoclonal antibodies, and flexible single-use advanced biologics. Non-specific fill-and-finish capacity that can quickly be adapted to accommodate a wide range of therapies is also needed. This capacity can be costly and time-consuming to put in place, with only a limited supply available in the US and globally. Even products that are easier to manufacture, including small-molecule oral formulations, face supply constraints. They are often produced overseas and may be vulnerable to supply disruptions during the pandemic.

Major pharmaceutical companies with substantial capital and experience are already undertaking this type of advance planning for their COVID-19 therapies. For example, based on projections of potential high demand for remdesivir, Gilead has ramped up US manufacturing capacity and is entering into licensing agreements with additional manufacturers outside the US. However, smaller biotechnology companies may not have the capacity to make such advance

arrangements, and available manufacturing supply may fall short of needed capacity later this year, so that effective treatments without such advance arrangements in place may end up facing shortages.

To avoid such shortages for treatments that are shown to be effective, advance planning should be undertaken now to include an assessment of each major type of manufacturing capacity, in relation to the expected time to emergency use availability and approval for the promising treatments in development. An estimate of needed manufacturing capacity would reflect the treatments expected to reach late-stage clinical trials over time (e.g., in the next several months, fall, winter, and into 2021) along with an estimate of potential demand for such treatments accounting for the possibility of larger outbreaks later this year. The analysis should expect that the vast majority of products not yet in clinical development and most of those in early clinical development will fail, but (in the event that more succeed) that some excess capacity is needed because the value of having multiple effective treatments is high.

The assessment should match the different types of advanced manufacturing capacity with the promising therapies currently in development. For example, over 20 monoclonal antibodies to the SARS-CoV-2 virus are in development now; while many are unlikely to succeed, additional capacity that could be made available to manufacture those that do would help avoid shortages. There should be an assessment of the potential needs not only of COVID-19 patients with different risk and severity levels, but also use in prophylaxis. Some of the potential treatments to avoid the complications of severe immune responses are also monoclonal antibodies. Thus, monoclonal antibody manufacturing capacity planning should assure adequate supply for multiple manufacturers of all of these treatments. Similar analyses are needed of manufacturing capacity and flexibility for adequate production of other types of products.

The assessment should include each major step of the manufacturing process – from the acquisition or production of active pharmaceutical ingredients and biologic components, to purification, to the provision of glass for finished dosage forms – to identify and address potential barriers and bottlenecks that could affect availability. This assessment may identify practical opportunities to make existing manufacturing capacity nimbler and more flexible, as we describe below. Given that manufacturing capacity in other countries may be required for domestic production of COVID-19 therapeutics, the assessment should differentiate US-based capacity needs and gaps.

BARDA in collaboration with other government agencies involved in the COVID-19 response has already undertaken such assessments as part of its work to support product availability. To assure coordination with product developers (especially smaller companies with less resources), and to assess whether large companies that have already contracted for forward capacity are prepared to redirect it if their compound does not succeed, steps to increase manufacturing capacity and fill gaps should be reported publicly and updated regularly.

Develop plans for sufficient ramp-up of advanced manufacturing capacity

There are three sources of increased manufacturing capacity to address shortfalls identified in COVID-19 capacity assessments: using current capacity more efficiently, redirecting existing capacity to new treatments, and building additional capacity.

Working with FDA and other agencies, manufacturers should identify ways to optimize use of current manufacturing capacity, and prepare for flexibility in that capacity to support potential ramp-up in production of new therapies. For example, FDA has previously encouraged companies to adopt continuous manufacturing techniques instead of batch certification, both to increase productivity and enable more rapid shifts of production lines to avoid shortages. Companies with relevant capacity should also increase production to stockpile other drugs now so that more capacity is available when effective COVID-19 therapies are identified, and seek opportunities to increase production at other manufacturing facilities outside the US.

With support from BARDA, new manufacturing capacity should be added where critical to address potential shortages, using current best practices and supporting technologies. Building new advanced manufacturing capacity takes time, but it is not too late to undertake further activities now if assessments suggest key gaps. For example, recent advances in the technology used to manufacture therapeutic monoclonal antibodies have allowed new therapies to enter production in just 10-12 months, and with careful planning and investment this can be reduced further. Regulators can support efforts to bring these drugs into production: FDA should provide technical assistance during clinical development to precertify potential production facilities, before clinical trials are completed.

As limited advanced manufacturing capacity is repurposed toward producing therapies for COVID-19, stakeholders must ensure that such repurposing does not result in shortages of critical therapies for other conditions. Efforts to repurpose existing manufacturing capacity should include planning to avoid disruptions in access for patients who need products that may be repurposed for COVID-19 treatment. The recent increase in demand for hydroxychloroquine showed the importance of including existing products in planning. This may also be important for immune modulators that show promise in treating COVID-19 and yet are critical for patients with autoimmune conditions and other immune-related disorders.

To support these efforts, a public-private collaboration that includes FDA, biotechnology and manufacturer associations, and relevant companies could identify opportunities for manufacturers to shift existing capacity to produce the most promising therapies quickly, even if the production is for companies that are normally competitors. Such collaboration should be supported by financial incentives for companies that make their capacity available for production of effective therapies.

Provide financial support for expanded manufacturing and timely, adequate availability

New financial incentives and payment models will be needed to ensure sufficient investment in the manufacturing of COVID-19 therapies. Many manufacturers are planning ahead for manufacturing their own products in development. However, investing in large-scale manufacturing capacity before trial results are known entails significant financial risk, which may limit the amount of product available soon after trial completion. Even large manufacturers may have difficulty preparing to go at risk for the full scope of COVID-19 treatments likely needed, and advance financing of sufficient manufacturing capacity is likely to be particularly challenging for smaller product developers with less available capital.

The US government should expand investments now to secure adequate manufacturing capacity to meet potential COVID-19 patient needs. Given the cost involved in redirecting or developing new manufacturing capacity, additional public investments are needed to close gaps in any needed capacity. BARDA and other agencies are working to increase such capacity, both by working with specific product developers and by investing in advanced manufacturing technologies that can help scale that capacity. Such investments should include, for example, parenteral manufacturing capacity that could be quickly dedicated to augmenting manufacturing capacity for any particular parenteral drug that shows clinical effectiveness; and monoclonal antibody manufacturing capacity that could be quickly recruited for additional manufacturing of an antibody that shows clinical effectiveness.

Such payments for capacity development should be augmented by large-scale advance payment contracts for producing the therapies. Many manufacturers have already committed to producing COVID-19 therapies on a not-for-profit basis linked to cost of goods sold during the pandemic emergency. Because exact supply needs are hard to predict, advance payment contracts for a sufficient volume of production will enable all parties to share risk. Working out model versions of these contracts now will help avoid delays due to uncertainties about costs or needed manufacturing scale after products demonstrate effectiveness, and will also help avoid shortages.

Two types of large-scale, advance payment contracts should be explored. First, Federal funding administered through BARDA should support large-scale purchases of effective therapies, to reduce uncertainty for manufacturers and payers about the scale and cost of new COVID-19 therapeutics and to help ensure adequate supply. BARDA's authority and funding to supply the Strategic National Stockpile can be a basis for these contracts. Model contracts should be developed in collaboration with product developers and potential manufacturers. These Federal contracts could assure capacity for surge needs (e.g., large outbreaks), uninsured individuals, and to address potential shortages in public programs. With sufficient funding, they could also be used to provide access to therapies in publicly- and privately-insured populations.

Second, the Centers for Medicare & Medicaid Services (CMS) and private payers should explore the development of advance purchase contracts for adequate therapeutic supplies for their covered populations given the current public health emergency. Such contracts would be

implemented only for therapeutics that reach the market based on adequate evidence of safety and effectiveness, and could replace fee-for-service payment for individual drug purchases. These population-based payments would commit manufacturers to providing a minimum amount of a product expected to meet the needs for the covered population in the event of significant viral activity, for a population-based aggregate price. While that price may be significantly lower on a per-unit basis than might be achieved through traditional fee-for-service pricing, high per-unit prices and potentially high copays are not conducive to providing access to patients who need treatment to control the pandemic.

This approach is consistent with Congressional actions to limit copays for COVID-19 testing and treatments. Thus, this approach would reflect the special circumstances of pricing during the public health emergency, would help avoid shortages despite considerable uncertainty about the course of the pandemic, and would help assure that outbreaks can be rapidly treated. Because the marginal cost of production is low compared to the average price for most drug therapies, the approach should enable payers to commit to paying for a larger product supply than if only per-unit pricing was available, while allowing manufacturers to cover their costs for providing a larger supply.

A model contract for such emergency population-based purchasing could be developed by CMS for Medicare, alongside models for state adoption in Medicaid. Private payers would likely adopt similar models if available. Congress could encourage such contracts, for example in Medicare Advantage or Medicaid managed care plans, through authorizing partial matching funds or providing other guidance for providers and manufacturers who move away from fee-for-service contracts. These emergency supply contracts should also be exempt from usual pricing regulations such as Medicaid best price that are used in nonemergent circumstances. Even if such contracts cannot be executed in the short term as alternatives to fee-for-service pricing, their development would encourage needed collaborations and sharing of information among government, manufacturers, and payers to assure adequate access for COVID-19 treatments.

While challenging, the alternative to such advance manufacturing planning and purchase contracts is far less desirable. Shortages would be more likely to emerge especially in the event of further outbreaks or a surge in cases. This would be particularly challenging for specific insured or uninsured populations that do not secure advance contracts, requiring difficult government-directed determinations about priority access to therapies. The use of the Defense Procurement Act could address manufacturing shortages, but the time required to shift manufacturing lines for complex biologic products is likely to be longer than for protective equipment or ventilators, and would likely disrupt supplies of other needed drugs.

Conduct effective real-world data collection and studies after emergency use authorizations and approvals

The use of new COVID-19 therapeutics will be supported by meaningful evidence on safety and effectiveness resulting from randomized trials completed prior to product approval. However, pivotal trials for initial approval are likely to be based on evidence of safety and efficacy in specific

types of COVID-19 patients and treatment contexts, such as hospitalized patients with severe illness. Moreover, in the absence of robust treatment options, FDA will likely implement emergency use authorizations for treatments with promising clinical results before trials are complete. And there are also likely to be substantial gaps in the evidence available on products already on the market that are hypothesized to have activity against COVID-19, where significant "off-label" use may occur.

As a result, clinicians, patients, and the public will want additional evidence on new COVID-19 treatments following their initial approval or emergency availability, including evidence on:

- **effects in patient subgroups (e.g., elderly with complex conditions, different demographic subgroups)**
- **prophylaxis or earlier-stage treatment for drugs approved for patients with more severe COVID-19 cases**
- **effectiveness of treatment combinations**
- **comparative effectiveness and cost effectiveness of alternative COVID-19 treatment strategies as more become available over time**

Recent developments in real-world evidence systems and electronic data analytic capabilities provide new opportunities to address these critical evidence gaps. Analyses of "big data" from electronic medical records, insurance claims, patient-generated data, and other sources can support analyses of the evolving natural history of COVID-19 infections in different types of patients, and can help understand syndromes and risks such as late inflammatory syndromes in children and the consequences of alternative approaches to breathing assistance and ventilation. Such analyses can help improve clinical trial evidence, by guiding clinical trial design (e.g., informing statistical power calculations) and by making it easier for more sites of care to implement clinical trials using the tools like common data models and master protocols that we described previously. In addition, the improving infrastructure for conducting real-world studies can augment such clinical trial evidence.

Leverage existing RWE infrastructure to fill key evidence gaps

FDA, CMS, Federal research funders, private entities, and companies with expertise in large data analysis are supporting RWE studies to provide evidence on COVID-19 questions. These studies are leveraging a range of observational study networks using secondary electronic data generated through care delivery, common data models, and shared protocols for interventional studies analogous to those described for clinical trials above.

Existing distributed data networks such as FDA's Sentinel Initiative, the Patient Centered Outcomes Research Network (PCORnet), the Observational Health Data Sciences and Informatics (OHDSI) program, large health care systems (e.g., University of California Health System, US Veterans Health Administration), and EHR vendors (e.g., EPIC and Cerner), are also using their datasets to address priority questions involving therapeutics. These approaches can enable consistent, parallel analyses across multiple settings and data sources, and can be used to

conduct fast studies across a large number of patients and health care organizations. For example, the PCORI-funded HERO registry, which uses PCORnet, aims to understand the impact of COVID-19 in health care workers across hundreds of hospitals and other health care systems. In addition to evaluating clinical questions, Sentinel is also being used to answer questions about the drug supply chain (e.g., assessing products used in the inpatient and outpatient settings to anticipate potential drug shortages).

In addition, some organizations have made deidentified, HIPAA-compliant data available for research use. The COVID-19 Research Collaborative, for example, is a pro-bono initiative of data companies, data platform companies, and researchers that are collaborating to share and link claims, EHR, and mortality data and make them available to researchers. Supplemental Table 3 summarizes many of these activities and the evidence gaps they are aiming to fill.

Further steps are underway to leverage these efforts to accelerate the development of needed evidence. The Reagan-Udall Foundation and Friends of Cancer Research COVID-19 Evidence Accelerator, for example, is a public-private collaboration supported by the FDA that is bringing together a broad community of methodological experts, public health officials, diverse data sources and RWE evidence initiatives to take steps to cross-validate findings on priority questions identified by the FDA and stakeholders. By developing a common set of core data elements that can be analyzed using common protocols by a range of RWE groups, the Evidence Accelerator can facilitate more comparable and robust results. It also facilitates expert exchange and analysis to address key questions and methodologic issues. The data remains with its originator, and jointly developed analyses provides a research framework that can be applied to answer new questions over time. In a rapidly evolving clinical environment of COVID-19, confirmation of results and validation of methods across multiple sources of data can increase confidence in the findings, provide a stronger basis for clinical decisions and policymaking. In parallel, MITRE's COVID-19 Healthcare Coalition aims to integrate existing common data models by building a meta-data like model, mCOVID, to enable broader, more technically aligned analyses. EMR vendors and other groups are also supporting tools to make it easier for health care providers to contribute their electronic data to relevant studies.

To further accelerate needed evidence on therapeutics, broad multi-stakeholder collaborations like these should receive additional support to address key postmarket evidence questions – with the capabilities put in place ahead of product approvals so they are ready to use. Federal support should be linked to benchmarks for increasing the speed and capacity for conducting postmarket studies using the emerging distributed COVID RWE infrastructure. Funding should encourage the adoption of common data models, protocols for analyzing the data, and mechanisms to assess and improve these methods, to make available more generalizable RWE results from comparable analyses across a broad range of settings and participants. Studies that involve vulnerable and understudied populations should be prioritized.

This RWE infrastructure could be supported as part of the comprehensive response envisioned in CARES Act appropriations. While FDA-identified priorities should be addressed, the same infrastructure could be used for additional evidence questions. The recent reauthorization of

PCORI with $7 billion of additional funding could support accelerated evidence on comparative effectiveness questions involving alternative treatment approaches for COVID-19, as more treatments reach the market or the use of existing treatments might be varied (e.g., different timing or duration of treatment). The Agency for Healthcare Research and Quality (AHRQ) and NIH could also provide support. But practical steps need to be implemented rapidly, so that the infrastructure will be available to address key postmarket evidence questions ahead of further approvals and emergency use authorizations.

Link payment to a multi-stakeholder strategy for virtual COVID-19 registries and postmarket studies

The steps just described have the potential to create a readily-available infrastructure for better evidence to augment clinical trials on using COVID-19 treatments effectively. This includes a comprehensive approach to post-approval monitoring of safety, confirmation of benefits in real-world populations and vulnerable subgroups if patients, and long-term outcome assessment. **With the emerging opportunities for developing real-world evidence, payment contracts for COVID-19 treatments should also encourage manufacturers and health care providers to participate in the implementation of a COVID-19 evidence network.**

First, participation in this enhanced infrastructure to develop better evidence could be linked to EUAs and approvals, and to broader coverage in indications where evidence is suggestive but not conclusive. At a minimum, consideration of how such an evidence network could augment evidence available at the time of approval could become a regular component of purchasing contracts for COVID-19 therapeutics. Second, building on the current Medicare payment bonus for providers who participate in COVID-19 clinical trials, Medicare could provide financial incentives for providers who participate in the real-world evidence network.

Ideally, a collaboration involving sponsors, participating organizations, and payers would produce a virtual registry or registries to address key questions using RWE networks prior to product approval, to address postmarket safety questions for FDA as well as address additional types of questions relevant to patients, clinicians, and payers. Participation by providers would be voluntary, but would be supported by tools developed by the network participants to incorporate and standardizing data, and assuring its appropriate and secure use, with minimal cost and disruption for health care organizations. The tools and financial incentives would enable much broader participation by more providers in more settings of care.

The COVID-19 evidence collaboration could conduct faster and more comprehensive distributed analyses of key questions beyond those that are feasible to conduct using traditional FDA postmarket approaches or through activities involving single data sources. Insurers can conduct parallel studies using claims data, or potentially provide key data, like hospital admissions or the occurrence of other complications for studies in the outpatient setting, that are not captured in hospital-based datasets. Other data holders could conduct supplemental analyses using distinctive features of their own datasets.

This work would complement planning for advance purchases and timely distribution of therapeutics for the full duration of the COVID-19 threat, and would provide an infrastructure for addressing future questions involving the public health impact of other treatments.

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Table 1: Promising COVID-19 Therapeutics in Development

Therapy & Company	Key Clinical Trial Population(s)	Anticipated Trial Timeline	Therapeutic Manufacturing Capacity
Antiviral Therapeutics			
Remdesivir Gilead Sciences, Inc.	• Patients hospitalized with severe COVID-19 • Patients hospitalized with COVID-19	Severe disease results released April 2020 (ref) Moderate disease results expected May 2020 (ref)	• More than 140,000 treatment courses by the end of May 2020 • More than 500,000 treatment courses by October 2020 • More than 1 million treatment courses by December 2020 • Several million treatment courses in 2021, if required (ref)
Convalescent Plasma			
Convalescent plasma	• Patients hospitalized with COVID-19 • Patients hospitalized with severe COVID-19 • Patients hospitalized with severe COVID-19 on mechanical ventilation	Early expanded access safety metrics reported May 2020 (ref) Multiple phase 3 trials ongoing (ref)	
Hyperimmune Globulin			
Hyperimmune globulin (H-IG) Emergent BioSolutions Inc. -and- Grifols Shared Services North America, Inc.	• Patients hospitalized with severe COVID-19 pneumonia • Participants at risk of SARS-CoV-2 infection (prophylaxis)	Clinical study to begin as early as Q3 2020 (ref)	Emergent BioSolutions partnered with BARDA and NIAID. (ref) Emergent has initiated plasma collection efforts for both human and equine platforms with a goal of manufacturing clinical material within the next four to five months in anticipation of beginning a clinical study. (ref) Grifols partnered with BARDA and the Joint Program Executive Office for Chemical,

			Biological, Radiological and Nuclear Defense (JPEO-CBRND). ([ref](#))
SAB-185 (polyclonal hyperimmune globulin) SAB Biotherapeutics, Inc.	• Clinical trial population(s) to be determined		Partnership with CSL Behring, BARDA, and JPEO-CBRND. SAB Biotherapeutics' novel immunotherapy platform provides a method to rapidly manufacture without the need for human plasma. ([ref](#))
Interleukin-6 (IL-6) Receptor Antagonists & Inhibitors			
Sarilumab (Kevzara) Regeneron Pharmaceuticals Inc.	• Patients hospitalized with COVID-19 • Patients with severe community-acquired pneumonia resulting from SARS-CoV-2 infection	Preliminary phase 2 results released April 2020 ([ref](#)) Phase 3 results expected June 2020 ([ref](#)) Part of the REMAP-CAP adaptive platform trial ([ref](#))	No specific information reported. ([ref](#))
Siltuximab (Sylvant) EUSA Pharma	• Patients hospitalized with COVID-19 • Patients hospitalized with COVID-19 pneumonia	Compassionate use data reported April 2020 ([ref](#))	No specific information reported. ([ref](#))
Tocilizumab (Actemra) F. Hoffmann-La Roche Ltd & Genentech, Inc.	• Patients hospitalized with non-critical COVID-19 • Patients hospitalized with severe COVID-19 • Patients hospitalized with COVID-19 and cytokine release syndrome • Patients with severe community-acquired pneumonia resulting from SARS-CoV-2 infection	Roche trial results expected in May or June 2020 ([ref](#)) Part of the REMAP-CAP adaptive platform trial ([ref](#))	Partnership with BARDA. ([ref](#))

Janus Kinase (JAK) Inhibitors			
Baricitinib (Olumiant) Eli Lilly and Company	• Patients hospitalized with COVID-19 • Patients hospitalized with severe COVID-19		Partnership with the National Institute of Allergy and Infectious Diseases (NIAID). ([ref](#)) Lilly currently does not anticipate shortages for any of its medicines, including baricitinib, which remains widely available in countries where it is approved.
Ruxolitinib (Jakafi) Incyte Corporation	• Patients hospitalized with COVID-19 and cytokine release syndrome • Patients hospitalized with COVID-19-associated Acute Respiratory Distress Syndrome (ARDS)	Phase 3 trial ongoing ([ref](#))	At present, there is ample commercial and clinical supply of ruxolitinib in the United States to meet the needs of U.S. patients receiving ruxolitinib in its approved indications and those participating in clinical trials. Incyte is increasing manufacturing efforts to respond to anticipated supply needs related to COVID-19 studies and working closely with distribution partners to monitor the supply of ruxolitinib. ([ref](#))
Tofacitinib (Xeljanz) Pfizer Inc.	• Patients hospitalized with COVID-19 and interstitial pneumonia	Phase 2 trial ongoing ([ref](#))	No specific information reported. ([ref](#))
Interleukin-1 (IL-1) Receptor Antagonist			
Anakinra (Kineret) Shanghai CP Guojian Pharmaceutical	• Patients with severe community-acquired pneumonia resulting from SARS-CoV-2 infection	Part of the REMAP-CAP adaptive platform trial ([ref](#))	
Novel Antibody Therapeutics			
S309 Vir Biotechnology, Inc.	• Patients with COVID-19 • Participants at risk of SARS-CoV-2 infection (prophylaxis)	Clinical trials "this summer" ([ref](#))	Collaboration with Samsung for capacity to produce hundreds of thousands of doses by year end and tens of millions of doses next year. Investing in production capacity at risk ahead of product approval.
Multi-antibody cocktail Regeneron Pharmaceuticals Inc.	• Non-hospitalized patients • Hospitalized patients	Initial clinical testing at the beginning of summer ([ref](#))	The company is working toward the goal of producing hundreds of thousands of

	• Participants at risk of SARS-CoV-2 infection (prophylaxis)		prophylactic doses per month by the end of summer. (ref) The company is working with the U.S. Health & Human Services' Biomedical Advanced Research and Defense Authority (BARDA) to increase capacity even further.
Antibody therapy Adaptive Biotechnologies Corporation	• Clinical trial population(s) to be determined		Partnership with Amgen. Amgen will leverage its antibody engineering and drug development capabilities to select, develop and manufacture antibodies. (ref)
VIR-7831 & VIR-7832 Vir Biotechnology, Inc.	• Clinical trial population(s) to be determined	Phase 2 clinical trial within the next three to five months (ref)	Partnership with GSK. (ref)

Table 2: Examples of COVID-19 Master Protocols and Trial Networks

Trial	Leadership	Anticipated Interventions*	Protocol/Study Detail Availability	Approach
Inpatient Settings				
RECOVERY Trial†	Sponsor: University of Oxford CI: Peter Horby, MD, PhD Study sites: 176 active sites	lopinavir-ritonavir low-dose corticosteroids (dexamethasone) hydroxychloroquine azithromycin	Published online at recoverytrial.net	Randomised, controlled, platform trial Pragmatic design with adaptive elements and use of real-world data
Solidarity Trial	World Health Organization in collaboration with regional sponsors	remdesivir lopinavir/ritonavir lopinavir/ritonavir with interferon beta-1a chloroquine or hydroxychloroquine	Canadian arm published online at clinicaltrials.gov/ct2/show/NCT04330690	Randomized, open-label, controlled clinical trial with adaptive elements
REMAP-CAP COVID†	International trial steering committee Regional sponsors/coordinating centers: Monash University (Australia and New Zealand) Utrecht Medical Center (Europe) Imperial College London/ICNARC (UK)	anti-viral therapies (lopinavir/ritonavir; hydroxychloroquine; remdesivir) corticosteroid therapy (multiple dosing strategies) innate immune modulation therapy (interferon beta; anakinra; tocilizumab;	Published online at remapcap.org/coronavirus	Randomized embedded multifactorial adaptive platform (REMAP) design Uses RAR and Bayesian inference Tests multiple interventions concurrently, nested within different domains Stratified by moderate and severe disease categories

	University of Toronto (Canada) Global Coalition for Adaptive Research/University of Pittsburgh (US) Study sites: >160 active sites (more being added) in 13 countries	sarilumab; multiple others) ACE2-RAAS modulation (ARBs, ACEi, others) ACE2-kinin-kallikrein modulation high dose vitamin C simvastatin anticoagulation and anti-platelet strategies immunoglobulin and convalescent plasma interventions		
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)	Sponsor: National Institutes of Health	In development	In development	In development
Adaptive COVID-19 Treatment Trial I (ACTT I)	Sponsor: National Institute of Allergy and Infectious Diseases	remdesivir	Published online at clinicaltrials.gov/ct2/show/NCT04280705	
I-SPY COVID TRIAL (Response in an Adaptive Platform Trial to Reduce Mortality and Ventilator Requirements for	Sponsor: Quantum Leap Healthcare Collaborative PI: Carolyn Calfee, MD, UCSF; Kathleen Liu, MD, UCSF	(Tentative and under initial consideration for prioritization) Backbone/standard therapy: standard of	Published online at ispytrials.org/collaborate/covid-19-updates	Phase 2 interventional, multi-arm platform trial Flat randomization with adaptive components

Critically Ill Patients)†	Study sites: Approx 20 centers in the US with UCSF as lead site	care ventilatory management plus remdesivir (or alternative, will evolve as data emerges from this and other trials) Arm 1: remdesivir alone Arm 2: remdesivir w/ cenicriviroc [Allergan] Arm 3: remdesivir w/ icatibant [Takeda] Additional agents are undergoing review and prioritization (TBD)		
Outpatient Settings				
Healthcare Worker Exposure Response and Outcomes (HERO) – HCQ Trial†	Sponsor: Duke University / Adrian Hernandez, MD, MS PI: Susanna Naggie, MD Study sites: Approx 40 PCORnet sites in the US	hydroxychloroquine versus placebo as prophylaxis	Published online at https://heroesresearch.org/wp-content/uploads/2020/05/HERO-HCQ-Protocol-V2.0_5.1.20_clean.pdf	Double blind, placebo controlled study
Platform Randomized trial of INterventions against COVID-19	Sponsor: University of Oxford	hydroxychloroquine	Published online at phctrials.ox.ac.uk/principle-trial	Randomised, controlled platform trial in community care Prospective

in older peoPLE (PRINCIPLE) Trial†				Individual randomization Pragmatic elements
Efficacy of Novel Agents for Treatment of SARS-CoV-2 Infection Among High-Risk Outpatient Adults: An Adaptive Randomized Platform Trial	Sponsor: University of Washington / Bill and Melinda Gates Foundation	Control group: ascorbic acid rolic acid Interventional group: hydroxychloroquine sulfate azithromycin	Published online at https://clinicaltrials.gov/ct2/show/NCT04354428	Adaptive Randomized placebo-controlled Platform Trial Parallel design Double blind

* Table current as of 5/19/2020 – treatment arms in each protocol could be paused for futility, advanced or spun off given promising results, or newly included as additional treatments enter development
† Information provided by study teams

Table 3: Multi-Stakeholder Real-World Evidence Initiatives to Inform COVID-19 Therapeutics

Organization	Initiative Name	Description	Research Setting	Data Source	Data Models

Reagan-Udall Foundation for the FDA and Friends of Cancer Research	COVID-19 Evidence Accelerator	New, multi-stakeholder COVID-19-specific initiative that is developing a data shell with common data elements to answer the same research question across different data sources. Analyses to answer a research question are run in parallel, but qualitatively compared across researchers. New research questions can be rapidly added and aligned with different data partners. Data is housed by the collector. Additionally, weekly lab meetings are convened to share methods and advance COVID-19 RWE learnings.
		
		Current research questions include:
		• Among hospitalized patients with COVID-19, describe the following for hydroxychloroquine +/- azithromycin vs control:
		   o Characterize COVID-19 patient populations
		   o Characterize treatment (e.g., timing in COVID-19 illness trajectory; monotherapy vs co-prescription; dose)
		   o Characterize safety signals, including by subpopulations (e.g., age, diabetes, COPD)
		   o Describe comparative effectiveness on key outcomes
		   o Identify potential predictors of treatment safety and effectiveness
			Inpatient, Outpatient	Claims, EHR	Data shell with common data elements

COVID-19 Healthcare Coalition	mCOVID	New, multi-stakeholder COVID-19-specific initiative that is developing a minimum common data model with mapping to other data models, and creating standardized cohorts. Common research questions focusing on the inpatient setting are answered by researchers in parallel with the goal of pooling results in a meta-analysis. Data is housed by the	Inpatient, Outpatient	EHR	Mapping to OHDSI, I2B2, and exchange standards

		collector. Also developing data standardization tools such as a data dictionary and COVID-19 vocabulary. Current research questions include: • For patients with new COVID-19 infection, how does the addition of hydroxychloroquine (HCQ) affect the outcomes (1) severe disease (indicated by mechanical ventilation) and (2) inpatient death? • For patients with new COVID-19 infection, how does treatment with convalescent serum (CS) affect the outcomes (1) severe disease (indicated by mechanical ventilation) and (2) inpatient death?			such as FHIR
FDA Sentinel System	[FDA Sentinel System's Coronavirus (COVID-19) Activities]	Leveraging existing distributed data network and common data model to answer COVID-19-related questions regarding drug use, protocols for public health emergencies, and identification of new data sources and partners Current research questions include: • Near real-time monitoring of critical drugs for the care of patients with COVID-19 (also includes drug utilization in outpatient care) • Methods to monitor medical countermeasure safety and effectiveness (expanded to capture data on hospitalized patients diagnosed with COVID-19) • Horizon scan of EHR databases to identify EHR sources to strengthen the Sentinel System (expanded to identify data sources capable of monitoring the diagnosis and treatment of COVID-19 patients) • Natural history study to identify cohorts of patients diagnosed with COVID-19 in ambulatory and inpatient settings and to monitor their treatment patterns and disease progression (Planned) • Evaluating the impact of treatments used for COVID-19 using RWD (Planned)	Inpatient, Outpatient	Claims, EHR	Various data models possible, including Sentinel common data model, PCORnet, HCSRN, modified versions of standard models, and data source specific models as appropriate for the question

		• Validation of claims-based phenotypes for COVID-19 positive patients (Planned)			
Cerner	HealtheDataLab	Leveraging existing Cerner EHR records to develop database of de-identified COVID-19 patient data including COVID-19-related demographics to help track spread and surge, underlying illnesses and chronic conditions, treatments, lab results and clinical complications and outcomes that could help drive important medical decisions. Stored on Cerner HealtheDataLab™, powered by AWS. This initiative is in alignment with the Cerner Learning Health Network launched in 2019.	Inpatient, Outpatient	EHR	
CD2H and NCATS	National COVID Cohort Collaborative (N3C)	New, multi-stakeholder COVID-19 Initiative in partnership with distributed data networks. Goal of N3C is to develop a national, centralized, secure portal for hosting row level COVID-19 clinical data and deploying and evaluating methods and tools for clinicians, researchers, and health care to support COVID-19 analytics. N3C will apply a common data model to all data. Data resides with collector, but limited dataset will be stored in secure enclave. Four workstreams include: 1) Data Partnership & Governance, 2) Phenotype & Data Acquisition, 3) Data Ingestion & Harmonization, 4) Collaborative Analytics.	Inpatient, Outpatient	Claims, EHR	Mapping data models from various distributed data networks (PCORnet, TriNetX, OHDSI, ACT/i2b2) to OMOP
PCORI and Duke University	Preventing COVID-19 Infections: Healthcare Worker Exposure Response and Outcomes (HERO) Registry and HERO-	Leveraging existing PCORnet distributed data network for COVID-19 research to develop registry of health care workers on front lines who are at risk for developing COVID-19 infection. Participants can provide health information about relevant COVID-19 risk factors, medical encounters, and health status. As part of the HERO-HCQ trial, approximately 15,000 registry participants will be randomized to either one month of HCQ or placebo to determine whether HCQ is effective in decreasing the rate of COVID-19 infection. 40 medical centers in total have been selected to participate in the trial.	Health care workers exposed to inpatient and outpatient settings	Direct to participant	

	Hydroxy-chloroquine (HCQ) Trial				
University of California Health System	COVID-19 Data Collection in UC Health Data Warehouse	The UC Health system adapted ongoing data collection, aggregation, and mapping efforts in existing UC Health Data Warehouse to include data elements of COVID-related importance (e.g., test results, confirmed cases by geography, age and gender). UC Health Data Warehouse has data from six of the UC medical schools and systems (UC San Diego Health, UCR Health, UCI Health, UCLA Health, UCSF Health, and UC Davis Health). The current COVID-19 related repository has inpatient and ambulatory care data on more than 56,000 tested patients (of which more than 1,800 were positive for the virus).	Inpatient, Outpatient	EHR	OMOP
Aetion and HealthVerity	Real-Time Insights and Evidence Platform	Expanded existing partnership to offer new real-world evidence system designed for biopharma manufacturers and regulators to assess treatment approaches for COVID-19. The platform uses real-time data to offer insights about the usage, safety, and clinical effectiveness of proposed COVID-19 interventions. Also can provide insights on disease progression of COVID-19 across demographic subgroups and how COVID-19 is treated and managed over time in various settings. Additionally, Aetion is partnering with FDA through a research collaborative agreement to evaluate priority research questions including understanding the the natural history of the disease as well as treatment and diagnostic patterns using real-world data through its Evidence Platform®.	Inpatient, Outpatient	Claims, EHR	
US Department of Veteran Affairs		Leveraging existing data warehouse with common data model for observational studies to characterize COVID-19 patients, treatments, and outcomes.	Inpatient, Outpatient	EHR	OMOP

EPIC	[EPIC Health Research Network](#)	Leveraging existing EHR platform to conduct COVID-19 observational studies. Created online platform (Epic Health Research Network) to share findings. Report topics include comorbidities in COVID-19 patients, COVID-19 hospitalization statistics, racial disparities amongst COVID-19 patients.	Inpatient, Outpatient	EHR	
Public/Private Consortium	[COVID-19 Research Database](#)	New, COVID-19-specific initiative creating new data repository using existing collaborator-provided datasets. Data repository comprised of HIPAA-compliant, de-identified and limited longitudinal, patient-level data sets made available to public health and policy researchers. Datavant provides linking technology. Mirador responsible for statistical certification for linked data. Other collaborators include: Advarra, Aetion, AnalyticsIQ, Arcadia, BHE, BRG, Change Healthcare, Clarify, Datavant, Elsevier, Glooko, Health Care Cost Institute, Healthjump, Helix, Medidata, Munich RE, Mirador Analytics, Office Ally, OMNY, Parexel, Prognos Heath, Qiagen, Quertle, SAS, Snowflake, Sumitomo Dainippon Pharma, Symphony Health, Veradigm, Vizient.	Inpatient, Outpatient	Claims, EHR, Consumer Data	