COVID-19 Lessons Learned

CLINICAL EVALUATION OF THERAPEUTICS

Workshop Summary

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REAGAN-UDALL FOUNDATION FOR THE FDA

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List of Abbreviations

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AI	artificial intelligence
ARDS	acute respiratory distress syndrome
BARDA	Biomedical Advanced Research and Development Authority
CMS	Centers for Medicare & Medicaid Services
CoVPN	COVID-19 Prevention Network
COVID-19	coronavirus disease 2019
CRO	contract research organization
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
HHS	Health and Human Services
IRB	institutional review board
NIH	National Institutes of Health

Executive Summary

In May 2020, the U.S. government program Operation Warp Speed (now known as the Countermeasures Acceleration Group) was created to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. The program's Therapeutics team developed and implemented a two-pronged strategy, focusing on therapeutic candidates to (1) attack the virus and (2) manage its complications. In early 2021, the team launched a Clinical Evaluation of Therapeutics Lessons Learned Initiative to collect lessons learned from its COVID-19 response experience up to that point and distill them into actionable recommendations—for both immediate action and long-term preparations. In September 2021, federal leadership and key stakeholders came together for a virtual workshop hosted by the US Food and Drug Administration (FDA) to disseminate the findings and review the recommendations to enhance the scoping, prioritization, and communication of research activities within the context of a public health emergency.[1] While lessons will continue "to be learned," improvement can be made now. Within the discussions, five key themes emerged:

- **Plan ahead to ensure effective clinical trial design:** Within a public health emergency, research progresses rapidly, and established protocols and guidance are needed to ensure the generation of clinically actionable results
- **Enhance clinical trial infrastructure and agility:** Establish and expand clinical trial networks that can be readily "warmed up" to engage in pandemic research
- **Retain and expand the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) framework:** A central system for evaluating investigational therapies will make it easier for researchers to engage in the pandemic response
- **Support community research:** Clinical trials embedded within community care are critical for health equity and will require coordinated efforts to develop
- **Start now:** Many of the needs outlined in this document still exist within the ongoing COVID-19 pandemic, and future responses will be enhanced by early preparedness

This document provides a summary of the virtual workshop discussions and identification of lessons learned during the first year of the COVID-19 pandemic. Successes and struggles are highlighted, and opportunities to adapt to the ongoing COVID-19 pandemic and improve response for future public health emergencies are presented. Recommendations from the Clinical Evaluation of Therapeutics Lessons Learned Initiative[2] are elaborated on, and key considerations in the execution of these recommendations are discussed. Emphasis is placed on recommendations for the expansion of clinical trial networks into community settings and the resources that will be needed to support these efforts.

The lessons learned and recommendations outlined in this document are not intended to represent the U.S. government's final opinion or recommendations on these matters, as the COVID-19 pandemic is still ongoing.

1 More information on the September 28 workshop, including the discussion document with the recommendations and a meeting recording, is available on the workshop website: https://reaganudall.org/news-and-events/events/virtual-public-workshop-covid-19-lessons-learned-clinical-evaluation.

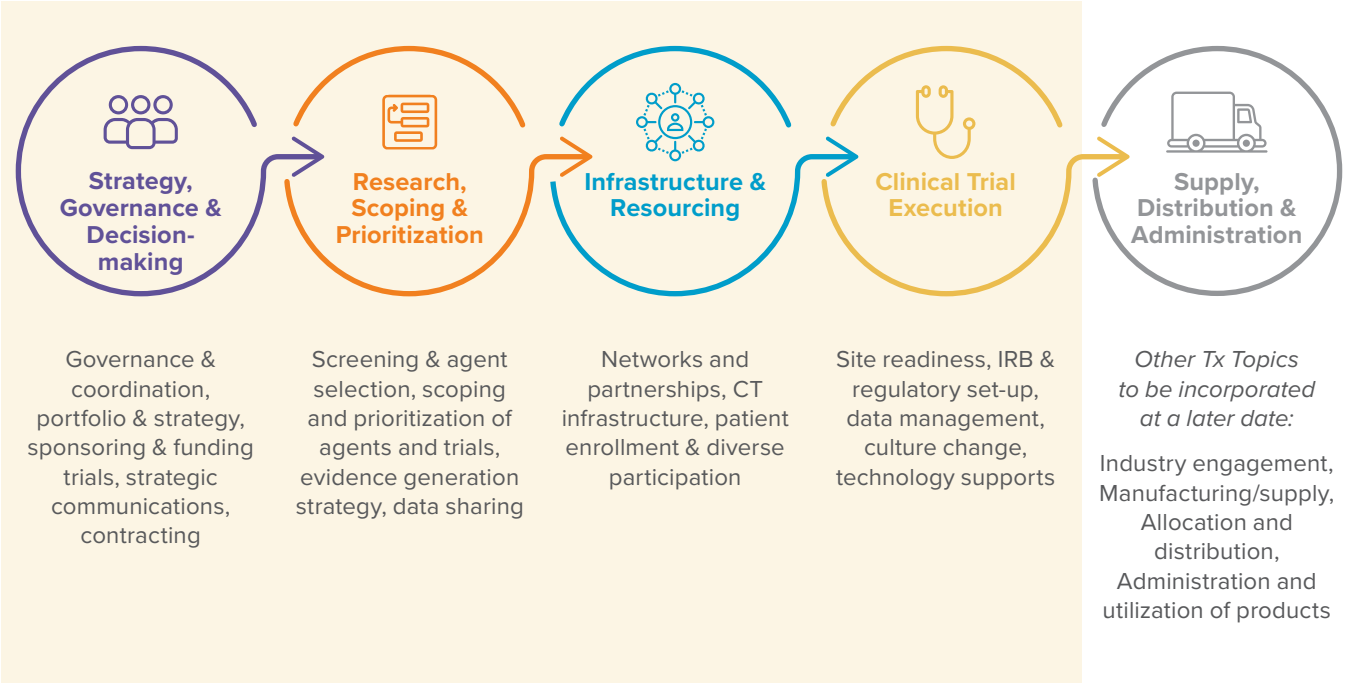
2 A full list of recommendations from the Clinical Evaluation of Therapeutics Lessons Learned Initiative is available in the Appendix.

Background

In May 2020, then Health and Human Services (HHS) Secretary Alex Azar and Defense Secretary Mark Esper created Operation Warp Speed, now known as the Countermeasures Acceleration Group. This U.S. government program was intended to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. The Therapeutics team, led by Dr. Janet Woodcock with overall leadership/ program management from Col. Deydre Teyhen and Dr. Kevin Bugin, developed a baseline view of the current portfolio and investments in COVID-19 across the Department of Defense, National Institutes of Health (NIH), and Biomedical Advanced Research and Development Authority (BARDA).

Informed by these efforts, the team defined the Operation Warp Speed Therapeutics strategy, which embodied a two-pronged approach, focusing on candidates to (1) attack the virus and (2) manage its complications. The Therapeutics leadership team held discussions with priority therapeutics manufacturers to identify specific areas where the U.S. government could accelerate development. The Therapeutics leadership team coordinated budgets to enable funding of contracts for procurement of product under Advance Purchasing Agreements, execution of platform clinical trials, and launch of communications activities to support trials and monoclonal antibody distribution and administration. As priority therapeutics manufacturers with Advance Purchasing Agreements with the U.S. Government began to prepare for potential Emergency Use Authorizations (EUAs), the Therapeutics leadership team provided direct preparatory support for the allocation and distribution of outpatient therapeutics. This support included leading the engagement with the Centers for Medicare & Medicaid Services (CMS) on the reimbursement path for outpatient drugs in the event of an EUA.

FIGURE 1. Lessons Learned were identified across five topic areas, with four being within scope of this initial effort and discussion.



In early 2021, members of the Therapeutics team launched a Clinical Evaluation of Therapeutics Lessons Learned Initiative to collect lessons learned from its COVID-19 response experience up to that point related to the clinical evaluation of therapeutics and distill them into actionable recommendations. The Federal COVID-19 Response Team for Therapeutics convened multistakeholder working groups[3] to review the lessons learned and develop recommendations to address them. Recommendations were developed by Working Group members, including leaders from across government bodies, think tanks, nonprofits, and industry associations, and reflect feedback and guidance from the Initiative's leadership group, which includes representatives from HHS, the Department of Defense, and Veterans Affairs.

In September 2021, federal leadership and key stakeholders came together for a virtual workshop hosted by the Reagan-Udall Foundation for the FDA (at the FDA's request), to disseminate these findings and review actionable recommendations to enhance the scope, prioritization, and communication of research activities within the context of a public health emergency.[4] To supplement the input gathered at the workshop, stakeholders were encouraged to submit comments on the workshop topics to a public docket[5] until December 28, 2021.[6]

3 See Appendix for a full list of stakeholders

4 This project is supported by the FDA of the U.S. Department of Health and Human Services (HHS) as part of an award of $41,665 in federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

5 A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as the FDA. More information can be found at www.regulations.gov.

6 The public docket for this workshop is available here: https://www.regulations.gov/docket/FDA-2021-N-0977.

Lessons Learned

RESEARCH, SCOPING, & PRIORITIZATION

Recommendations: Research, Scoping & Prioritization

- ↗ **RSP●1:** Rapidly collect and disseminate enabling information such as pathogen identification, sequencing, and natural history data (through natural history registries).
- ↗ **RSP●2:** Ensure the clinical trial ecosystem creates actionable evidence through developing strategy, guidelines, templates, incentives, and capacity building (eg, prioritize randomized trials).
- ↗ **RSP●3:** Enable the open sharing of research strategy and plans amongst stakeholders in the clinical trial ecosystem to coordinate activities, including in funding announcements.
- ↗ **RSP●4:** Establish efficient and effective systems for sharing early research data and results with other researchers outside of publication channels.

LESSON 1

Recommendations 1–4

The groundwork for a pandemic response plan should be laid in advance such that it can be leveraged to support the immediate and equitable dissemination of information and research guidance.

The academic and medical communities were eager to get involved during the early stages of the COVID-19 pandemic, and it can be expected that research will begin immediately in the setting of a public health emergency. However, very few trials in the early stage of the pandemic were adequately designed and powered to yield clinically actionable results, and many of them were duplicative or chasing weak scientific and clinical leads. With some exceptions, by the time larger, well-designed trials were deploying, patient populations and clinical capacity had been depleted.

Smaller companies and research units struggled to identify areas of need, making integration into larger research protocols difficult. Moreover, access to emerging data was challenging, with the research community relying on potentially misleading information about the virus and disease. This made it challenging for key stakeholders to stay up to date with rapidly evolving information about SARS-CoV-2, COVID-19, and potential therapeutic agents; smaller groups in particular struggled to identify key stages within the clinical history of the disease where there was a need for novel therapeutic intervention.

The sooner the infrastructure is in place to support pandemic research, the sooner a coordinated response can begin. There is an opportunity now to leverage the experiences from the COVID-19 pandemic to develop a **blueprint for a pandemic response strategy and tactical plan** for therapeutic development that will provide guidance to support the unified response to a future pandemic or public health emergency. The ideal response strategy and tactical plan will include considerations for not only the U.S. government and large, established research organizations, but smaller companies and academic institutions as well.

One of the key goals of an effective pandemic response plan will be the development and dissemination of **guidance to support trial design** within a public health emergency to ensure the yield of clinically actionable results. When developing clinical trial guidance, experiences from ACTIV (discussed in greater detail below) should be reviewed to determine not only what scientific considerations will need to be made in evaluating novel therapeutics and clinical trial results, but also practical considerations, such as manufacturing and distribution. There is also a need for a **unified, academic resource** for researchers to easily access emerging information about the disease/condition, as well as a means to effectively communicate emerging research to the scientific community. **Additional pandemic preparedness research** will be necessary to identify needs and support investments in pandemic preparedness and response efforts at both the government and industry level. Such research will illuminate additional market-shaping mechanisms to promote investment in pandemic preparedness, such as advanced purchasing agreements and stockpiling.

There is also a need for **clinical trial networks conducting ongoing platform clinical trials** that can be "kept warm" and then repurposed in the pandemic response to support the implementation of effective research. Having existing networks and platform trials in place will allow more rapid scientific engagement so that investigators have the opportunity to participate in the pandemic response without exhausting clinical trial resource pools with small—and likely uninformative—trials. Platform trials should be shaped to support nuanced aspects of the pandemic response, including the following:

- **Community care.** Platform trials and clinical trial networks should be integrated within community care settings, and community providers should be engaged in this research. Many communities, including those that are historically underserved, did not have access to emerging COVID-19 research, which influenced the quality of care that they were able to receive. Community engagement cannot just be initiated in response to a public health emergency. Significant and sustained time and effort are required to establish these relationships. Specific recommendations for developing community partnerships are outlined in the Infrastructure & Resourcing and Clinical Trial Execution sections.
- **Therapeutic development and regulatory approval.** For drugs with clear, large treatment effects, navigating requirements for regulatory agencies is easier than for agents with smaller effect sizes. A platform clinical trial can provide guidance and support regarding optimal trial design for potential therapeutics with smaller but potentially clinically meaningful effects on disease outcomes, in which interpretation of results and confounding factors may be challenging.
- **Non-COVID-related clinical trials.** Many modifications were needed to support clinical trials for other indications during the COVID-19 pandemic. Established clinical trial networks could help support non-pandemic–related clinical trials in adopting procedures in a changing health care environment (e.g., use of local clinics, offsite monitoring, remote collection of consent).

LESSON 2

Recommendations 2–3

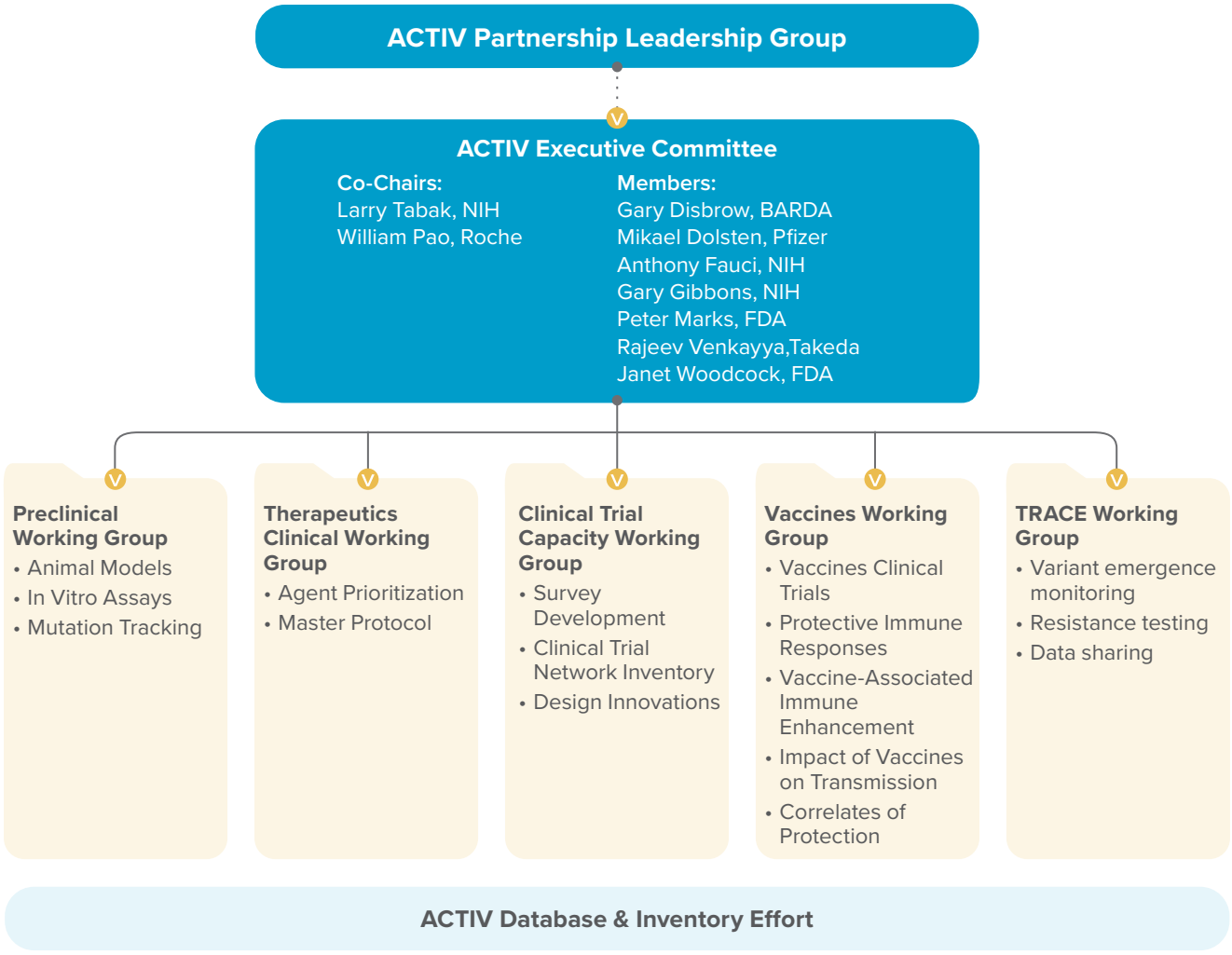
The ACTIV structure[7] (See Figure 2.) provided a useful, central system for evaluating novel therapeutics and should be retained and expanded for evaluation of products across the disease spectrum.

7 More information about ACTIV is available here: https://www.nih.gov/research-training/medical-research-initiatives/activ.

8 More information about the COVID R&D Alliance is available here: https://www.covidrdalliance.com/.

As pandemic research and development has progressed, a variety of government- and industry-sponsored coalitions emerged to identify promising therapeutics for COVID-19. Among these, the Therapeutics Clinical Working Group within ACTIV developed key protocols for prioritization and testing of agents, with the overarching goal of producing clinically actionable results. Individualized criteria and protocols were developed iteratively as new information about COVID-19 emerged. Similar initiatives self-assembled within the industry setting, such as the COVID R&D Alliance,[8] which ultimately adopted similar criteria for evaluating potential therapeutics.

FIGURE 2. ACTIV Public-Private Partnership.



In the initial stages of ACTIV, priority was given to agents targeting the most urgent need within the spectrum of disease (i.e., treating those hospitalized with COVID-19). While companies understood that there was a need to quickly operationalize around near-term products targeting the most urgent need, there were many "biologically plausible" products that did not fit into these strategic goals. It was challenging for companies and researchers to assess the value of therapeutics that fit into the disease spectrum less clearly (e.g., those preventing COVID-19 or treating mild disease). It was unclear at what point in the disease state these products should be tested and how they would be assessed. As the pandemic continued and ACTIV priorities expanded, it remained challenging for many smaller companies to identify the greatest therapeutic needs.

Criteria and protocols should be established supporting the development of products across the disease spectrum to make it easier for companies to engage at all stages. The easiest way to do this is by leveraging the existing frameworks developed for COVID-19 rather than rebuilding the therapeutic prioritization pipeline from scratch with each public health emergency. For example, the ACTIV framework can be **retained and expanded** to provide a research system for stakeholders to "plug into," with a clear path for development and relevant end points needed for evaluation. When developing criteria for prioritization of novel agents, considerations should include the scientific/clinical profile in addition to the **scalability** of production and distribution and the **long-term projections** for the disease/condition. Experiences from BARDA, which developed a prioritization process and mechanisms to support access to research supplies, can also be leveraged.

Additionally, many agents got stuck in the "valley of death" between phase 1 and phase 2/3 trials. Across the clinical trial ecosystem, there is a significant barrier at this stage for many therapeutics. Efforts are needed to help bridge the gap between early- and late-phase trials to expand the repertoire of potential therapeutic agents. For example, during vaccine development, Operation Warp Speed worked with companies to collapse trial phases while retaining scientific integrity. Similar support for non-vaccine therapeutics could have helped promising investigational therapeutics to overcome this hurdle and bolster the repertoire of agents in late-phase clinical trials.

There is also potential to use artificial intelligence (AI) and machine learning at various points in the research process. For example, AI can be used for data mining medical literature or supporting screening of potential agents; such methods may be integrated into future ACTIV frameworks.

LESSON 3

Recommendation 2

Pandemic response plans must take a more long-term view of the disease/condition, and a more robust pipeline is needed to support the development of therapeutic agents across the disease spectrum.

During the COVID-19 pandemic response, vaccines were treated as an end-all solution, but eradication is unlikely for a respiratory virus. Therapeutics were originally considered to be a bridge to the vaccine, but COVID-19 is going to be a significant public health concern well into the future. A more robust pipeline to support earlier development of a range of therapeutics was needed, informed by a broader view of how the pandemic would evolve over time.

Funding was a major limitation to the development of a robust therapeutic pipeline. If more resources were put into the development of a diverse antiviral repertoire, some therapies currently in the pipeline may be further along in development. **Additional, consistent funding** is needed to maintain the development of a robust therapeutic catalog to support the pandemic response. Pandemic therapeutic response plans require a **multipronged approach** to treatment, which will contribute to overall preparedness in the event of a transition from pandemic to endemic. Development of diverse therapeutics will also provide spillover benefits to related diseases and conditions, as is already emerging with COVID-19 and other respiratory conditions.

A broader view of therapeutic research may help to preserve the existing research and development landscape within a given field. As the field of antiviral research and development shifted to a niche aspect of COVID-19 research, other research areas such as HIV went largely dormant. Non–COVID-19-related questions were perceived as "soft problems." As a result, there was an exodus of experienced medicinal chemists and biologists from antiviral research and development to other areas, which may hinder antiviral research moving forward.

INFRASTRUCTURE & RESOURCING

Recommendations: Infrastructure & Resourcing

- ↗ **IR♦1:** Identify and leverage existing clinical trial network infrastructure (including NIH-funded networks, nonprofit & industry/CRO sites networks) and public-private partnerships (e.g., ACTIV) to maintain a "warm base" for public health emergencies and that can be deployed against high priority unmet needs.
- ↗ **IR♦2:** Build, engage, and support more community-based institutions/networks to improve the diversity and representativeness of clinical trials and ability to deploy pragmatic trials.
- ↗ **IR♦3:** Remove post-pandemic barriers to expanded adoption of decentralized/hybrid trials and remote monitoring tools.
- ↗ **IR♦4:** Research, develop, and share best practices on managing patient enrollment with a focus on prioritized trials/platforms while enabling co-enrollment.
- ↗ **IR♦5:** Determine best practices for increasing participation in trials from underrepresented communities and create action plans for improvement.

LESSON 1

Recommendations 2 & 5

Infrastructure is needed to develop community partnerships and engage and support community clinics to participate in clinical trial research.

Current large clinical trial networks can be thought of as experienced, ready networks. Many of these are maintained by global clinical research organizations (CROs). Within these organizations, established project management processes allowed some clinical trials to move forward faster. However, CROs may not be best positioned to ensure community engagement within clinical trials. Despite efforts to democratize research, many patients remain underserved and underrepresented within COVID-19 clinical research, and the infrastructure and relationships needed to effectively reach these communities are lacking. In the future, authentic, community-driven engagement can be facilitated by **embedding clinical trials** into community health care settings. The pandemic highlighted that a sound and experienced regulatory infrastructure does not currently exist to support connection with and integration of underserved communities within clinical trial research. An effective public health response requires a "both/and" strategy—not an "either/or"—and new and existing clinical trial networks must be equipped to engage community sites in ongoing and future research.

Community centers and hospitals may require **dedicated staff and/or resources** to support the implementation and management of clinical trials. Training and support for research at expansion sites during the pandemic was a major limitation, and some aspects of clinical trial project management (e.g., central institutional review board [IRB] and ethics committee submissions, contracting, site documentation) may be beyond the scope of smaller hospitals' capabilities. Additionally, staff at community health care facilities are often overburdened and lack the bandwidth to accommodate additional responsibilities. Providing dedicated support (e.g., personnel, funding) can help overcome some of these barriers. Personnel support from academic centers with experience

can help "grease the wheels" to move things forward in the form of both training and staffing. Preexisting relationships provide the greatest opportunity to move forward quickly, and it is important to establish these partnerships before the next public health emergency.

Resourcing needs for community centers will be dependent on what kind of research is performed at these sites. Some types of trials may be more easily implemented within the community setting than others (such as pragmatic trials, which require less infrastructure and are less risky for both patients and providers). Ultimately, community-based investigations should be **driven by communities** themselves. Rather than directing community clinics to participate in research, larger organizations should collaborate with these clinics to identify relevant clinical questions and the resources needed to support these investigations.

Clinical trial accessibility is not only about physical placement within the community, but assurance that the questions being asked address the needs of the community participants involved. It is therefore critical that the development of research infrastructure incorporates the perspectives, preferences, and needs of the respective community. These endeavors will be multipronged and will include enhancing awareness, improving access, and optimizing community communication and engagement.

The establishment of community relationships will also require initiatives to understand, address, and respond to any mistrust within the community, particularly related to **management and use of health information**. Privacy and confidentiality are major considerations that will need to be addressed operationally. This will include more granularity about what information is needed and how it is being handled, as well as clear communication about how the information will be used to benefit patients. Logistical aspects of electronic health information should be considered, including what the data will look like, how it will be stored, and how it will be shared. Additional technology infrastructure may be needed support the protection of sensitive patient-level health information.

LESSON 2

Recommendations 3 & 5

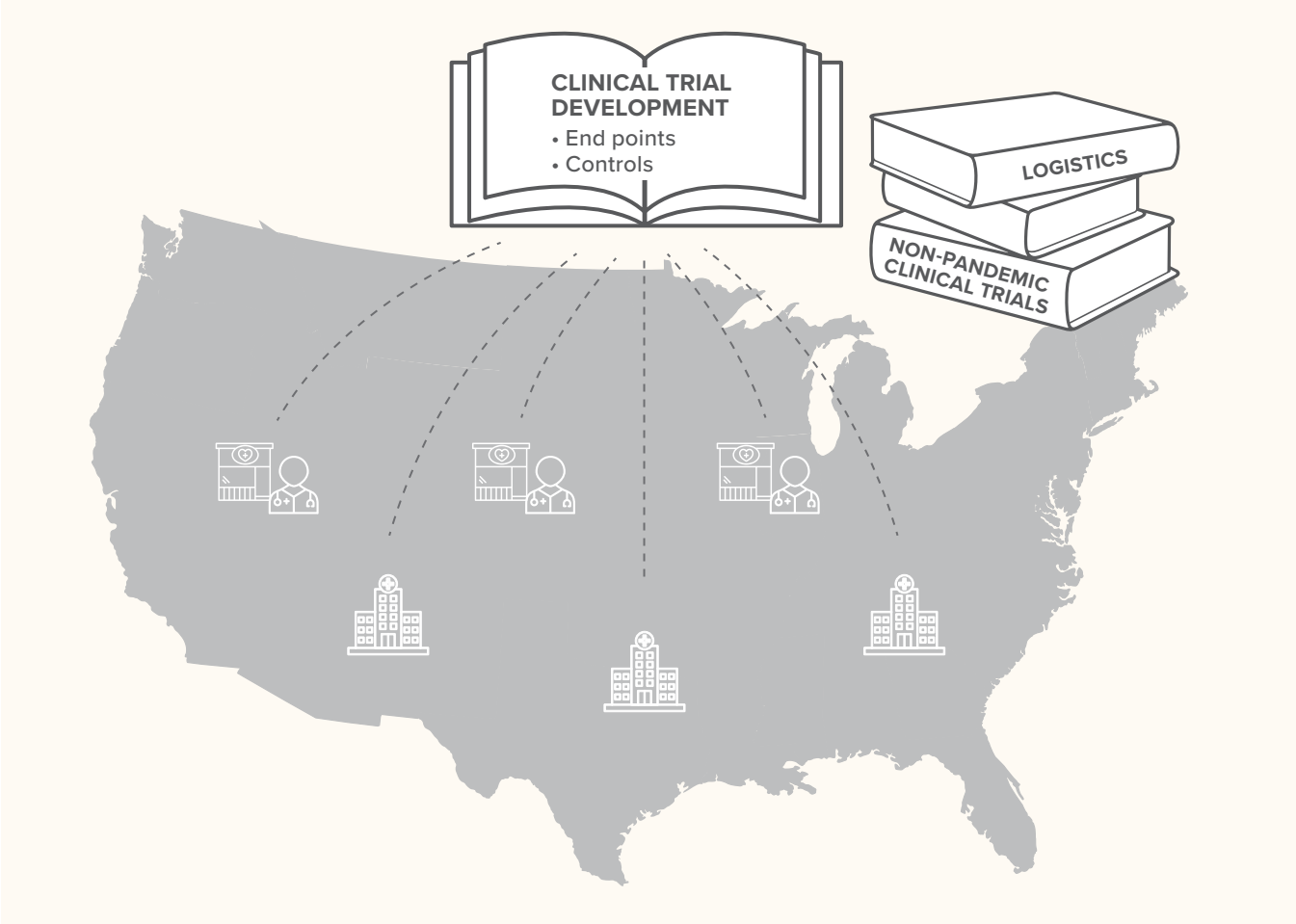
Pandemic "playbooks" are needed to provide guidance on clinical trial development, including assessment of resource capabilities and navigation of regulatory requirements.

During the early stages of the pandemic, clinicians were tasked with treating patients without access to relevant tools or information, such as the natural history of the disease. Research efforts began rapidly but were poorly coordinated, developed, and organized. Most—if not all—early trials lacked the statistical power to contribute to generalized learning. At the most basic level, there was not an agreed-upon definition of an adequately designed clinical trial and key outcomes for assessment, which made it nearly impossible for people to effectively design and implement COVID-19 therapeutic research. More guidance on trial design was needed, not only at the institutional level, but also at federal and global levels as well, to ensure that end results and even clinical trial definitions were comparable and relevant to clinical practice.

There is a need for a series of **pandemic playbooks** (See Figure 3.) to outline effective clinical trial development, addressing scientific considerations such as end points and controls as well as logistical considerations. Supply chain issues, for example, represented a new and unexpected challenge that even established clinical trial platforms were unprepared to address, and guidance on how to adequately resource trials within the unique setting of a public health emergency is needed. In many cases, individual sites navigated emerging,

shared challenges and changes alone, which was both inefficient and untenable over the long term. Larger and smaller clinical trials experienced unique needs based on experience and resource capabilities. Tailored recommendations to support more effective trial design and management can help research institutions address and respond to atypical research settings such as those that emerged during the COVID-19 pandemic.

FIGURE 3. Pandemic playbooks can address clinical trial development, logistics, and navigation of regulatory requirements.



It is important that clinical trial guidance addresses both scientific and logistical issues related to **equity** as well. During the COVID-19 pandemic, there was a rapid transition from in-person to remote activities in clinical trials—efforts that were supported by ongoing decentralization efforts and regulatory flexibility. While these processes were critical to ensuring the continuity of safe research, increased use of telehealth has exacerbated disparities in access to health care for some populations. To prevent the creation of another subset of "haves and have nots," clinical guidance should consider and address access to technology and social determinants of health in a standardized, routine manner that is not stigmatizing or discriminatory.

Another important consideration for pandemic response playbooks is the management of non–pandemic-related clinical trials. As the clinical trial ecosystem rapidly shifted to address issues related to COVID-19, most other clinical research was paused or discontinued entirely. The pandemic disrupted the progress of innovative experimental medications for even the most vulnerable patients, including those with life-threatening diseases

(e.g., cancer, cardiovascular disease). While critical non–pandemic-related research must be allowed to continue, considerations are needed to mitigate the impact on and from infrastructure strain.

LESSON 3

Recommendations 1 & 2

Community clinics and large clinical trial networks should be engaged in ongoing pandemic- and non–pandemic-related research in the interim to keep these systems "warm" in anticipation of future public health emergencies.

Many clinical trial networks and partnerships that led the pandemic response, such as ACTIV and the COVID-19 Prevention Network (CoVPN), were built on the foundation of existing clinical trial infrastructure and highlighted the need for clinical trial networks that can be rapidly engaged to support the coordination of effective research in a public health emergency. A dedicated pandemic trial network is unlikely to be effective, so the key question is how to keep the general **clinical trial infrastructure "warm and ready"** to be engaged for a public health emergency in the interim. Both community clinics and large clinical trial networks can be engaged in pandemic- and non–pandemic-related research, including comparative effectiveness research on emerging therapeutics in a variety of health care settings. Such studies will require adequate funding and resources. Recommendations for supporting community clinics to undertake research are provided in ***Infrastructure & Resourcing Lesson 1***.

As clinical trials become decentralized, considerations must be made regarding the differing organizational needs of various trials (e.g., comparative vs investigational), as well as inherent risks to study participants, providers, and clinical trial staff. Certain centers have different capabilities to support clinical trials based on their local resources, which may determine their ability to address certain research issues. Early learning and relationship-building opportunities within communities should begin with trials that require less preexisting infrastructure, such as pragmatic trials, which mirror real-world clinical practices and require less risk for both patients and investigators, and tackle relevant, prioritized research questions for communities.

CLINICAL TRIAL EXECUTION

Recommendations: Clinical Trial Execution

- ↗ **CTE▲1:** Reform regulatory oversight to avoid impediments in trial conduct and review/maintain effective public health emergency regulatory flexibilities, including development of best practices for IRBs, indemnity, streamlining FDA collaboration across centers, and fit-for-purpose human resources protection training.
- ↗ **CTE▲2:** Develop tools, best practices, and resources for timely and effective trial participation, including site readiness assessment tools.
- ↗ **CTE▲3:** Assure that regulatory and prioritization framework for priority questions and data requests will generate optimal and timely clinical site participation.
- ↗ **CTE▲4:** Develop a retrospective assessment report for federal agencies, funders, academic and industry partners on driving culture change in pandemic trial participation, informed by clinical and patient communities. Engage and leverage "early adopter" health systems and community providers to link effort to clinical trial culture change.
- ↗ **CTE▲5:** Improve technology support, capacity, and motivations: capabilities for automated clinical trial data collection via electronic health record and electronic data capture integration, automated lab data, tools for remote patient monitoring and data collection, electronic registries (for natural history and conversion to trials), and registry/trial payment incentives to encourage adoption.

LESSON 1

Recommendations 2 & 4

Systems must be in place early to support research within traditionally nonacademic hospitals and community care settings.

In considering how to support research within the community setting, it is important to build mutually beneficial relationships between academic and community centers that nourish and serve one another. These relationships take considerable time that is not available during a public health emergency. Efforts must be made to **nourish these relationships** before they are needed for a pandemic response, which will allow for natural expansion to accommodate urgent needs.

Fundamentally, health care systems are designed to treat patients in a safe, responsible manner. When asking these systems to expand their clinical capacity to include research, it is important to be mindful of where vulnerabilities exist that may compromise patient care. **Support will be needed** (See Figure 4.) to help community centers understand and mitigate the potential risks, not only for their patients but also their payrolls, reputation, and staff morale. Reassurances will be needed that investigational agents have been carefully vetted and prioritized before being tested in their patients. Payrolls are already strained in many settings, and systems may not be willing or able to accommodate large payroll expansions needed to support clinical trial administration. Additionally, the added workload and stress of regulatory compliance, which can sometimes feel at odds with the needs and interests of the people who are participating in research, can place strain on staff morale.

If health care systems have access to the infrastructure and support to undertake these efforts, as well as representation in the design and steering processes, they may be more willing and able to participate.

FIGURE 4. Support research within traditionally nonacademic hospitals and community care settings.

Integration within the community setting will also require a **culture change** that fosters participant understanding of their role within the clinical trial process. Successful engagement of patients and providers within the community will require reframing the narrative around clinical trials and presenting a true story about what it means to work together with the health care delivery team to find solutions that will benefit the community.

To support community research, new pathways are needed to **develop clinical trialists** within these settings and to engage people at all levels of the research pipeline, including pharmacists, PhDs, and research coordinators. There is a need to rethink the MD-centric clinical trial investigator model that has historically been utilized. Pharmacists and clinical hospitalists, for example, are effective "boots on the ground" who can serve important clinical trial functions. Additional infrastructure and support for pharmacy is also needed, particularly for inpatient clinical trials. Investigational pharmacy is a unique field, and many sites do not have this kind of support.

LESSON 2

Recommendations 2, 3, & 4

Dedicated efforts are needed to address both systemic and patient-level barriers to support diverse participation in clinical trials.

During a public health emergency, people are eager to help. However, across clinical trials, many populations remain underrepresented. Within the scientific literature, much of the discussion is one-sided, focused primarily

on patient-level barriers (i.e., mistrust). Systemic barriers and upstream **social determinants of health** are often left out of the conversation, which represent key opportunities to affect change. Solutions promoting diverse clinical trial participation will not be based solely on individual decision making, and it is important to understand the ways in which systemic interventions can promote change. Specific social determinants of health, including access to high-quality health care, language barriers, and clinician biases, should be considered when designing clinical trials and developing inclusion criteria.

Clinical trial diversity should reflect the burden of the disease or condition. To this end, traditional **inclusion and exclusion criteria** for clinical trial participation must be reevaluated. The narrow scope of these criteria often has the unintended consequence of excluding the most vulnerable—and clinically relevant—populations, including those who are medically underserved, people with comorbidities, and people with disproportionately greater health risks. As a result, findings from studies with narrow enrollment criteria may have limited generalizability, with important implications for health equity.

Building trust within communities is necessary to support diverse clinical trial participation and will take time and prioritization of efforts across all sectors. Successful recruitment of diverse clinical trial populations during the COVID-19 pandemic were based on **direct engagement and physical outreach** with target populations, including working with faith-based and community organizations to promote educational efforts. As part of these efforts, anxieties and fears surrounding clinical trial participation must be directly acknowledged and addressed in a sincere and authentic manner. Strategies to address hesitancies should be incorporated at all levels of the clinical trial process.

Enrollment of minority or underserved populations in clinical trials may require additional support and resources to not only enroll but **retain** these patients in trials. Transient populations, for example, may benefit from outreach to facilitate completion of trial requirements. These additional requirements should be considered early in the planning process, and costs to support these needs should be built into funding models.

LESSON 3

Recommendations 1, 3, & 5

Effective clinical trial execution requires standardized and fit-for-purpose research requirements and clinical trial guidance, which may be achieved through simplification and standardization of protocols and frameworks.

As clinical trials expand into the community setting, there is a need for **standardization and simplification** of research protocols. Many aspects of clinical trial administration and regulatory requirements remain challenging, including contracting and IRBs, and it can be difficult for smaller care networks to navigate these processes. In addition to support and training to overcome these barriers, standardization and streamlining of these requirements will support the diversification of the broader clinical trial ecosystem.

Inherent in the standardization of clinical trial requirements is the simplification of clinical trial tools. In the early stages of the COVID-19 pandemic, limited guidance was provided on the utilization of practical tools related to clinical trial execution and data storage. Experiences from the pandemic highlighted the lack of a **holistic data collection framework**. As guidance is developed on proper clinical trial design, considerations should be made to the development and use of such tools, with emphasis on accessibility, usability, and validity. Integration of

these tools within clinical trial guidance will support the development of robust and harmonized data collection strategies and address data utility, interoperability, and regulations related to data privacy. Proactive consideration of the requirements and limitations of international use can extend the impact of these protocols.

As clinical trial standards and guidance are developed, “fit-for-purpose” requirements are needed. Because pandemic research aims to move quickly and efficiently, requirements for clinical trial intensity should be tiered based on preexisting information. For example, while novel investigational agents may require a more intensive approach designed to detect rare adverse events and potential drug interactions, a simpler approach may be sufficient for a repurposed drug with an established safety profile. Within scientific and regulatory requirements, there is a need for **rigorous modularity** to support rapid and effective clinical trial research.

CONCLUSION

The perspectives and experiences shared during this workshop provide valuable insights on the efforts needed to improve response for future public health emergencies and broadly support efficient and meaningful clinical research, particularly in the community setting. While many of these challenges, pain points, and potential solutions have been discussed before, the COVID-19 pandemic has provided the catalyst to enact sweeping changes to the clinical research ecosystem. As Dr. Kevin Bugin voiced during his closing remarks, "This is a very long journey. We're trying to make changes that [people] have been talking about in the clinical research space for years, if not decades." Substantial progress has already been made and will continue to be made as the clinical, academic, and industry communities, as well as the federal government, build upon the lessons learned.

Appendix

STAKEHOLDERS INVOLVED

The following stakeholders shared lessons learned from their organization's experiences and supported the development of the COVID-19 Lessons Learned: Clinical Evaluation of Therapeutics Discussion Document.

U.S. GOVERNMENT

- Department of Health and Human Services (HHS)
  - U.S. Food and Drug Administration (FDA)
  - National Institutes of Health (NIH)
    - National Institute of Allergy and Infectious Diseases (NIAID)
    - National Heart, Lung, and Blood Institute (NHLBI)
  - Office of the Secretary (OS)
  - Biomedical Advanced Research and Development Authority (BARDA)
- Department of Defense (DoD)
  - Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND)
- Veterans Affairs

NONGOVERNMENTAL ORGANIZATIONS

- Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) at the Foundation for the National Institutes of Health
- National Academies of Sciences, Engineering, and Medicine
- Milken Institute FasterCures
- Clinical Trials Transformation Initiative
- Multi-Regional Clinical Trials Center
- Duke-Margolis Health Policy Center at Duke University
- TransCelerate
- Intermountain
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- Biotechnology Innovation Organization (BIO)
- Association of Clinical Research Organizations (ACRO)
- REMAP-CAP (Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia)
- I-SPY Trials
- Humana

AGENDA

SEPTEMBER 28, 2021		1:00–5:30 PM ET
1:00 PM	**WELCOME AND INTRODUCTION**	
	Kevin Bugin, PhD, Acting Deputy Director of Operations, Office of New Drugs, Center for Drug Evaluation and Research, US FDA and formerly Therapeutics Chief of Staff, Federal COVID-19 Response (previously known as Operation Warp Speed) **Susan C. Winckler, RPh, Esq.**, CEO, Reagan-Udall Foundation for the FDA	
1:15 PM	**OPENING PLENARY**	
	Janet Woodcock, MD, Acting Commissioner of Food and Drugs, US FDA **Francis S. Collins, MD, PhD**, Director, NIH	
1:45 PM	**RESEARCH, SCOPING, & PRIORITIZATION PANEL**	
	Moderators: **Stacey Adam, PhD**, Associate Vice President, Research Partnerships, Foundation for the NIH **Michael Santos, PhD**, Vice President, Science, Foundation for the NIH	**Panelists:** **Phyllis Arthur, MBA**, Vice President, Infectious Diseases and Emerging Science Policy, BIO **Elliott Levy, MD**, COVID R&D Consortium **Sarah Read, MD**, Deputy Director, Division of AIDS, NIAID and ACTIV Therapeutics Clinical Working Group Co-Chair **Janet Woodcock, MD**, Acting Commissioner of Food and Drugs, US FDA
2:45 PM	**INFRASTRUCTURE & RESOURCING PANEL**	
	Moderators: **Esther Krofah**, Executive Director, FasterCures and Center for Public Health, Milken Institute **Kristin Schneeman**, Director, FasterCures	**Panelists:** **Barbara Bierer, MD**, Faculty Director, Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard; Professor of Medicine, Harvard Medical School and Brigham and Women's Hospital **Michael Kurilla, MD, PhD**, Director, Division of Clinical Innovation, National Center for Advancing Translational Sciences, NIH **James Mayne, PhD**, Vice President, Science Advocacy, PhRMA **Doug Peddicord, PhD**, Executive Director, ACRO, and President, Washington Health Strategies Group
3:45 PM	**CLINICAL TRIAL EXECUTION PANEL**	
	Moderators: **Mark McClellan, MD, PhD**, Robert J. Margolis Professor of Business, Medicine, and Policy, and Founding Director of the Duke-Margolis Center for Health Policy, Duke University **Sarah Sheehan, MPA**, Managing Associate, Duke-Margolis Center for Health Policy	**Panelists:** **Samuel Brown, MD, MS**, Senior Medical Director for Clinical Trials, Intermountain Healthcare; Professor of Medicine, Intermountain Medical Center and University of Utah **Janice Chang**, Chief Operating Officer, TransCelerate BioPharma Inc. **D. Clark Files, MD**, Associate Professor, Pulmonary, Critical Care, Allergy, and Immunologic Diseases, Wake Forest School of Medicine and Co-Chair, I-SPY COVID Clinical Operations Group **Monica Webb Hooper, PhD**, Deputy Director, National Institute on Minority Health and Health Disparities **Kate Zenlea, MPH, CPH**, Managing Director, The Global Health Initiative at Henry Ford Health System
4:45 PM	**PUBLIC COMMENT**	
	Open to those who registered in advance	
5:15 PM	**CLOSING PLENARY**	
	Kevin Bugin, PhD, Acting Deputy Director of Operations, Office of New Drugs, Center for Drug Evaluation and Research, US FDA and formerly Therapeutics Chief of Staff, Federal COVID-19 Response (previously known as Operation Warp Speed)	