COVID-19 Lessons Learned: Clinical Evaluation of Therapeutics

Discussion Document

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I.   Glossary of Terms

- **ACRO** – Association of Clinical Research Organizations
- **ACTIV** – Accelerating COVID-19 Therapeutic Interventions and Vaccines
- **ACTT3** – Adaptive COVID-19 Treatment Trial 3
- **AHRQ** – Agency for Healthcare Research and Quality
- **ASPE** – Assistant Secretary for Planning and Evaluation
- **ASPR** – Assistant Secretary for Preparedness and Response
- **BARDA** – Biomedical Advanced Research and Development Authority
- **BIO** – Biotechnology Innovation Organization
- **CDRH** – Center for Devices and Radiological Health
- **CEAL** – Community Engagement Alliance against COVID-19
- **CHC** – Community Health Centers
- **cIRB** – Central Institutional Review Board
- **CRO** – Contract Research Organization
- **CT** – Clinical Trial
- **CTSN** – Cardiothoracic Surgical Trials Network
- **CTTI** – Clinical Trials Transformation Initiative
- **DB** – Database
- **DCT** – Decentralized Trial
- **DoD** – Department of Defense
- **DPA** – Data Protection Authority
- **DSMB** – Data and Safety Monitoring Boards
- **eCRF** – Electronic Case Report Form
- **EDC** – Electronic Data Capture
- **EHR** – Electronic Health Record
- **EMA** – European Medicines Agency
- **EMR** – Electronic Medical Record
- **EUA** – Emergency Use Authorization
- **FDA** – U.S. Food and Drug Administration
- **FNIH** – Foundation for the National Institutes of Health
- **FQHC** – Federally Qualified Health Centers
- **GAO** – Government Accountability Office
- **GDPR** – General Data Protection Regulation
- **HHS** – Department of Health and Human Services
- **HIPAA** – Health Insurance Portability and Accountability Act of 1996
- **HRP** – Human Resources Protection
- **HRSA** – Health Resources and Services Administration
- **ICH** – International Council for Harmonisation of Technical Requirements of Pharmaceutical for Human Use
- **ICMRA** – International Coalition of Medicines Regulatory Authorities
- **INSIGHT** – International Network for Strategic Initiatives in Global HIV Trials
- **IO** – Immediate Office
- **IP** – Inpatient
- **IRB** – Institutional Review Board
- **JPEO-CBRND** – Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense
- **MCRT** – Multi-Regional Clinical Trials Center
- **MOA** – Mode of Action

- **N3C** – National COVID Cohort Collaborative
- **NASEM** – National Academics of Sciences, Engineering, and Medicine
- **NCATS** – National Center for Advancing Translational Sciences
- **NCI** – National Cancer Institute
- **NHLBI** – National Health, Lung, and Blood Institute
- **NIAID** – National Institute for Allergy and Infectious Diseases
- **NIH** – National Institute of Health
- **OCR** – Office for Civil Rights
- **OHRP** – Office for Human Research Protections
- **OP** – Out Patient
- **OS** – Office of the Secretary (in HHS)
- **OWS** – Operation Warp Speed
- **PETAL** – Prevention and Early Treatment of Acute Lung Injury
- **PHE** – Public Health Emergency
- **PHEMCE** – Public Health Emergency Medical Countermeasures Enterprise
- **PhRMA** – Pharmaceutical Research and Manufacturers of America
- **PI** – Principal Investigator
- **PMO** – Project Management Office
- **PPP** – Public Private Partnership
- **R&D** – Research and Development
- **RCT** – Randomized Controlled Trial
- **REMAP-CAP** – Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia
- **SME** – Subject Matter Expert
- **SOP** – Standard Operating Procedure
- **TPP** – Target Product Profile
- **Tx** – Therapeutics
- **UN** – United Nations
- **VA** – Veterans Affairs

II.   Executive Summary

In May 2020, the US government (USG) program Operation Warp Speed (now known as the Federal COVID-19 Response or Countermeasures Acceleration Groups) 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 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 and distill them into actionable recommendations. Through interviews, discussions, and shared materials, a set of lessons learned were collected across three broad categories: (1) a need to centralize USG structures and processes, (2) ensure the clinical research system is fit for purpose and ready for a public health emergency (PHE), and (3) improving the overall efficiency and effectiveness of clinical trials (CT). Within these broad categories, eight themes emerged:

- **Coordinate the response**: Central, cross-USG governance with strong processes to drive swift and coordinated CT PHE action
- **Use one voice:** Clear, consistent, and open USG communication with CT landscape to ensure efficient progress towards common goals

- **Move fast on R&D investments:** Streamline USG contracting processes in a PHE to prevent delays on potentially life\-saving R&D
- **Enhance CT infrastructure and agility:** USG-supported CT infrastructure expansion beyond PHE to ensure ability to quickly deploy trials
- **Plan ahead to shape CT response quickly:** Tools and guidelines for clinical trial design to quickly shape response from PHE inception
- **Be more efficient with CT resources:** Best practices and guidance for clinical trial execution to improve trial efficiency and participation
- **Collect and share data**: Open data collection and sharing to avoid duplication and ensure efficient deployment of resources for CT execution

This document focuses on a subset of actionable recommendations, developed by multi-stakeholder working groups[1], emerging from these themes. These recommendations address what works and what we need to enhance in terms of scoping, prioritizing, and communicating about research activities in a PHE setting. For example, the COVID-19 therapeutic response demonstrated that randomized controlled trials outperform other trials in providing actionable evidence. We also see the positive impact of master protocol platforms trials. On the other hand, we lack a system that supports the timely sharing of research activities and data amongst stakeholders and with the public.

The recommendations in this document also address building and maintaining a more agile and integrated CT infrastructure. Building CT site capacity and networks for participation in large multi-center trials is challenging, and further complicated by the burdens of a PHE. Importantly, community-based sites and networks are more optimally positioned to increase trial participation from under-represented communities. Lastly, the document presents recommendations to stand up and run effective CTs, which requires significant experience, resources, and tools. Exploring the use or broader use of common tools, such as electronic informed consent, site qualification tools, or enhanced information technology in the site setting could raise the bar for CT execution across the ecosystem, ensuring a higher probability of study success.

The recommendations outlined in this document are not intended to represent the USG's final opinion or recommendations on these matters and are considered a starting point for ongoing discussions.

III.   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 Federal COVID-19 Response or Countermeasures Acceleration Groups), the US government (USG) program to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics (collectively known as countermeasures). 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 the COVID-19 space across Department of Defense (DoD), National Institutes of Health, and Biomedical Advanced Research and Development Authority (BARDA). The team also identified critical operational challenges to overcome and accelerate novel neutralizing antibody (nAb) therapeutics (incl. reimbursement and legal barriers to shared capacity).

Informed by these efforts, the team defined the OWS Therapeutics strategy, which embodied a two-pronged approach, focusing on candidates to 1) attack the virus and 2) manage complications. The Therapeutics Leadership team held C-level discussions with priority therapeutics manufacturers to identify specific areas where USG could accelerate their programs. As priority therapeutics manufacturers began to prepare for

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[1] The working groups include leaders from across government, think tanks, nonprofits, and industry associations. See Appendix for list of stakeholders

potential Emergency Use Authorizations (EUAs), the Therapeutics Leadership team provided direct support to Lilly and Regeneron in preparation for a potential EUA for their 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. The Therapeutics Leadership team coordinated budgets across workstreams to enable funding of contracts for procurement of product under Advance Purchasing Agreements (APAs), execution of platform clinical trials, and launch of communications activities to support trials and monoclonal antibody distribution and administration

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 related to the clinical evaluation of therapeutics and distill them into actionable recommendations. The Federal COVID-19 Response Team for Therapeutics convened multi-stakeholder working groups[2] to review the lessons learned and develop recommendations to address them. The recommendations and potential approaches to address the recommendations were developed by Working Group members (incl. leaders from across government, think tanks, nonprofits, and industry associations) and reflect feedback and guidance from the Initiative's leadership group (incl. representatives from HHS, DoD, and the VA). The recommendations outlined in this document are not intended to represent the USG's final opinion or recommendations on these matters and are considered a starting point for ongoing discussions.

IV.   Recommendations

A.   Research, Scoping & Prioritization

Recommendation 1:

Rapidly collect and disseminate enabling information such as pathogen ID, sequencing, and natural history data (through natural history registries).

Context for the Recommendation

Goals in developing this recommendation:

- Increase the availability of information in a PHE to rapidly accelerate R&D response
- Leverage databases and platforms for other disease areas outside of a PHE

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

- **Success with early dissemination of pathogen identification and sequence**, and repurposing of existing databases (e.g., GISAID) to make sequence information available

- **Challenges with systematic collection of natural history data** that would have better informed therapeutic development

- **Pathogen evolution** and limited availability of information and samples across the US and world

- **Data rights and privacy barriers** to collection and dissemination of information that were difficult to address in real time during a PHE

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[2] See Appendix for list of stakeholders

Key lessons learned identified (examples):

- **Existing platforms and tools can be deployed faster than new tools**: This emphasizes the value of evaluating what is available for use in a PHE and may motivate the creation of new platforms and tools to be prepared/adapted for use during a PHE.

- **Communication is important to raise awareness**: Not all stakeholders were aware of opportunities to contribute or access information from the different platforms available

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Convene stakeholders of key databases adapted for COVID-19 variant sequencing and natural history to identify obstacles to collection and sharing

2. Decide if existing databases should be prepared for future emergency use and/or if PHE-specific databases should be established

3. Establish PHE governance for databases (accessibility, privacy protection, etc.)

4. Proactive communications to raise awareness of potential database contributors (academics, sequencing labs, provider systems, etc. – anyone with data to contribute)

Recommendation 2:

Ensure the CT ecosystem creates actionable evidence through developing strategy, guidelines, templates, incentives, and capacity building (e.g., prioritize randomized trials).

Context for the Recommendation

Goals in developing this recommendation:

- Ensure that more candidate therapeutics are evaluated faster and more effectively across all stages of development
- Ensure patients do not participate in trials that do not provide actionable evidence
- Improve evidence generation outside of PHE through building capacity

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

- **Limited resources led to competition between trials.** Numerous trials competed for the same patient populations and sites, due to lack of trial prioritization and sites having limited resourcing to support multiple trials

- **Many trials were not designed for actionable results**. Many COVID-19 therapeutics trial designs included issues with randomization, endpoint selection, data collection, and power that limited the interpretability and utility of their safety and efficacy data

Key lessons learned identified (examples):

- **In a PHE, there are strong incentives for investigators and institutions to rapidly launch small trials:** In an information vacuum, and with a desire to help patients, there are scientific and patient care motivations to do something small rather than wait to be part of something more comprehensive. This underscores the importance of extremely rapid organization of the research response, before many small efforts proliferate.

- **RCTs outperformed other trials in providing actionable evidence:** This suggests that RCTs should be preferred to other trial designs in future PHEs.

- **Master protocol platform trials were successful:** Despite the challenges of designing and implementing master protocol platform trials, which assessed multiple therapeutic interventions, during a PHE, existing and new trials were executed successfully.

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Engage Principal Investigators of uninformative studies to understand motivations and barriers

2. Develop framework of incentives, guardrails, and capacity building to focus CT resources during PHE on generating actionable evidence

3. Negotiate improved incentives with academic medical centers and journals (reward better aligned with actionable evidence)
4. Build CT literacy for researchers, providers, and patients (including those with previous CT experience) with guidelines, templates, and training

5. Establish a mechanism for developing and communicating guidance for generating actionable evidence in the specific PHE (and what to avoid)

Recommendation 3:

Enable the open sharing of research strategy and plans amongst stakeholders in the CT ecosystem to coordinate activities, including in funding announcements.

Context for the Recommendation

Goals in developing this recommendation:

- Reduce redundancy in research efforts and enable higher confidence about moving forward with activities
- Ensure more therapeutics candidates are evaluated faster across all stages of development

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

- **Many resources shared information on approved clinical trials:** There was an abundance of data on clinical trials after they reached the point of approval and registry with clinicaltrials.gov (or announcement via press release).

- **Lack of coordination of research activities:** Lack of awareness of research plans (i.e., prior to public announcement) led to undesirable redundancies (e.g., multiple different trials testing the same compound or mechanism of action in similar conditions).

- **Competition and anti-competition considerations are relevant**: Although there was extensive collaboration across the ecosystem, competitive concerns among academics and companies are still important, including ensuring that industry collaboration does not run afoul of anti-collusion laws and rules.

Key lesson learned identified (example):

- **Lack of a system to support continual sharing of research strategies as plans develop and change:** There is no easy system for stakeholders to share research plans and timely updates. This matters in a PHE, where many decisions are being made rapidly and by the time plans become publicly announced activities it may be too late to avoid redundancies.

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Determine the key information that needs to be shared to inform research coordination (i.e., minimize inappropriate duplication)

2. Develop templates for describing research plans, activities, and funding resources

3. Adapt/build a platform for sharing research plans (compound/mechanism of action and indication), activities, and funding opportunities

4. Analyze and address barriers to sharing/coordination (academic priority, financial interests, anti-trust law)

5. Set expectations and raise awareness about the need and opportunity to share research plans during a PHE

Recommendation 4:

Establish efficient and effective systems for sharing early research data and results with other researchers outside of publication channels.

Context for the Recommendation

Goals in developing this recommendation:

- Inform clinical decisions based on more data and timely (but not premature) research findings
- Enable faster and better secondary analyses (e.g., meta-analyses) through appropriate primary data sharing
- Improve information to providers, policymakers, and the public about scientific results

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

- **Preprints were the dominant channel for rapidly sharing research data and results**, but curation of the tremendous volume of non-reviewed information was a major challenge, particularly because non-expert audiences began using preprints as information sources.

- **Press releases were used to disseminate top-line information** (including financially material information) quickly, with the drawback that independent experts had little ability to comment on the results.

- **There was substantial demand for the immediate sharing of information that is not typically (immediately) public** (e.g., CT protocols, trial recruitment data while the trial is ongoing, data submitted for regulatory decisions).

- **This issue extends far beyond clinical evaluation of therapeutics** and addressing it may have benefits outside of PHEs.

- **Selective sharing of reviews with the public could support communication efforts:** FDA could diversify its approaches to help the public understand the Emergency Use Authorization pathway, for example, with selective sharing of scientific reviews alongside broader communication

Key lessons learned identified (examples):

- **Rapid data sharing is possible before publication:** Rapid data sharing across trials and/or trial networks was accomplished in some instances prior to publication. For example, steroid data for WHO meta-analysis was shared before the actual publications went out. A multi-platform RCT of therapeutic heparin also brought three platform trial networks together to share data.

- **Successful data sharing platforms already exist:** Shared clinical data across academic centers (e.g., NCATS's National COVID Cohort Collaborative) enabled over 50 academic medical centers that are Clinical and Translational Science Awardees (CTSAs) to harmonize their clinical data, an effort that had been in the works for years

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Convene an evaluation of the information dissemination and data sharing ecosystem (journals, preprints, press releases, databases)

2. Develop recommendations to improve primary data sharing (e.g., data sharing platforms)

3. Develop recommendations to improve communication of scientific results (e.g., through open access, preprints, non-traditional dissemination)

4. Develop recommendations to improve communication of secondary analysis of scientific results (including in the form of guidelines) to providers/policymakers/public

B.   Infrastructure and Resourcing

> **Recommendation 1:**
>
> **Identify and leverage existing clinical trial network infrastructure (incl. NIH-funded networks, nonprofit & industry/CRO sites networks) and public-private partnerships (e.g., ACTIV) to maintain a 'warm base' for public health emergencies (PHEs) and that can be deployed against high priority unmet needs.**

Context for the Recommendation

Goals in developing this recommendation:

- Minimize the time required for trial stand-up in a PHE, and incentivize research in other priority areas
- Maximize the value of existing infrastructure beyond the current PHE
- Maintain a more efficient and collaborative standing network with clinical research capacity to respond to a range of needs

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

- **Network activation during a PHE was difficult,** and networks were underprepared with over-reliance on academic institutions and large providers with inadequate access to communities, inconsistent processes, and non-scalable models

- **Trial networks which were stood up and had partnerships prior to the PHE were more successful:** Existing trial networks, such as PETAL[3] and CTSN[4], were successful at rapidly transitioning into COVID-19 with high enrollments in multiple ACTIV[5] and para-ACTIV trials as they already had the network stood up with partnerships in place

- **List of sites which existed prior to the PHE was insufficient:** Responding to the COVID-19 pandemic required adding additional sites to a pre-pandemic generated list of clinical trial sites that had been created by NIAID[6] for pandemic preparedness

Key lessons learned identified (examples):

- **Need a nationwide standing network:** Setup nationwide standing network of sites with clinical research capacity to immediately respond to a range of pandemics – across severity, investigator/research skills, patient populations, diseases (infectious, etc.)

- **Centralizing management between networks could support capacity coordination:** Centralize management and link different networks (e.g., PETAL, INSIGHT[7]) during a pandemic for optimal utilization of research capacity

- **Important to maintain COVID-19 trial infrastructure post-PHE:** Keep COVID-19 trial infrastructure in place to streamline and incentivize research in areas of high unmet need (consider

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[3] Prevention and Early Treatment of Acute Lung Injury
[4] Cardiothoracic Surgical Trials Network
[5] Accelerating COVID-19 Therapeutics Interventions and Vaccines
[6] National Institute for Allergy and Infectious Diseases
[7] International Network for Strategic Initiatives in Global HIV Trials

developing a Strategic National Stockpile of capacity for clinical research to be ready to be repurposed for a PHE)

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Maintain, expand (e.g., include other government-funded health systems like VA, DoD, CHCs[8], FQHCs[9]), and utilize NIH's Clinical Trial Capacity Inventory

2. Evaluate government-funded network/partnerships built/utilized for COVID-19, assess strengths/weaknesses/gaps

3. Parallel evaluation/assessment of non-government-funded and commercial networks

4. Create/enforce norms of transparency (e.g., protocols, enrollment, endpoints) across networks/sites to minimize overlap, especially in a PHE

5. Develop a plan for setting and funding research "challenges" to keep this research base warm (e.g., consider "drills" to ensure readiness)

Recommendation 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.

Context for the Recommendation

Goals in developing this recommendation:

*   Diversify and increase representation in trial participants
*   Create more extensive networks for large and simple trials

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

*   **Established trial networks lacked size and diversity:** Established networks do not have the full set of capabilities required in a PHE; creating networks large enough to ensure required size and geographic diversity to recruit patients throughout the pandemic was a pain point

*   **Trials could have better engaged local communities and community-based sites:** Networks relied on academic institutions and large providers with inadequate access to underserved communities. A forum was developed to engage different community groups for vaccine development, but not for therapeutics.

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[8] Community Health Centers
[9] Federally Qualified Health Centers

- **Interoperability issues with networks led to slowdown:** Lack of culture and resources to support coordination and enable interoperability led to siloed strategies, competing for patient enrollment, and challenges with contracting and IRB[10]

Key lessons learned identified (examples):

- **National integrated trial network is needed:** Develop nationwide standing network with clinical research capacity to immediately respond to a PHE, make it easier for networks to pair and integrate under a single unified trial system, consider flexible, expedited contracting mechanisms, and/or mandate use of central IRB.

- **National network of community sites and simplifying processes could support community site enrollment:** Set up a nationwide network of community sites to reach out to the broader population and specifically many racial and ethnic minority communities that the virus has hardest hit. Simplify processes, documentation, equipment needs, and expectations from sites to take part in clinical research to enable community sites to join more extensive networks/trials.

- **Trial networks could be more pragmatic:** Develop a more pragmatic trial network to reach more participants through community-based settings and run larger, simpler trials.

- **Network capabilities should be tracked and infrastructure kept warm:** Track, manage, and maintain a list of networks' capabilities and keep them warm. For example, after awarding EUA[11] to IPs[12], continue to keep the supporting sites and trials running under open-label to keep the sites warm and collect additional data for safety.

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Build on list of current networks and capabilities, identify gaps & barriers, and develop a roadmap to address. Bring in outside expertise and partner with other organizations. Look at best practices in community-based research networks in cancer (e.g., NCI[13] Oncology Research Program)

2. Define infrastructure requirements to be part of a network of networks (e.g., universal payment plan, interoperability standards, quick contracting mechanisms). Consider international coordination

3. Identify & fund research priorities for expanded networks to "practice on" and "keep warm" their capabilities (e.g. REMAP-CAP[14] as a model). Establish governance to manage and deploy resources to sites (e.g., data coordinating center)

Recommendation 3:

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[10] Institutional Review Board
[11] Emergency Use Authorization
[12] Inpatient
[13] National Cancer Institute
[14] Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

> **Remove post-pandemic barriers to expanded adoption of decentralized/hybrid trials and remote monitoring tools.**

Context for the Recommendation

Goals in developing this recommendation:

- Ensure ability to maintain decentralized/ hybrid trials outside of the current PHE through continuous guidance from FDA to product sponsors
- By maintaining decentralized/ hybrid trials, increase overall patient enrollment, ensure higher likelihood of adequately powered trials, and increase patient diversity from underserved communities & those unable to access academic research institutions

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

- **DCTs[15] can improve patient enrollment and representation, and help capture real world data:** Value of DCTs was recognized before the current COVID-19 pandemic (e.g., increased participation and diversity, reduced burden on patients, improved recruitment and retention, more data capture that translates to the real world)

- **DCTs and remote tools have been critical to trial continuity:** DCTs, hybrid trials, and remote tools have been instrumental in supporting CT continuity during the pandemic, and have become a necessity, not a novelty

- **Some regulatory considerations can pose hurdles to remote trials:** State-level requirements related to cross-state physician licensure, drug supply chain management, safety, and follow-up reporting were at times a barrier to telehealth and remote/tech-enabled trials. International regulatory issues and processes (e.g., data protection regulations in Europe) also prevented further coordination

Key lessons learned identified (examples):

- **Helpful to track and gather lessons learned from decentralized trials:** Keep track of all studies using decentralized trial practices and speak with the sponsor and participants about their experience with the decentralized practices to leverage learnings and hear how certain practices are working

- **Leveraging remote and digital technologies could enable participant interaction:** Encourage and facilitate trials adopting decentralized and remote approaches, including remote check-ins with participants (by phone or video), virtual visits, shipment of study products directly to patients' homes, home visits by clinical staff for evaluations, remote consents (e.g., eConsent forms), remote monitoring, and use of mobile devices

- **Guidance is needed on use of remote and digital technologies:** This need has already resulted in the FDA creating a framework for how industry could scale and sustain decentralized clinical trials and digital monitoring tools post-pandemic, including issuance of three primary guidances: (a) guidance on the use of decentralized clinical trial tools and methods beyond the PHE; (b) guidance on the use of digital health technologies to capture study-related data directly from patients; and (c) guidance on data integrity issues arising from trial disruption

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[15] Decentralized Trials

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Review pandemic guidance on non-COVID trial conduct, track sponsors' experience using remote tools during COVID 19, and determine need for post-pandemic guidance/flexibilities to enable more decentralized/hybrid trials. Enable international collaboration

2. Ensure alignment on remote data collection standards across FDA

3. Extend telemedicine/remote monitoring flexibilities & reimbursement beyond PHE. Initiate a dialogue with states about streamlining requirements on a permanent basis

4. Identify existing laws, regulation, guidance impacting conduct of DCTs

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Recommendation 4:

Research, develop, and share best practices on managing patient enrollment with a focus on prioritized trials/platforms while enabling co-enrollment.

Context for the Recommendation

Goals in developing this recommendation:

- Increase ability (e.g., by aligning messaging) to fully enroll prioritized trials
- Optimize the most critical and limited resource in trials – patients
- Ensure appropriately powered trials that lead to actionable evidence

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

- **Restrictions on co-enrollment hindered recruitment for high priority trials:** There were multiple high-priority NIH-funded trials (e.g., ACTT3[16], ACTIV-1, convalescent plasma); barring of co-enrollment with other studies for 5 days made it difficult to recruit patients who did not want to be excluded from other trials

- **Coordinated communications plan with streamlined requirements and aligned messaging would have enabled more successful recruitment:** Lack of a communication plan across therapeutics research led to challenges with recruiting patients and providers to studies. Messages such as "if you are sick stay home", "there are no treatments", and "vaccines are what we should be focusing on" hindered enrollment, as did requirements to clear recruitment materials for communications across multiple trials

- **Funding options for marketing were not clear to sites:** Sites were either not aware they could request marketing funds to support local market advertising or were not familiar with the fund request process

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[16] Adaptive COVID-19 Treatment Trial 3

Key lessons learned identified (examples):

- **Collaboration with other networks can support co-enrollment:** Allow sites to co-enroll on other trials, collaborate with other networks to support co-enrollment and separate on the back end (e.g., REMAP-US serving as site network for ACTIV-4)

- **Co-enrollment best practices include integrated research tools and alignment:** For example, leveraging integrated EHR[17] through EHR-enabled clinical research tools, align regulators and IRBs, and align inclusion, exclusion and endpoints

- **Comprehensive and nationally coordinated communications plan is needed:** Develop comprehensive communication plan early-on to promote broader awareness of the trials and safety of therapeutics, generate comparable excitement for clinical research across vaccines and therapeutics, and challenge disinformation on treatments. Leverage a call center to assist sites with recruitment, flyers, pamphlets, patient education information/flipbooks, and large-scale campaigns

- **Sites should be made aware of marketing options and aligned on messaging:** Proactively communicate the site marketing/advertising options and develop standard language for sites to use when developing their own local campaigns

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Establish effective communications strategies EARLY across enrolling trial sites, disseminate information to target stakeholders on prioritized trials/platforms and engage patient organizations on messaging
2. Establish best practices, guidelines for effective co-enrollment practices, align regulators and IRBs, harmonize endpoints & data capture
3. Evaluate REMAP-COVID as a model for embedding EHR-enabled clinical research tools as part of routine clinical care, and create a playbook for extending the model for other priority trials
4. Build broader clinical trial awareness among the public and providers during a PHE

Recommendation 5:

Determine best practices for increasing participation in trials from under-represented communities and create action plans for improvement.

Context for the Recommendation

Goals in developing this recommendation:

- Document and promote promising strategies for more representative trials
- Leverage current use case to initiate efforts across broader clinical trials to increase diversity and equity

Pain points, bright spots, mistakes to avoid, watchouts identified (examples):

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[17] Electronic Health Record

- **Trials lacked diversity across participants:** Most trial participation came from academic institutions – involving local community sites could improve representation. Other trials (e.g., ACTIV) increased diversity by reaching out to trusted voices within the community

- **Even when community sites were represented in trials, minority participation was low:** Some manufacturers relied heavily on community sites but still noted they struggled with interest in participation from minority groups

- **Sites lacked awareness of marketing support options (e.g., Spanish language advertising materials):** Little-to-no awareness amongst sites of available marketing support and planned media campaigns; for example, whether English/Spanish advertising materials would be made available or that a large-scale public relations campaign was planned

- **Technology-heavy requirements can exclude certain populations:** Though important to leverage technological advances, telehealth, and/or remote systems and technology-supported enrollment can be a problem for portions of the population (e.g., elderly, rural, lower-income)

Key lessons learned identified (examples):

- **Recruitment materials should be linguistically and culturally tailored:** Develop and disseminate culturally and linguistically tailored recruitment materials, and assist sites with translating materials or cultural adaptations necessary to reach patient pool

- **Disseminating messages through community partners could enhance trust:** Identify trusted voices – partner with community organizations, faith-based groups, and leaders to disseminate information and build trust in clinical research

- **Helpful to simplify participation requirements and provide additional enrollment assistance:** Ease practicing clinicians' participation in a broader range of care settings to ensure representative enrollment, for example, site readiness assessment, "concierge" assistance, and broad and simple inclusion criteria

- **Deliberate efforts to reach underserved communities are needed:** Address racial and ethnic disparities in research by creating accountability for sponsors, improving data collection and use, broadening eligibility criteria and changing study designs, and bringing trials to communities. ACTIV was able to increase diversity in trials by deliberately putting in place efforts to reach underserved communities, such as setting up pan-trial CEAL[18] teams to reach out to faith-based groups, barbershops, etc.

- **Enrollment process should be inclusive of patients with limited access to technologies:** Provide low-tech options, for example, obtaining consent through telephone for patients in remote areas

- **Coordinated community outreach can be leveraged:** Consider incorporating manufacturer-run trials in USG community outreach

Potential Approaches to Address Recommendation

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[18] Community Engagement Alliance against COVID-19

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Convene leaders working to move clinical research into communities to share learnings and identify priorities for future action

2. Capture lessons learned about effective minority engagement during pandemic (e.g., Community-based organizations, Faith-based organizations, NIH's CEAL initiative, Moderna/Pfizer's vaccine trial recruitment)

3. Convene commission (GAO[19] study) for deeper analysis of challenges with and solutions for engaging under-represented communities in R&D

4. Establish permanent interagency working group/forum for engagement with community groups to create roadmap and action plans

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[19] Government Accountability Office

C.   Clinical Trial Execution

Recommendation 1:

Reform regulatory oversight to avoid impediments in trial conduct and review/ maintain effective public health emergency (PHE) regulatory flexibilities (incl. development of best practices for IRBs/ cIRBs[20], indemnity, streamlining FDA collaboration across centers, fit-for-purpose HRP[21] training).

Context for the Recommendation

Goals in developing this recommendation:

- Reduce real/ perceived regulatory barriers to trial participation while still providing appropriate patient protections, leading to enhanced trial participation and evidence generation
- Increase capacity for trials due to reduced burden of training key trial personnel, including frontline providers
- Enable faster, more seamless regulatory decision-making

Pain points, bright spots, mistakes to avoid, watchouts identified (select illustrative examples):

- **Continually evolving regulations led to interpretation challenges:** Regulatory guidance for clinical trial conduct evolved globally throughout the pandemic, presenting interpretation and implementation challenges

- **Conflicting guidance within FDA resulted in unclear expectations:** Processes, decisions, authority, and data requirements differed between FDA divisions, leading to different guidance on trial conduct and evidence requirements depending on the FDA division reviewing

- **FDA was innovative during PHE**: FDA was very flexible/innovative throughout the pandemic, but there may be an opportunity to apply some of the innovations even outside the pandemic context

- **Regulatory flexibility facilitated trial acceleration in some cases:** In some instances, FDA being flexible in considering safety data from earlier interim analysis resulted in accelerated timelines

- **Duplicative IRBs slowed the review process:** Many sites used a local IRB rather than solely using the established cIRB, slowing down the review process

- **Data collection requirements were burdensome for many sites:** Many sites didn't have the capabilities to do the intense collection and data management required for platform trials

Key lessons learned identified (examples):

- **Planning a regulatory strategy early on could result in faster approvals:** Expedite approvals with advanced planning on regulatory strategy across products in a platform trial setting

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[20] Central Institutional Review Boards
[21] Human Resource Protection

- **Collaboration and communication across FDA could enable streamlined approvals:** Ensure FDA's review staff collaborate and communicate to ensure internal harmony of decision making across the organization to streamline approvals

- **Establishing best practices for using IRBs could expedite approvals and prevent redundancies:** Develop best practices for using a cIRB such as standing up one trusted cIRB across all studies from day one and ensuring the cIRB has adequate authority over local IRBs to expedite approvals and prevent redundancies

- **Tools to support site registration could accelerate site start up**: Implement supports to facilitate site activation such as the use of a cIRB, tools to address contracting and indemnity issues, and tools to support efficient screening, patient consent, and randomization

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point

1. Develop straightforward policies and guidance to expedite trial-site contracting during public health emergencies (e.g., overviews of legal and regulatory compliance requirements expected for site activation and trial participation during a PHE)

2. Provide clear data collection requirements for trials that match the capabilities of existing networks and meet evidence needs efficiently

3. Develop best practices for IRB oversight, evidenced by local IRB trust to rely on trial network's central IRB of record

4. Develop efficient, fit-for-purpose Human Resource Protection training that enables broader provider participation in safe, high-quality trials

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Recommendation 2:

Develop tools, best practices, and resources for timely and effective trial participation, including site readiness assessment tools.

Context for the Recommendation

Goals in developing this recommendation:

- Reduce costs and barriers to timely site participation, enabling more rapid and extensive evidence generation
- Enable accurate and timely identification of sites to participate in key PHE trials, to support "pandemic ready" sites, and to speed site activation and recruitment of additional sites when needed

Pain points, bright spots, mistakes to avoid, watchouts identified (select illustrative examples):

- **Inadequate site preparation led to slow start up:** Sites were not adequately prepared to shift their focus and conduct CTs during the COVID-19 pandemic

- **Lack of standardized reopening process for sites resulted in slow patient recruitment**: There was a lack of standardized processes to streamline and accelerate site reopening and enrollment during protocol updates

- **Sites lacked a standardized readiness assessment**: Sites lack a standardized and approved process and method to ensure they were ready to conduct CTs in the manner required for the COVID-19 pandemic

Key lessons learned identified (examples):

- **Tools and central IRB could expedite site preparedness:** Implement supports to expedite site activation, including a cIRB, tools to address contracting and indemnity issues, and tools to support efficient screening, patient consent, and randomization

- **Quick confidentiality agreements could enable rapid site registration:** Build mechanisms to expedite site registration, opening, and patient enrollment, including processes to support quick execution of confidentiality agreement with appropriate indemnification

- **Readiness assessments and additional assistance could enable practicing clinicians to participate in trials**: Implement steps such as a site readiness assessment and "concierge" assistance to ease practicing clinicians' participation in CTs

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Develop site readiness assessment checklist to assess network infrastructure/capabilities (EHR[22], staffing, training, and pharmacy capacity as well as legal and financial review capacity) for each major type of PHE trial, to predict likely participation

2. Review of existing resources and development of best practice documents and shared tools that guide and support trial conduct in existing networks and new systems. These resources should include reusable tools and guidance to support efficient site contracting and straightforward approaches for regulatory compliance (e.g., IRB and indemnity agreements, HIPPA[23] compliance) as well as resources to address drug/pharmacy supply, staffing, technology, and equipment requirements

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[22] Electronic Health Record
[23] Health Insurance Portability and Accountability Act of 1996

Recommendation 3:

Assure that regulatory and prioritization framework for priority questions and data requests will generate optimal and timely clinical site participation.

Context for the Recommendation

Goals in developing this recommendation:

- Increase the ability to predict and achieve meaningful trial participation, representativeness, patient accrual, and thus increase the likelihood of meeting design goals

Pain points, bright spots, mistakes to avoid, watchouts identified (select illustrative examples):

- **Sites were not able to properly collect and manage data:** Many sites do not have the capabilities for the intense collection and data management critical for clinical trials

- **Lack of central management led to limited visibility on evolving priorities, milestones, and reporting:** Limited visibility on evolving priorities, multiple versions of milestones, siloed comms across teams, inconsistent reporting across trials, limited access to readily available data

- **Lack of coordination between research questions and site capabilities resulted in some sites being unable to administer via multiple modes:** Many sites do not have the resources/infrastructure/capability to administer via multiple modes (e.g., IV administration over a long duration for OP[24] was a challenge for ACTIV-2)

Key lessons learned identified (examples):

- **Proactive alignment on digital data collection strategy could ensure appropriate data are collected:** Prospective discussion of digital data collection tool(s) with health authorities could ensure data collected are acceptable

- **Balancing simple vs. robust data collection could reduce burdens and promote diverse participation while ensuring robust data:** Simplifying data requirements from trials, leveraging integrated EHR, and streamlining safety & reporting processes would reduce the burden on sites and personnel and result in higher and more diverse participation. However, important to weigh this against more robust data collection (co-morbidities, etc.), risking a less diverse trial

- **Simplifying trial design could reduce burdens on sites and providers**: Design simpler trials that can get maybe not all possible data, but all clinically relevant data reliably from electronic data systems (integrated EMRs[25]), reduce the need for site-specific intrusions and burdens on medical practice by focusing on data clinicians are collecting anyway

- **Managing sites with differing capabilities could result in better matching of sites to research questions**: Consider "tiers" of sites, some with capacity for rapid Phase 2 screening and some with capacity for more extensive "academic" data collection and monitoring of drugs with limited safety experience and limitations in knowledge on the mechanism of action

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[24] Out Patient
[25] Electronic Medical Record

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Assess priority research questions and requirements for trial design and data collection to support decision making compare with overall trial site readiness and capacity to identify mismatches

2. Develop plan for implementing feasible steps to address mismatch and incentivizing enrollment in meaningful trials (or acknowledge/plan for trials to take place elsewhere, including ex-US sites)

Recommendation 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.

Context for the Recommendation

Goals in developing this recommendation:

- Drive culture change around trial participation, with expectation and confidence that effective trials will be broadly integrated into care delivery in response to the next PHE

Pain points, bright spots, mistakes to avoid, watchouts identified (select illustrative examples):

- **Providers lacked clinical trial know-how**: There was a lack of sufficient education and tools for providers to conduct trials and create actionable evidence while providing care

- **CT ecosystem culture did not support sharing of resources to support research:** There was not a culture of sharing resources to support clinical research across stakeholders – CTs often engaged in siloed behavior such as developing siloed strategies for enrollment across trials and competing for patients

- **Networks had inefficiencies and lacked representation from community sites:** Existing CT networks often had an over-reliance on academic institutions and large providers with inadequate access to communities, inconsistent processes, non-scalable models, and poor accountability

Key lessons learned identified (examples):

- **Diverse patient enrollment is needed:** NIH and other funders should ensure that CT recruitment focuses on diverse patient populations with attention to demographic characteristics and disease-stage

- **Deliberate training and resourcing could drive culture change in CT landscape**: Strengthen training and resourcing across CT landscape to drive culture change to encourage information and resource sharing within clinical research

- **Tiered site participation could improve network efficiencies**: Consider "tiers" of sites, some with capacity for rapid Phase 2 screening and some with capacity for more extensive "academic" data collection (including ability to monitor drugs with limited safety experience and knowledge on the mechanism of action)

- **Embedding clinical research capability into care could improve provider clinical trial know-how**: All healthcare provider workforce (physicians, nurses, specific therapists, etc.) should be reinvigorated, trained, and provided real tools as part of their curricula to contribute to the generation of evidence, observation, and clinical research. "Early adopter" health systems and community providers could be particular areas of focus

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Translate and release Lessons Learned products on this issue to support engagement with health system clinicians, public health officials, and the public to describe a feasible vision for more efficient, broad, and timely conduct of informative PHE trials

2. Report on feasibility of a PHE clinical trial strategy with tiered levels of trial participation tailored to the therapeutic context and compound characteristics (e.g., repurposed vs new drugs), showing how a range of academic and community-based health care organizations, frontline clinicians, and interested patients can participate in priority and other trials

3. Implement USG public engagement process with health systems, health system clinicians, and other stakeholders to accelerate culture change

4. Develop plan for Medicare/public payments for participation in effective trials (building on COVID-19 Medicare quality bonus for trial participation)

Recommendation 5:

Improve technology support, capacity, and motivations: capabilities for automated clinical trial data collection via: EHR and EDC[26] integration, automated lab data, tools for remote patient monitoring & data collection, electronic registries (for natural history and conversion to trials), and registry/trial payment incentives to encourage adoption.

Context for the Recommendation

Goals in developing this recommendation:

- Reduce data collection burden leading to reduced trial costs and greater participation
- Support modeling and hypothesis generation/ refinement through use of registries

Pain points, bright spots, mistakes to avoid, watchouts identified (select illustrative examples):

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[26] Electronic Data Capture

- **Lack of consideration for data integrity and flow resulted in suboptimal system interoperability and data security:** Data integrity and flow was not sufficiently considered when using digital data collection tools, telemedicine, home health visits, etc.

- **Data collection and management requirements were burdensome for many sites**: Many sites do not have the capabilities and digital tools to do the intense collection and data management necessary for clinical trials

- **DCTs[27] were critical to supporting trials**: The value of DCTs was recognized before the current COVID-19 pandemic, and DCTs or hybrid trials were instrumental in supporting clinical trial continuity during the pandemic

- **Lack of a central registry limited therapeutics innovation**: The lack of a central registry type approach to track patients and gather disease natural history was a big barrier to coming up with effective therapeutics

Key lessons learned identified (examples):

- **Building functional plans could ensure data can be accepted from all sources:** Building the necessary functional plans could ensure that sponsor systems (e.g., EDC) can accept data from all planned sources, as well as incorporate time to provide training for sites, participants, and others as needed

- **Building solutions for remote data monitoring could enable DCTs**: Identifying the data elements that are a priority and building the solutions available to collect and monitor data remotely could enable DCTs

- **Leveraging digital tools could enable DCTs**: Digital technology could facilitate a decentralized clinical trial approach: virtual visits, remote consent, remote monitoring, home delivery of medications, or home visits by clinical staff for evaluation

- **Aligning on central data collection source would improve reporting efficiency**: A unified source for data collection and active encouragement to adopt eCRF[28] would drive efficiency in reporting

- **Simplifying data requirements and integrating EHR would reduce reporting burdens**: Critical to simplify data requirements from trials, leverage integrated EHR, and streamline safety and reporting processes to reduce the burden on sites and personnel

Potential Approaches to Address Recommendation

Note: This is not an exhaustive or finalized plan; rather, it is a set of considerations meant to serve as a starting point.

1. Develop validated common data models supported by data interoperability standards, APIs[29], and other tools to integrate collection of critical CT data with clinical workflows for high-quality care

2. Provide tools and financial support to convert routine observational registry capabilities to trial capabilities, including tools to support efficient informed consent and randomization

3. Implement registry/trial payments with incentives for adoption of electronic participation tool

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[27] Decentralized Trials
[28] Electronic Case Report Form
[29] Application Program Interfaces

V.   Appendix

A.   Stakeholders involved

The following stakeholders shared lessons learned from their organization's experience and supported the development of recommendations.

USG	

	Department of Health and Human Services (HHS)
	• U.S. Food and Drug Administration (FDA)
	• National Institute of Health (NIH)
	   o National Institute of Allergy and Infectious Diseases (NIAID)
	   o 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 (VA)
Ex-USG (including industry, nonprofits, think tanks, trade groups, etc.)	
	Accelerating COVID-19 Therapeutic Interventions and Vaccines at the Foundation for the National Institutes of Health (ACTIV/FNIH)
	National Academies of Sciences, Engineering, and Medicine (NASEM)
	Milken Institute FasterCures
	Clinical Trials Transformation Initiative (CTTI)
	Multi-Regional Clinical Trials Center (MCRT)
	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)
	iSpy Trials
	Humana

B. Sources

This insights from this document were drawn directly from conversations and input from the stakeholders listed above, as well as material provided by these stakeholders not yet in the public domain (and thus not listed here). Other public sources, listed below, also informed this document.

- **ACRO** – Bringing the Trial to the Patient: A Quality by Design Manual for Decentralized Clinical Trials – link here
- **Clinical Trials (journal)** – An ethics framework for consolidating and prioritizing COVID-10 clinical trials – link here
- **Clinical Research Resources Office** – Regulatory Binder Tabs for BMC/BU Medical Campus Clinical Research Studies – link here
- **Crimson Contagion** – 2019 Functional Exercise After-Action Report – link here
- **CTTI** – Master Protocol Studies – link here
- **FasterCures** – Lessons Learned from COVID-19: Are there Silver Linings for Biomedical Innovation? – link here
- **FDA** – PREPP (Pandemic Recovery and Preparedness Plan) Initiative Report – link here
- **FDA** – Trends in COVID-19 therapeutic clinical trials – link here
- **COVID-19 Research Working Group** (physicians, researchers, advocates) – Toward a Comprehensive and Coordinated COVID-19 Research Agenda – link here
- **TransCelerate** – Modernizing Clinical Trial Conduct – link here