COVID-19 Lessons Learned: Clinical Evaluation of Therapeutics

September 28, 2021
1-5:30pm Eastern
Welcome

Susan C. Winckler, RPh, Esq.
Reagan-Udall Foundation for the FDA
Thank you for joining

This workshop is being recorded. A transcript will be available on regulations.gov.

If you’d like to ask a question, you may enter it in the Q&A. We will get to as many questions as time allows.

If you signed up to provide a public comment during registration, you will have a minute-and-a-half to provide your statement during that portion of the workshop. We will call speakers to the microphone alphabetically by last name and will unmute you when it is your turn to speak.

Speakers and presenters cannot address questions regarding any pending regulatory action.
## Agenda

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*Open to those who registered in advance. This is an open public comment forum; neither the Foundation nor FDA will respond.*
Introduction

Kevin Bugin, PhD
U.S. Food and Drug Administration &
former Federal COVID-19 Response or Countermeasures
Acceleration Groups
Welcome and Thank You
Why Are We Here Today?

• Why did we conduct lessons learned for therapeutics?
• Timing
• Purpose of workshop
• Goals
Today’s Discussion

• Panel discussions
  • Research, Scoping, & Prioritization
  • Infrastructure & Resourcing
  • Clinical Trial Execution
Next Steps

• Today is another step in our journey. It is not the end goal.
• There will be a meeting recording posted. The slides are currently available at ReaganUdall.org
• There will be a summary that builds on the pre-read, incorporating today’s discussion and public comments
• The docket will remain open (ID:FDA-2021-N-0977), please submit comments and ideas, and we’ll be summarizing that public feedback once it closes
• We hope that our panel members, participants, and our leaders across the clinical trial ecosystem will carry forward the lessons learned today and put them in place to ready us for the future of this pandemic and future pandemics response
Janet Woodcock, MD
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
Federal COVID-19 Response: Clinical Evaluation of Therapeutics Lessons Learned Public Workshop

Opening Remarks

• September 28, 2021
In May 2020, the Operation Warp Speed (OWS) therapeutics effort was established with the following mission:

- Accelerate **clinical development and manufacturing scale-up** of candidates most likely to have a broad public impact
- Enable **broad distribution and availability of Tx** until wide-spread access to a vaccine(s) could be achieved
- Provide **continued access for those infected** with COVID-19

The OWS therapeutic strategy focused on candidates that **attack the virus or prevent/manage complications** associated with COVID-19

In January 2021, OWS was transitioned to the **Federal COVID-19 Response**
The Therapeutics (Tx) effort facilitated broad interagency coordination to enable accelerated Tx development and availability.
Context for this Lessons Learned Initiative

• The coordinated Federal Response for COVID-19 therapeutics produced tremendous insights related to the clinical evaluation of therapeutics

• These insights can be applied to the broader clinical trial landscape and improve the clinical trial ecosystem's preparedness for the next public health emergency

• While there continues to be a public health emergency, there was a need to focus on the clinical evaluation of therapeutics early in 2021 to explore immediate application of lessons and initiation of longer-term efforts

• Analysis and collection of lessons learned took place from January to May of 2021
Over the course of the first half of 2021, we captured lessons learned, developed recommendations, and considerations for implementation.

Compiled a **comprehensive 70+ page fact-base** based on interviews with stakeholders and lessons learned documentation with key context, lessons learned, and sources.

Synthesized **29 key recommendations** based on lessons learned. Process was led by working groups and aligned with leadership.

Developed considerations to address recommendations to provide details and reference for implementation process. Meant as starting points for discussion.

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**Lessons Learned: Fact-base**

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**29 recommendations have been developed across the 4 topic areas**

1. High-level coordinating structures
2. Enabling research projects and collaborations
3. Strategic and regulatory, recommendations
4. Information technology and data
5. Deployment and scaling
6. Lessons learned

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**Infrastructure & Resourcing: Recommendations, Considerations, and Stakeholders**

- **Infrastructure & Resourcing (IV)**

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www.fda.gov
Working groups were formed around key topic areas with oversight from a USG leadership group.

**Leadership Group**
- Janet Woodcock (FDA)
- Kevin Bugin* (FDA)
- Ashley Parker (NIH)
- Lynn Marks (BARDA)
- Kim Armstrong (BARDA)
- Nicole Kilgore (JPEO)
- Jason Roos (JPEO)
- Victoria Davey (VA)

**Key roles**

- **Leadership Group**: Oversee overall initiative and provide input on cross-agency & stakeholder buy-in.

- **WG Leads**: Coordinate and provide input to the development of lessons learned in the topic areas assigned to them based on expertise.

- **WG Partners**: Share lessons learned from their organization's experience and support development of recommendations.

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*Reach out to Kevin Bugin (PM for initiative) with any further questions: Kevin.Bugin@fda.hhs.gov

www.fda.gov
Lessons Learned were identified across five topic areas, with four being within scope of this initial effort and discussion today.

1. **Strategy, Governance & Decision-making**
   - Governance & coordination, portfolio & strategy, sponsoring & funding trials, strategic comms., contracting

2. **Research, Scoping & Prioritization of Tx**
   - Screening & agent selection, scoping and prioritization of agents and trials, evidence generation strategy, data sharing

3. **Infrastructure & Resourcing**
   - Networks and partnerships, CT infrastructure, patient enrollment & diverse participation

4. **Clinical Trial Execution**
   - Site readiness, IRB & regulatory set-up, data management, culture change, technology supports

5. **Supply, Distribution & Administration**

Other Tx Topics to be incorporated at a later date:
- Industry engagement, Manufacturing / supply, Allocation and distribution
- Administration and utilization of products
Many of the Tx lessons learned discussed today can be found in the recently shared President’s Pandemic Preparedness Plan (Sept. 2021)

• Strength the U.S. Public Health System
  • Invest in public health labs and digital infrastructure
  • Prioritize vulnerable communities
  • Support evidence-based communication

• Improve Regulatory Capacity
  • Platform technologies
  • Clinical trial networks
  • Improved regulatory capacity and approaches at FDA

• Enhanced Program Management
  • Mission Control
  • International Coordination

www.fda.gov
American Pandemic Preparedness Plan

- I. Transforming Medical Defenses
  - Develop vaccines, therapeutics, and diagnostics
- II. Ensuring Situational Awareness
  - Improve real-time monitoring, early warning/predictors and tracking of variants
- III. Strengthening Public Health Systems
  - Invest in digital infrastructure
  - Diversifying scientific workforce
  - Prioritize vulnerable communities and support community engagement
- IV. Building Core Capabilities
  - Improve regulatory approval and capacity for platform technologies and clinical trial networks
  - Secure biosafety and biosecurity measures
- V. Managing the Mission
  - Centralized program management and international coordination
NIH COVID-19 Initiatives:
Experience that can inform the American Pandemic Preparedness Plan

- Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Public Private Partnership
- Rapid Acceleration of Diagnostics (RADx)
- Tracking Resistance and Coronavirus Evolution (TRACE)
- Antiviral Program for Pandemics (APP)
- Community Engagement Alliance (CEAL)
ACTIV Public-Private Partnership

LAUNCH
- On April 17, 2020, NIH announced the launch of a public-private partnership, Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

MISSION
- Develop a coordinated research response to speed COVID-19 treatment and vaccine options
  - Establish a collaborative framework for prioritizing therapeutic candidates and accelerating vaccine evaluation
  - Accelerate randomized clinical trials of promising agents and leverage existing clinical trial networks while maintaining rigorous safety standards
  - Coordinate regulatory processes and leverage assets among all partners
ACTIV Stakeholders

20 INDUSTRY LEADERS

8 GOVERNMENT LEADERS

4 NON-PROFIT

PROGRAM MANAGEMENT

H-CORE (Formerly Operation Warp Speed)
ACTIV Focus Area Objectives & Composition

Each focus area is a Working Group that contains several subgroups to oversee tactical operations:

**Objective**
- **Preclinical**: Develop a collaborative, streamlined forum to identify preclinical treatments
- **Therapeutics – Clinical**: Accelerate clinical testing of the most promising vaccines and treatments
- **Clinical Trial Capacity**: Improve clinical trial capacity and effectiveness
- **Vaccines**: Accelerate the evaluation of vaccine candidates to enable rapid authorization or approval

**Sub-Groups**
- **Preclinical**: Animal Models, In Vitro Assays, Mutational Tracking
- **Therapeutics – Clinical**: Agent Prioritization, Master Protocol
- **Clinical Trial Capacity**: Survey Development, Clinical Trial Network Inventory, Innovations
- **Vaccines**: Vaccines Clinical Trials, Protective Immune Responses, Vaccine-Associated Immune Enhancement, Impact of Vaccines on Transmission, Correlates of Protection
ACTIV Master Protocols:
COVID-19 Therapeutics Prioritized for Testing

- **ACTIV-1 Immune Modulators**
  - Phase 3 inpatient trial: Cenicriviroc, Orencia® (abatacept), Remicade® (Infliximab)

- **ACTIV-2 Monoclonal Antibodies and Other Therapies**
  - Phase 2/3 outpatient trial: AZD7442 (IV)* (IM)*, Brii-196 & Brii-198, BMS-986414 and BMS-986413, LY-CoV-555, SAB-185, Camostat Mesylate, SNG001 IFN-beta

- **ACTIV-3 Monoclonal Antibodies and Other Therapies**
  - Phase 3 inpatient trial: AZD7442, Brii-196 & Brii-198, LY-CoV-555, Zyesami™ (aviptadil acetate) and Veklury® (remdesivir), VIR-7831, Ensovibep (MP0420), Pfizer PF-07304814

- **ACTIV-4 Antithrombotics and Host Tissue Therapies**
  - Phase 3 outpatient trial: Eliquis® (apixaban), Aspirin
  - Phase 3 inpatient trial: Un-fractionated (UF) Heparin, Low Molecular Weight (LMW) Heparin, Unfractionated Heparin and P2Y12 Inhibitors, TXA127, TRV027, APN01, Fostamatinib
  - Phase 3 convalescent trial: Eliquis® (apixaban)

- **ACTIV-5 Big Effect Trial**
  - Phase 2 inpatient trial: Skyrisi™ (risankizumab), Lenzilumab, Danicopan

- **ACTIV-6 Repurposed Drugs**
  - Phase 3 outpatient trial: Ivermectin, Fluvoxamine, Fluticasone

*Enrollment ceased at company’s request
Denotes agent lack of efficacy
Denotes proven agent efficacy
Rigorous Testing is Essential:

Potentially Promising Therapeutics That Failed In Well-Powered Placebo-Controlled Randomized Trials

- Hydroxychloroquine (HCQ)
- Chloroquine (CQ)
- HCQ or CQ plus azithromycin
- Lopinavir/ritonavir (HIV drugs)
- Full dose heparin for ICU patients
- Many monoclonal antibodies for inpatients
- Hyperimmune globulin for inpatients
Different Therapies at Different Stages of COVID-19

COVID-19+ Disease Progression

No Symptoms | Outpatient Mild Symptoms | Inpatient No Oxygen | Inpatient Low-flow Oxygen | Inpatient High-flow Oxygen | Mechanical Ventilation

Anti-viral Strategies
Immunomodulatory Strategies
Anti-coagulation Strategies
Accelerate development of a portfolio of safe and effective AVs that directly act against SARS-CoV-2 and other viruses of pandemic potential.

**Antiviral Program for Pandemics (APP)**

### Discovery

Build a sustainable platform to discover new antivirals by:
- Establishing multi-investigator, and multi-disciplinary discovery groups (AViDD Centers)
- Using structural and systems methods to identify potential drug targets shared across key viral pathogens
- Progressing promising candidates to IND-enabling work

### Development

Accelerate clinical testing of promising antiviral candidates by:
- Supporting key non-clinical and early clinical studies
- Establishing public-private partnerships to supplement private sector capabilities (including facilitating third-party collaborations)
- De-risking candidates for further late-stage development
Coronaviruses: Selected Targets for Therapeutics

- Vaccine or neutralizing antibody
- Assembly of polymerase complex
- Fusion inhibitors
- Receptor blockade
- Protease inhibitors block polyprotein processing
- Transcription replication
- Protein Pol
- mRNAs
- Translation
- Exocytosis
- Budding
- Virus release

ACTIV Tracking Resistance And Coronavirus Evolution (TRACE)

TRACE workflow

1. Monitor global emergence and circulation of SARS-CoV-2 mutations
2. Cross-reference against database of experimentally/clinically phenotyped mutants
3. Characterization in vitro through critical-path assays
4. Characterization in vivo through critical-path assays
5. Rapidly share data readouts with scientific community

Feed data back into resistance database in (2)

TRACE Priorities

- Publish weekly TRACE report summarizing shifting trends in emerging viral variants
- Collect available industry and government agency data on variants in one place
- Generate datasets using standardized protocols and common reference reagents
NIH Community Engagement Alliance (CEAL)

- Community-engaged research and outreach focused on COVID-19 awareness and education to address misinformation and mistrust
- Promote and facilitate inclusion of diverse racial and ethnic populations in clinical trials
  - Prevention, vaccine, therapeutics, diagnostics
- CEAL research teams
  - More than 20 states (Alabama, Arizona, Arkansas, California, Colorado, DC Metro Area, Florida, Georgia, Illinois, Louisiana, Massachusetts, Michigan, Mississippi, Missouri, New Mexico, New York, North Carolina, Pennsylvania, Puerto Rico, Tennessee, and Texas)
Conclusion

- Substantial and rapid progress has been made in prioritizing and testing therapeutics for various stages of COVID-19
- In a pandemic, well-intentioned but poorly designed and underpowered trials can do more harm than good. Academic medical centers must guard against this.
- Through ACTIV and NIH trials, multiple therapies have been proven beneficial; others have been demonstrated to have no value
- Repurposing existing drugs must always be the first approach, and can provide quick “singles” and “doubles”, but generally not “home runs”
- Going forward, the highest priority for coronaviruses is to develop and test targeted antiviral drugs
- Those may need to be used in combination to avoid resistance
- Many lessons have been learned to prepare for future pandemics:
  - Partnerships, master protocols, coordinated trial networks, global reach…
NIH... Turning Discovery Into Health
www.nih.gov/hope
directorsblog.nih.gov
@NIHDirector
Research, Scoping, & Prioritization

Moderated by

Stacey Adam, PhD
Foundation for the National Institutes of Health

Michael Santos, PhD
Foundation for the National Institutes of Health

Panelists

Janet Woodcock, MD
U.S. Food and Drug Administration

Phyllis Arthur, MBA
BIO

Elliott Levy, MD
COVID R&D Consortium

Sarah Read, MD
National Institute of Allergy and Infectious Diseases
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Therapeutics-Clinical Work Group Co-Chair
Recommendations
Research, Scoping, & Prioritization

**Recommendation 1:** Rapidly collect and disseminate enabling information such as pathogen ID, sequencing, and natural history data (through natural history registries).

**Recommendation 2:** Ensure the clinical trial (CT) ecosystem creates actionable evidence through developing strategy, guidelines, templates, incentives, and capacity building (e.g., prioritize randomized trials).

**Recommendation 3:** Enable the open sharing of research strategy and plans amongst stakeholders in the CT ecosystem to coordinate activities, including in funding announcements.

**Recommendation 4:** Establish efficient and effective systems for sharing early research data and results with other researchers outside of publication channels.
Infrastructure & Resourcing

Moderated by

**Esther Krofah**
*FasterCures and Center for Public Health, Milken Institute*

**Kristin Schneeman**
*Director, FasterCures*

Panelists

**Barbara Bierer, MD**
*Multi-Regional Clinical Trials Center of Brigham and Women’s Hospital and Harvard*

**Michael Kurilla, MD, PhD**
*National Center for Advancing Translational Sciences, National Institutes of Health*

**James Mayne, PhD**
*Pharmaceutical Research & Manufacturers of America*

**Doug Peddicord, PhD**
*Association of Clinical Research Organizations and Washington Health Strategies Group*
Recommendations
Infrastructure & 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.

**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.

**Recommendation 3:** Remove post-pandemic barriers to expanded adoption of decentralized/hybrid trials and remote monitoring tools.

**Recommendation 4:** Research, develop, and share best practices on managing patient enrollment with a focus on prioritized trials/platforms while enabling co-enrollment.

**Recommendation 5:** Determine best practices for increasing participation in trials from under-represented communities and create action plans for improvement.
Clinical Trial Execution

Moderated by

Mark McClellan, MD, PhD
Duke-Margolis Center for Health Policy

Sarah Sheehan, MPA
Duke Margolis Center for Health Policy

Panelists

Samuel Brown, MD, MS
Intermountain Medical Center and University of Utah

Janice Chang
TransCelerate BioPharma Inc.

Clark Files, MD
Wake Forest School of Medicine

Monica Webb Hooper, PhD
National Institute on Minority Health and Health Disparities

Kate Zenlea, MPH, CPH
The Global Health Initiative at Henry Ford Health System
Recommendations
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, indemnity, streamlining FDA collaboration across centers, fit-for-purpose HRP training).

**Recommendation 2:** Develop tools, best practices, and resources for timely and effective trial participation, including site readiness assessment tools.

**Recommendation 3:** Assure that regulatory and prioritization framework for priority questions and data requests will generate optimal and timely clinical site participation.

**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.

**Recommendation 5:** Improve technology support, capacity, and motivations: capabilities for automated clinical trial data collection via: EHR and EDC 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.
Public Comment

Limited to one-and-a-half minutes per speaker

This is an open public comment forum; neither the Foundation nor FDA will respond to comments.

Additional comments may be submitted through the public docket (Docket ID:FDA-2021-N-0977) at Regulations.gov.
Closing Plenary

Kevin Bugin, PhD
U.S. Food and Drug Administration & former Federal COVID-19 Response or Countermeasures Acceleration Groups
Takeaways from Opening Keynote

• Important to take time to take stock even when still in the pandemic—we’ve made substantial progress since April 2020

• Initial clinical research efforts for therapeutics were “scattershot” which created barriers to generating actionable evidence early

• Remarkable collaboration was seen with ACTIV between NIH, FDA, HHS, CDC, academia and industry

• Extraordinary “all-of-government” collaboration in response to COVID-19 and this was carried forward to the collaborative Lessons Learned effort we discussed today

• President’s American Pandemic Preparedness Plan lays out an ambitious plan for future pandemics
Takeaways
Panel 1: Research, Scoping, & Prioritization

• In a public health emergency, there is a strong desire to help patients – everyone jumps in and tries to help. A preparedness plan that communicates what can be done from Day 1 and when and how additional information and guidance will be disseminated will improve coordination and efficiency.

• When determining criteria for scoping and prioritization, need to consider scientific considerations (e.g., mechanism of action, safety database) as well as scalability (e.g., availability of clinical supply, manufacturing).

• In addition to the immediate-term goals, keep the long-term pipeline and broader view in mind – bridging the ‘valley of death’ is an important intermediate goal as well.

• Must ensure trials are designed to yield actionable evidence.

• Systematic communication channels to promote timely information-sharing is critical.

• Need strong and continuous investment in pandemic preparedness, including infrastructure at the community-level and therapeutic areas such as antiviral R&D.
Takeaways
Panel 2: Infrastructure & Resourcing

• There are networks and infrastructure, but it exists in different states of readiness, and interoperability or rapid coordination that new or larger networks necessitate was difficult in real-time – Key question: how do we keep the needed infrastructure “warm and ready”?

• The underlying infrastructure and resources circumstances were changing.
  • Shifts in more remote/decentralized trial practices, and digital health tools, while needed, were a struggle to implement for new sites in particular
  • Basic need issues, such as PPE and clinical research professionals limited
  • Emerging variants, standard of care evolution, etc.

• Collaboration with and across industry and with regulators, key enabler of the flexibility and progress that was needed during the evolution of clinical trials during the PHE

• We did not have the infrastructure to effectively reach out to underserved / underrepresented patients. We need to engage with more community sites and bring them into the networks. Identifying and addressing their needs may be the answer to the key question
Takeaways
Panel 3: Clinical Trial Execution

- Importance of right-sizing the research question and appropriately matching that up to the capacity at sites from the get-go (including getting capacity at new sites/networks up to a new normal)
  - This requires engagement of community trial sites going forward
  - Beginning with the social determinants of health in mind (i.e., access to high quality healthcare)
  - Keep in mind eligibility criteria and its impact on diversity

- Clinical research needs to be as simplified, standardized, and supported as much as possible (include thinking internationally)
  - Regulatory requirements (central, sIRBs), administrative (informed consent), and legal indemnification should be clearer
  - Address the overhead (payrolls and risk management)
  - Contracting and other agreements
  - Investigational drug/pharmacy management
Takeaways

Panel 3: Clinical Trial Execution cont’d

• “What do clinicians and healthcare providers do: Do they treat? Or do they respect, treat and learn?”

• Training the next generation is an opportunity to accelerate culture change for the next gen of clinical care providers and clinical researchers

• Integrating novel tools and technology into the clinical care (needs to be widely available)

• Culture change is needed. We need:
  • True stories that demonstrate a real value proposition for communities
  • Adjustments to broader systems, frameworks, and incentives to enable research in clinical care
  • Relationships that reinforce changes over time
Next steps

• Again, today is another step in a journey and not intended to be the end of this conversation

• We hope that our panel members, participants, and our leaders across the clinical trial ecosystem will carry forward the lessons learned today and put them in place to ready us for the future of this pandemic and future pandemics response

Reminders:

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