



CLINICAL  
TRIALS  
**TRANSFORMATION**  
INITIATIVE

*March 31, 2020*

# **Conduct of Clinical Trials during the COVID-19 Pandemic**

M. Khair ElZarrad, FDA, CDER

Pamela Tenaerts and Sara Calvert, CTTI

Colleen Rouse, Cleveland Clinic

David Borasky, WIRB-Copernicus Group (WCG)

Cindy Geoghegan, Individual Patient Representative/Caregiver

# Welcome

*Contains Nonbinding Recommendations*

## **FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic**

### **Guidance for Industry, Investigators, and Institutional Review Boards**

March 2020

Updated on March 27, 2020

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on clinical trial conduct during the COVID-19 pandemic, please email [Clinicaltrialconduct-COVID19@fda.hhs.gov](mailto:Clinicaltrialconduct-COVID19@fda.hhs.gov).

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)  
Oncology Center of Excellence (OCE)  
Office of Good Clinical Practice (OGCP)



▶ For further questions on clinical trial conduct during the COVID-19 pandemic, please email:

- [Clinicaltrialconduct-COVID19@fda.hhs.gov](mailto:Clinicaltrialconduct-COVID19@fda.hhs.gov)

▶ Contact information for FDA's review divisions is as follows:

- **CDER:** <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs>
- **CBER:** <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/contacts-center-biologics-evaluation-research-cber>
- **CDRH:** <https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization>

# Public-Private Partnership

## Co-founded by Duke University & FDA

Involves all stakeholders

- Approx. 80+ members
- Participation of 400+ more orgs

**MISSION:** To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials





# CTTI COVID-19 Activities

- ▶ Ongoing clinical trials during the pandemic
  - Survey and webinar today
- ▶ Considering additional activities to help the clinical trials enterprise right now
  - COVID-19 trials
  - Telemedicine
  - Patient perspective
- ▶ Considering additional activities to help the enterprise after the immediate crisis is over

# Ongoing Clinical Trials

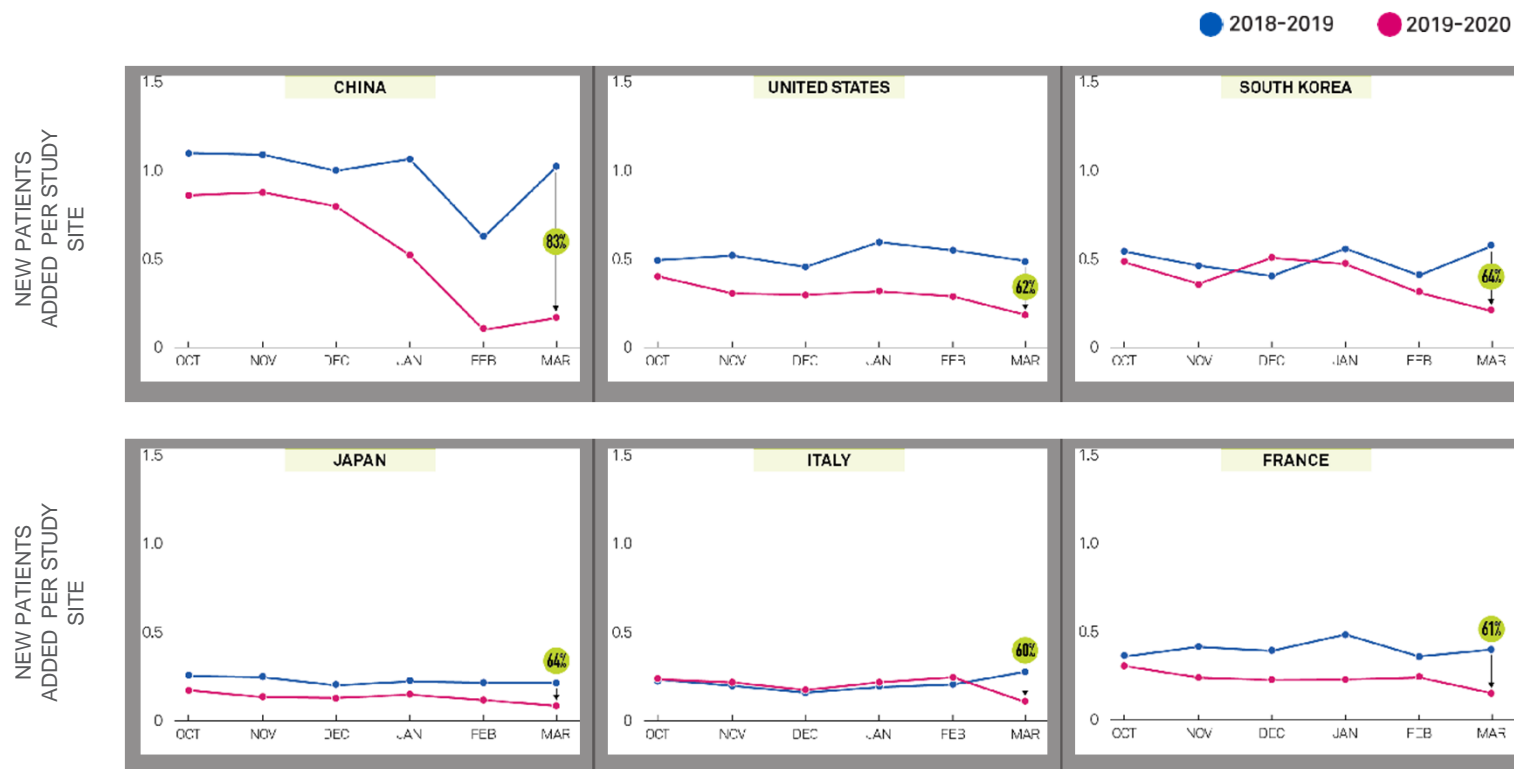
- ▶ **Introduction:** Pamela Tenaerts, *CTTI*
- ▶ **Opening Comments:** M. Khair ElZarrad, *FDA, CDER*
- ▶ **Survey and Best Practices:** Sara Calvert, *CTTI*
- ▶ **Best Practices**
  - **From Sites:** Colleen Rousse, *Cleveland Clinic*
  - **From IRBs:** David Borasky, *WCG*
  - **From Participants:** Cindy Geoghegan, *Patient*
- ▶ **Summary & Next Steps:** Pamela Tenaerts, *CTTI*



# Safety is Primary Consideration

- Safety of trial participants, study staff is most important factor
  - Avoiding/limiting potential exposures to the virus, avoiding interference with clinical care for COVID-19
  - Continuing study activities virtually (where feasible), or in-person when benefit is greater than risk
- Maintaining compliance with good clinical practice (GCP)
- Minimizing risks to trial integrity during the pandemic
- Preserving time, invested resources, & effort of participants already enrolled or completed

# Medidata: Global Impact COVID-19 on Clinical Trials



- ▶ China had 83% decrease in new patients entering trials Feb 2020
- ▶ Similar trends in other affected countries
- ▶ U.S. decline of 62% in the first half of March

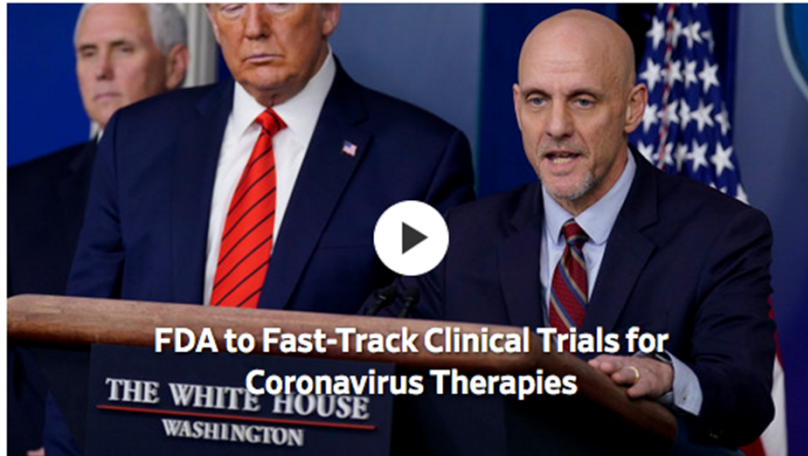


# Clinical Trials During Pandemic

## THE WALL STREET JOURNAL.

### Coronavirus Pandemic Delays Testing of New Drugs

Pharmaceutical companies adjust to patients skipping treatments and hospitals shifting focus to coronavirus



#### FDA to Fast-Track Clinical Trials for Coronavirus Therapies

FDA Commissioner Stephen Hahn said the agency will test chloroquine, an antimalarial drug, as a coronavirus treatment. The drug could serve as an intermediate therapy before a vaccine becomes available. Photo: Evan Vucci/Associated Press



## NEWS

CORONAVIRUS

NIGHTLY NEWS

### Cancer patients forced to delay treatment over coronavirus concerns

STAT

Topics Coronavirus Opinion Podcast Newsletters Reports Events

## As Covid-19 spreads, disruptions to clinical trial and drug development accelerate

By ADAM FEUERSTEIN @adamfeuerstein / MARCH 23, 2020



### 'This Is Us': Will the Clinical Trial Work? Why It May Not Help Rebecca

Meaghan Darwish | March 18, 2020 12:00 pm



Comment





# Emerging Questions / Confusion about Clinical Trials\*

- Scientific side:
  - Delayed startup
  - Sending study drugs
  - Short-term outcome measures: losing entire cohort
  - Ability to re-screen patients
  - What can be done at a distance with people currently enrolled?
  - Will funding be extended? Flexibility has been helpful
- Will labs be able to administer medications, and what does that mean for patients
- Whether therapeutic as well as non-therapeutic trials will be ended
  - Can natural history studies be done via telemedicine?
- Can non-therapeutic trials be done in a safe way?
- Concern about loss of clinical trials; how long can you extend primary endpoint assessments without losing entire trial
- What level of flexibility will FDA have as visit schedules change?
- Are open trials still enrolling patients?
- Consistency of care once pandemic has passed
- Language used... calling these “non-essential trials”; concern about trials being sidelined
- Information on testing kits and approval; untested/unapproved treatments
- Application for orphan drug status and pushback from consumer community

*\*From Patient Engagement Collaborative monthly teleconference, March 26, 2020*



# CTTI Request for Experiences & Insights, in Context of the New Guidance

Sara Calvert

*CTTI*

# Guidance Documents

*Contains Nonbinding Recommendations*

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## Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic

Version 2 (27/03/2020)

Key changes from v1 (20-03-2020): additional clarification on obtaining informed consent; link to methodological guidance on statistical considerations in relation to COVID-19 pandemic; advice on IMP stocks, safety reporting, conduct of audits; temporary halts

The European Medicines Agency (EMA), Good Clinical Practice (GCP) Inspectors Working Group, the Clinical Trials Facilitation and Coordination Group (CTFG, a working group of the Heads of Medicines Agency (HMA)), the Clinical Trials Expert Group (CTEG, a working group of the European Commission representing Ethics Committees and National Competent Authorities) and the European Commission (EC) acknowledge the impact of COVID-19 on the health system and broader society, and the impact it may have on clinical trials and trial participants<sup>1</sup>. Extraordinary measures may need to be implemented and trials adjusted due to e.g. trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks. Therefore, EMA, EC and HMA strongly support the efforts of the GCP Inspectors' Working Group for developing a harmonised EU/EEA-level guidance to mitigate the negative effects of the COVID-19 pandemic on the conduct of clinical trials.

The situation is evolving, and pragmatic actions may be required to deal with the challenges of conducting research, and in ensuring the rights, safety and wellbeing of participants. The points mentioned below are intended to provide guidance for all parties involved in clinical trials during this time.

Due to the urgency, this guidance is issued without prior public consultation. The sponsors should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Sponsors and investigators need to take into account that there might be specific national legislation and guidance in place<sup>2</sup>, which they should consult and which can be used to complement this guidance, or, with respect to particular matters may take priority over these recommendations. This document is however seeking to include most of the current guidance across Member States with the aim to serve as an EU-level harmonised set of recommendations. Hence, this guidance is agreed by the Clinical Trials Expert Group (CTEG) of the European Commission supported by the EMA, the Clinical Trials Facilitation and Coordination Group (CTFG) of the Heads of Medicines Agencies (HMA) and the GCP Inspectors' Working Group coordinated by the EMA.

<sup>1</sup>The word « participant » is used in this text as a synonym for the term “subject”, defined in Directive 2001/20/EC as “an individual who participates in a clinical trial as a recipient of the investigational medicinal product or a control”.

<sup>2</sup> Links to national recommendations can be found at CTFG website (<https://www.hma.eu/ctfg.html>)

# FDA Guidance Topics

## EMA and MHRA Guidance cover similar topics

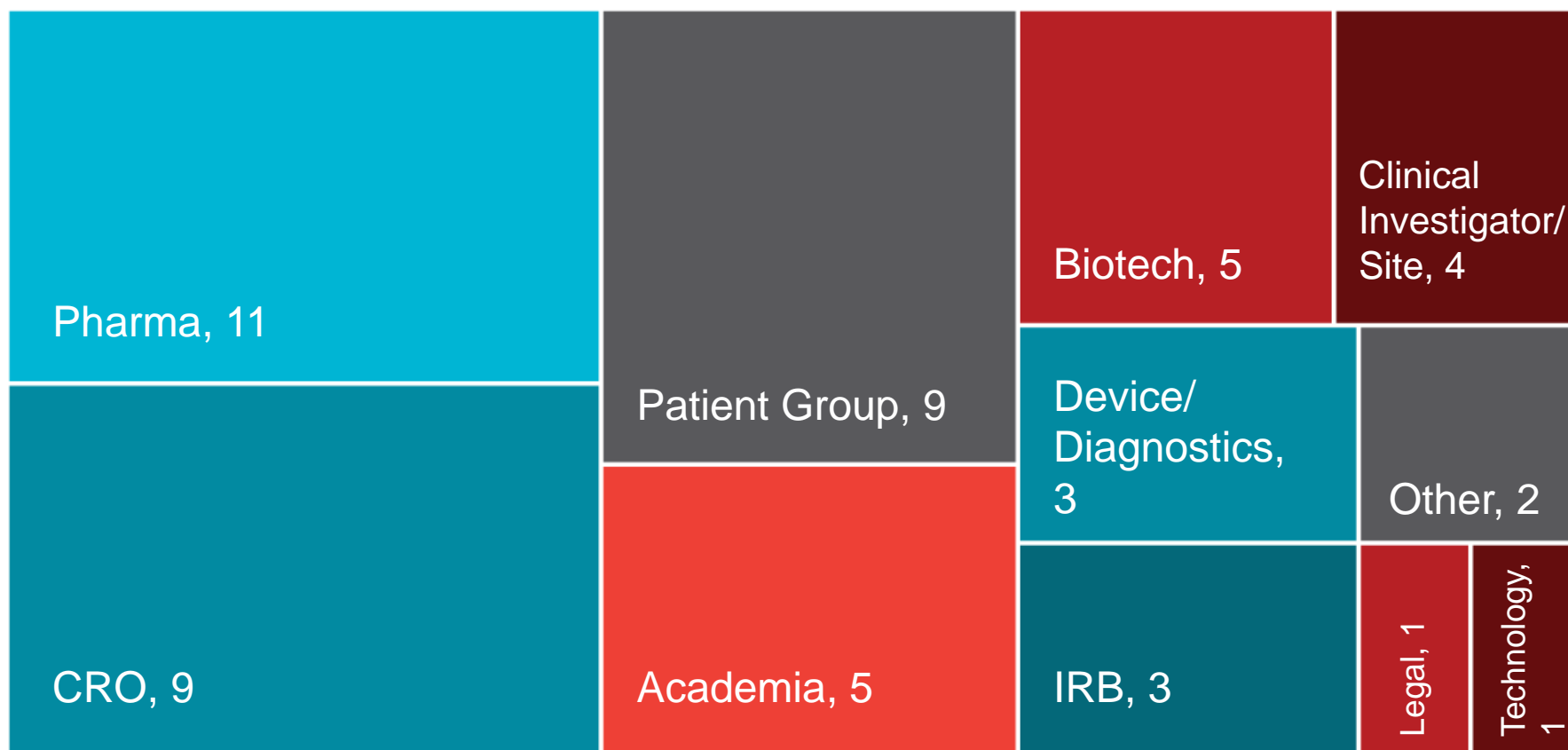
- ▶ Assessment of each study focusing on safety
- ▶ Establish or revise policies & procedures (contingency measures)
- ▶ Inform patients of status & impact of changes
- ▶ Pause enrollment, delay visits, extend trials/visit windows
- ▶ Remote/alternate visits for data collection and safety assessments
- ▶ Access to investigational medical product (IP or IMP)
- ▶ Central & remote monitoring programs
- ▶ Contacting IRB/IEC & FDA with changes
- ▶ COVID-19 screening procedures
- ▶ Documenting changes related to COVID-19
- ▶ Questions & Answers section

EMA also released methodological guidance. FDA also released guidance on use of non-invasive remote monitoring devices for patient monitoring during COVID-19.

# CTTI Request for Experiences

- ▶ CTTI collected feedback from March 23 - 30
- ▶ Survey distributed via:
  - Email to CTTI member organizations and public contacts
  - Posts on Twitter and LinkedIn
  - Encouraged trade, media, and other organizations to share
- ▶ In context of the new FDA guidance on the conduct of clinical trials of medical products during the current COVID-19 pandemic,
  - Do you have any experiences or best practices to share?
  - What have you tried?
  - What works well?
  - What have you thought of doing but have not tried yet?

# What best represents your role in the clinical trial ecosystem? (n=53)



## Do you have an experience related to any element of the new FDA guidance?

Frequent Responses	Example comments
<b>Conducting risk assessment</b>	<ul style="list-style-type: none"><li>• Conducting risk-benefit for all studies at organization</li><li>• Approach is county/region specific for global studies</li></ul>
<b>Remote/virtual study visits</b>	<ul style="list-style-type: none"><li>• Utilizing FaceTime, Zoom, other apps to conduct interviews/questionnaires/assessments</li><li>• Pivoting to telephone visits</li></ul>
<b>Study visits paused/delayed/suspended</b>	<ul style="list-style-type: none"><li>• Important not to disqualify patients for inability to attend visits during this time</li><li>• Expanding windows for completing study visits</li></ul>
<b>Enrollment hold/pause</b>	<ul style="list-style-type: none"><li>• Pausing new enrollments in majority of studies</li><li>• Exceptions for life-threatening illnesses/potential benefit</li></ul>
<b>Investigational product (IP) directly to patient from site</b>	<ul style="list-style-type: none"><li>• Shipping self-administered meds to patient home</li><li>• Need site staff or home health willing to travel patients' homes to administer parenteral meds</li></ul>
<b>Remote monitoring</b>	<ul style="list-style-type: none"><li>• Those teleworking need to have access to necessary documents</li><li>• If prior experience, increasing amount of risk-based/central monitoring</li></ul>





# Best Practices

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1. Keep Participants Informed
2. Perform Ongoing Risk Assessment
3. Pause (Most) New Study Starts & Enrollment
4. Pivot to Remote Study Visits
5. Switch to Remote Monitoring
6. Document with COVID-19 Tag
7. Communicate with IRBs (*David Borasky presentation*)

# 1. Keep Participants Informed

▶ “For all clinical trials, however, research staff should **keep participants informed about the effects of the coronavirus pandemic on their trial participation.** Participants should be informed of necessary changes in protocol and how this may affect the risk associated with study participation. For many randomized trials, communication from research staff is likely to help protect against dropout or nonadherence by reassuring participants that their trial involvement remains important, even during the pandemic.”

- From *Preserving Clinical Trial Integrity During the Coronavirus Pandemic*. JAMA March 25, 2020. doi:10.1001/jama.2020.4689

## 2. Perform Ongoing Risk Assessment

- Follow country, local, & institution rules & restrictions in place due to the virus
- Priority is safety of patients & research personnel over data integrity concerns
- Telework for study personnel
- Which activities can be performed remotely – study visits & monitoring
- Avoid interference or burden on clinical care
- Screening for COVID-19 symptoms prior to & at visits/when visits resume

### 3. Pause New Study Starts & Enrollment

- ▶ New enrollment suspended or paused in many responses
- ▶ Country & region-specific approach to pauses & restarts
- ▶ Limited exceptions:
  - Oncology or other trials where investigational treatment is among limited options
  - COVID-19 treatment or vaccine trials
- ▶ Ongoing visits also delayed or conducted with alternative methods unless in-person necessary
  - Important to collect data by other methods where possible
  - Allow expanded windows where delay not harmful

# Example: Risk Assessment Applied



Study Classification	Actions
<b>Tier 1</b> High Potential Direct Benefit to Research Participants	<ul style="list-style-type: none"><li>• Enrollment allowed</li><li>• Convert to virtual visits as much as possible</li></ul>
<b>Tier 2</b> Moderate Potential Direct Benefit to Research Participants	<ul style="list-style-type: none"><li>• Pause enrollment</li><li>• Convert to virtual visits as much as possible with likely all visits virtual/phone</li></ul>
<b>Tier 3</b> Primarily observational, behavioral studies without potential direct benefit	<ul style="list-style-type: none"><li>• Pause enrollment</li><li>• Convert all visits to virtual/phone</li></ul>

## 4. Pivot to Remote Study Visits

- Use time from paused enrollment to determine activities that can be performed remotely
- Utilize available resources: institutions, IRBs, patient groups have resources available & experience
  - Check for approved telemedicine platforms, programs
  - Investigate apps, non-invasive physical assessment devices
- Questionnaires, adverse events, other questions asked at study visits can be obtained via telephone
- Explore alternative distribution of investigational product
- Refer immediate safety concerns to PCP or other care provider

## 5. Switch to Remote Monitoring

- Most are postponing all on-site monitoring
- Implementation of remote, risk-based monitoring
  - Prioritization safety assessments & primary outcome measures
- Ensure secure methods to allow for access of subject data for remote review
  - Restricted access accounts in electronic health record, secure file sharing
  - Staff access while working from home
- Document all changes made to monitoring plan



## 6. Document with COVID-19 Tag

- Many IRBs have created COVID-19 specific submission flag or process for amendments, questions, new studies
- Add COVID-19 to all documentation - patient & study level
  - For reports to sponsor, IRB, & FDA when required
- *Example:* One clinical research site proactively created a template for missed assessments
  - Details any procedures that could not be performed virtually
  - Plan to perform missed procedures as soon as possible when on-site visits safe
  - Reported to the sponsor within 48 hours via templated form sent by email to the CRA

# Flexibility on Study-by-Study Basis

## Healy Center for ALS Research Mass General Hospital

### ➤ Actively engage with IRB

### ➤ Virtual study activities

- Consent via video visit or phone
- Safety assessments - adverse events, conmeds, abbreviated exam

### ➤ Investigating use of home health infusion/nurses

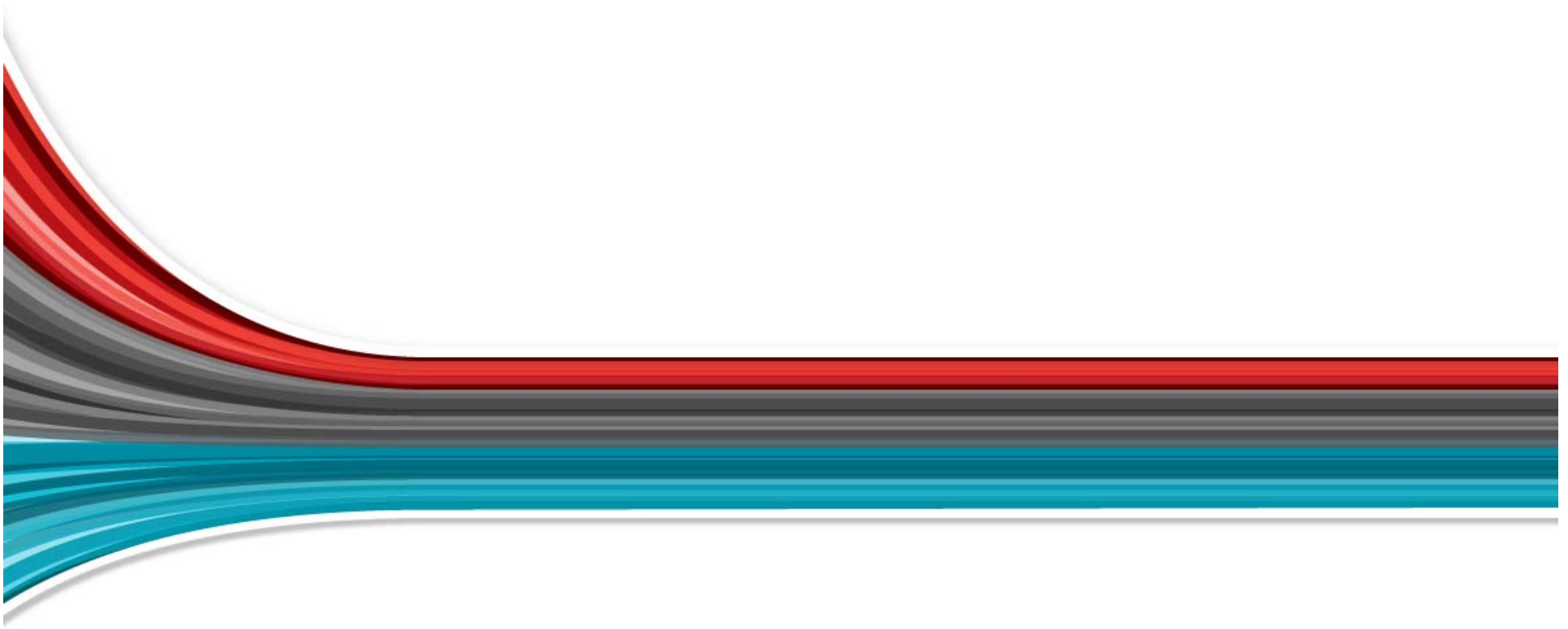
- Investigational product infusions
- Blood & urine collection for safety & biomarkers
  - Or use of off-site labs

### ➤ Staffing adjustments

- Rotating staff to minimize those on-site needed to cover study visits
- Telework (VPN, EHR, email etc.) for protocol follow-up
- Videoconference for staff meetings and check-ins

### ➤ Delivery of investigational product

- FedEx from institution
- Investigating home infusion services



# Academic Medical Center Practices

Colleen Rouse

*Cleveland Clinic*

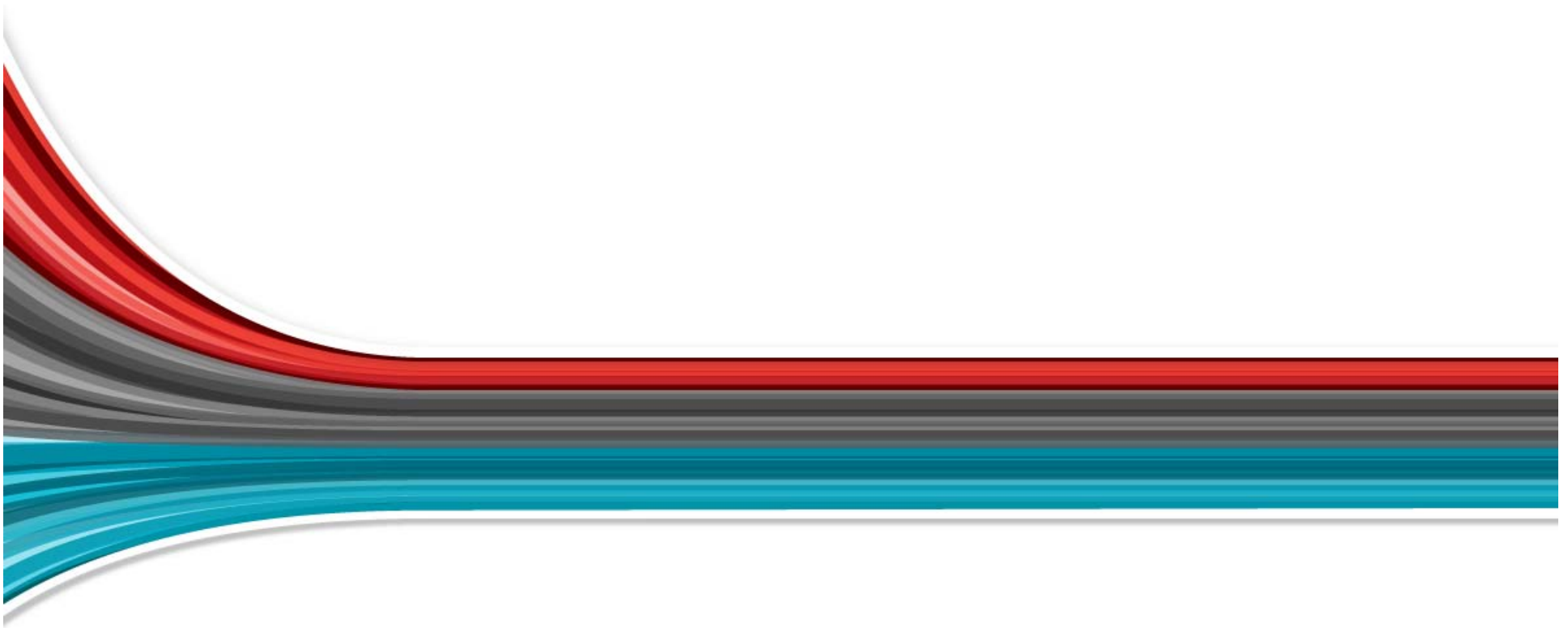
# Cleveland Clinic Approach to Trials During COVID-19

Strategy	Implementation
Sponsor Communication	<ul style="list-style-type: none"><li>• Determine what study changes related to protocol sponsor intends to make</li><li>• Notify sponsor of proposed logistical changes at site level</li></ul>
IRB Notification of Study Changes	<ul style="list-style-type: none"><li>• Provide specific information about what is changing via amendment after sponsor approval; document in study file</li><li>• Specify that changes were result of COVID-19</li></ul>
Recruitment into Research Studies	<ul style="list-style-type: none"><li>• Develop recruitment plan based on risk assessment that minimizes patient exposure – both for initial recruitment &amp; subsequent visits</li><li>• Minimal risk recruitment stopped</li><li>• Phone recruitment that requires patient to come in for screening visit stopped</li></ul>
Workforce Adjustment	<ul style="list-style-type: none"><li>• Divide study team into A and B and adjust on-site work accordingly</li><li>• Work with IT to setup network access (including eMR) from home computers or provide property passes to take laptops home</li><li>• Reminder to be mindful of surroundings, turn off any smart speakers</li></ul>

# Cleveland Clinic Approach to Trials During COVID-19

Strategy	Implementation
Study Participant Communication	<ul style="list-style-type: none"><li>• Discuss how risk has changed &amp; provide proposed study changes</li><li>• Determine subject's interest/ability in continued participation</li></ul>
Remote/virtual study visits	<ul style="list-style-type: none"><li>• Utilize ExpressCare online, Skype (or similar virtual conferencing software) for remote study visits.</li></ul>
Send study drug directly to patient from site	<ul style="list-style-type: none"><li>• Work within state pharmacy board guidelines</li></ul>
Explore alternate options for patients to obtain safety assessments	<ul style="list-style-type: none"><li>• Utilize less-crowded family health centers or home health for patients to have blood draws, ECGs &amp; imaging away from the hospital</li></ul>
Remote monitoring	<ul style="list-style-type: none"><li>• Use of Epic Anyconnect feature (or web-based virtual conferencing) to permit remote monitoring with sponsor agreement (limit monitor access to only enrolled subjects) – may require update to contract</li></ul>

**DOCUMENT, DOCUMENT, DOCUMENT**



# IRB Practices

David Borasky

*WIRB-Copernicus Group (WCG)*

# IRB Perspective: Supporting Research

▶ “Ensuring the safety of trial participants is paramount.”

- (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic)

▶ Tremendous strain on all

- Sites – diversion to clinical care; remote staff; inaccessible participants
- IRBs – institutional IRBs may shift staff, members to COVID support; independent IRBs shift to remote work
- Sponsors – measures to maintain / salvage studies under circumstances

▶ Goal of IRBs – provide reliable support in order to maintain research that is ethical, valid, compliant





# IRB Perspective: Supporting Research

▶ Unprecedented volume of changes to ongoing research

▶ Most common changes

- Elimination / reduction in frequency of study visits
- Shift from on-site to telemedicine, home healthcare
- Collection of labs offsite
- Changes to drug delivery – direct ship, delivery by site staff
- Other changes that do not require IRB approval
- Sponsors – measures to maintain / salvage studies under circumstances

# When is IRB Review Required?

- Regulations expect prospective review & approval
- Regs allow immediate changes when in best interest
  - Each IRB shall ... (a) Follow written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects. (21 CFR 56.108(a)(4))
  - IRBs interpreting in light of COVID-19 context
    - Check with your IRB to determine timeline for reporting changes to the IRB
  - IRBs can – & should be – nimble & efficient when managing such changes

# Considerations for Informed Consent

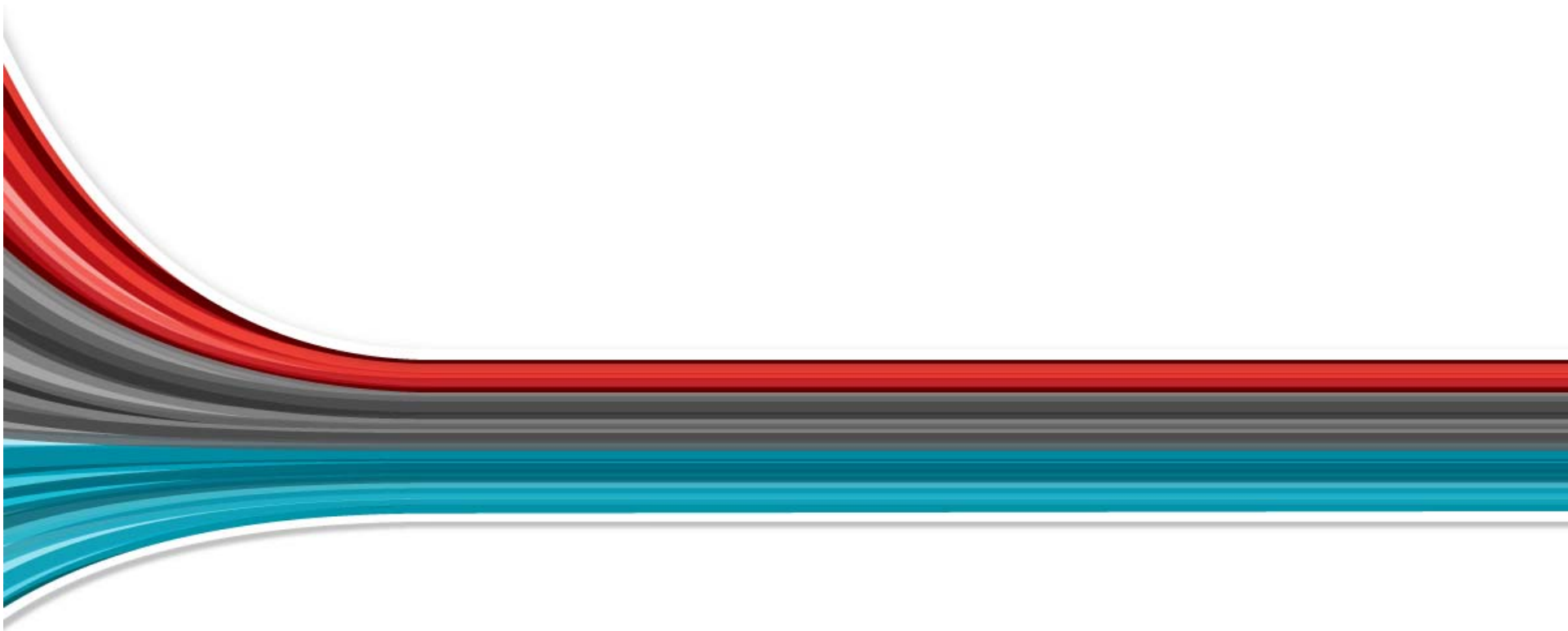
- Frequent question: *Do changes require “re-consent”?*
- SACHRP – “When there is a need to present participants with new information, IRBs should encourage use of the least burdensome approach for the participant.”
- “Re-consent” not a regulatory term
- New information can be presented in different formats
  - Revised consent document
  - Addendum to consent
  - Memo or other communication to subjects
  - Orally by phone or in person

## Bottom Line = Documentation

Regulators & IRB know that COVID-19  
will necessitate changes to almost all  
clinical research



Sites & sponsors should create clear  
documentation of all actions taken to  
manage ongoing research.



# Patient Perspectives

Cindy Geoghegan

*Individual Patient Representative/Caregiver*



# Patient Perspective:

## Safety of trial participants, study staff is most important

### “Safety” to trial participant in context of pandemic

- Continuously evaluating; daily prioritizing urgent needs (food, shelter, finances, family)

### Fear & anxiety

- Baseline fear of living with life-threatening illness can turn to terror
- Heightened “safety” warnings aimed at “high-risk, especially vulnerable”
  - Preexisting conditions, heart & respiratory ailments, diabetes, elderly
  - Healthcare shortages – physicians, nurses, supplies
- Enforcing of self-isolation and home quarantine in impacted areas; travel restrictions
- Worry about added risks to loved ones & caregivers



# Patient Perspective:

## Safety of trial participants, study staff is most important

### Sense of urgency –

- My disease is progressing as research stalls
- Am I “essential”? Is my treatment? Is my trial?
- We’ve been waiting for this trial for months, years? How quickly can it resume? What happens to my participation if trial doesn’t resume?
- What can I do now?



# Patient Communication Essential

*It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them.*

FDA Guidance

## ► Need for plan, process, decision-making

- Who informs, when, how?
- Resources for consistent, evidence-based information
- Essential information at patient-level
  - Study delays, suspended procedures, clinic closings
  - Transitions to remote, digital or home-based visits
- Support, training necessary for digital tools, monitoring, home collection

## ► Role of patient organizations in reviewing modifications, broader outreach, guidance

## ► Reference: CTTI Recommendations: Technical support (training) for digital tools, home collection ([CTTI MCT EPS](#))



# Summary & Next Steps

Pamela Tenaerts

*CTTI*



# Best Practices

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## Next Steps

- Post & communicate recorded webinar & slides
- Create best practices document
  - Submitted questions from today's webinar will be incorporated
- Situation will evolve
- Best practices document will be updated and communicated
  
- Additional CTTI efforts will be forthcoming



## Additional Resources:

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  - **CDRH:** <https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization>

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# THANK YOU.



[Sara.calvert@duke.edu](mailto:Sara.calvert@duke.edu)



[www.ctti-clinicaltrials.org](http://www.ctti-clinicaltrials.org)

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