

FDA, COVID-19, and Clinical Trials

FDA Small Business Regulatory Education for Industry 2021 Annual Conference

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- **No conflict of interest; no endorsement of products, institutions, companies**
- **Views and perspectives are those of the presenter and should not be attributed to FDA**

- **Provide overview of FDA efforts to support drug development during the COVID-19 pandemic, emphasizing clinical trials of “non-COVID” agency-regulated products**
- **Discuss how clinical trial conduct has changed during the COVID-19 pandemic, and consider future developments**
- **Describe developments related to the use of digital health technologies in clinical trials**

- Review of pre-market Investigational New Drug (IND) submissions and requests for Expanded Access involving investigational drugs
- Consolidate activities in Coronavirus Treatment Accelerator Program (CTAP): >600 development programs in planning; >450 trials reviewed
- Review of requests for Emergency Use Authorizations (EUAs); EUAs issued for monoclonals, antiviral, drugs in shortage, vaccines
- Issue guidance on various COVID-specific topics, e.g., *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention – Guidance for Industry*

- Develop guidance (i.e., recommendations) for industry, investigators, and institutional review boards related to addressing the impact of COVID-19
- Conduct outreach, hold listening sessions, and solicit feedback from stakeholders
- Convey up-to-date information to the public
- *Note: Centers for Drug Evaluation and Research (CDER), Biologics Evaluation and Research (CBER), as well as Devices and Radiological Health (CDRH) are working both individually and collectively*

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

- Initial release date 18 Mar 2020; multiple updates through 27 Jan 2021

<https://www.fda.gov/media/136238/download>

‘Conduct of Clinical Trials’ Guidance: Core Principles



- **Safety of trial participants is core focus of all recommendations**
 - ***“Ensuring the safety of trial participants is paramount”*** is first consideration mentioned in Conduct of Clinical Trials Guidance
 - **Focus also on protecting trial integrity and helping to maintain compliance with Good Clinical Practice**
- **For specific questions that depend on factors such as study population, type of investigational product, or trial endpoint, suggestion is to contact the appropriate FDA review division**

‘Conduct of Clinical Trials’ Guidance (cont’d)



- Guidance solicited inquiries on clinical trial conduct during the pandemic to a dedicated mailbox at Clinicaltrialconduct-COVID19@fda.hhs.gov
- COVID-19 Clinical Trial mailbox received and replied to >600 inquiries as of Jun 2021
- *Question & Answer* appendix developed and expanded over time based on major issues identified and inquiries received in mailbox
- Multiple updates to ‘COVID-19 Clinical Trial’ Guidance (latest in Jan 2021)

FDA COVID-19 Clinical Trials Mailbox – *Sent by Whom?*



INQUIRIES – ORGANIZATIONAL TYPES (N=414; data as of June 2020)	N	%
Industry/trade association	126	30
Academic institution/hospital/clinic/research site	120	29
Trial participant/patient/private citizen	60	14
Contract Research Organization (CRO)/CRO association	55	13
Institutional Review Board/Independent Ethics Committee	25	6
Government	23	6
Patient advocate	5	1

FDA COVID-19 Clinical Trials Mailbox – *What was focus?*



'TOP TEN' PRIMARY CATEGORIES OF QUESTIONS (N=414; data as of June 2020)

N

Covid-19-related study questions	85
Informing/interacting with FDA	41
Access to/issuance of COVID-19-related regulatory guidelines or resources	29
Investigational product distribution/supply/suspension	28
Informed consent process/content/documentation	26
Electronic signature/record/system compliance	23
Remote data monitoring/wearables & mobile technologies	23
Study/protocol amendment, change, deviation handling	18
Study delay/suspension/premature termination or resumption after pause	17
Study eligibility/screening procedures for Covid-19 and study participation	16

'Conduct of Clinical Trials' Guidance: Appendix

Appendix: Questions and Answers

Q1. Deciding whether to suspend, continue, or initiate trials	8
Q2. Deciding whether to continue administering product appearing to provide benefit	9
Q3. Managing protocol deviations and amendments	10
Q4. Submitting changes to IND and IDE protocol	11
Q5. Conducting remote (virtual) clinic visits	11
Q6. Capturing data on protocol and process deviations	12
Q7. Delivering low-risk investigational products to home	12
Q8. Disposal of unused investigational product	13
Q9. Changing site for delivering high-risk investigational product	14
Q10. Alternative monitoring approaches	14

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Q24. Reporting serious adverse events associated with COVID-19 in a non-COVID trial	32
Q25. Reviewing IND safety reports	33
Q26. Collecting electronic signatures and Part 11 compliance	34
Q27. Exclusion criteria for "investigational medical products"	35

Q5: Considerations for Certain Remote Study Visits



- **FDA regulations allow for changes to the protocol without prior FDA review or approval if intended to eliminate an apparent immediate hazard to trial participants**
- **When necessary, sponsors can:**
 - **conduct telephone or video visits as safety monitoring, for example**
 - **implement changes immediately, with subsequent review by IRB and notification to FDA**
 - **document changes as protocol deviations, until amendment can be approved**

Q14: Remote Outcome Assessments



- *[Inquiries regarding whether to conduct clinical outcome assessments (COAs) remotely]*
- Sponsors should:
 - consider if the remote technology is appropriate for the type of clinical data capture
 - consider ways to ensure consistency between in-person and remote assessments (if only some outcome assessments will be captured remotely)
 - adequately prepare investigators; develop procedures for participant technical support

Q6: Deviations and Amendments



- **Protocol deviations are generally reported to FDA in clinical study reports**
- **Global changes to study conduct would generally be reported as a protocol amendment**
- **During the rapidly evolving circumstances of a pandemic, a sequence of changes may be needed; consolidating several protocol modifications in a single protocol amendment would be acceptable but should be done expeditiously**

Q7. Investigational Products Administered at Home



- **Home delivery may be appropriate for certain self-administered investigational products, as long as no additional risks to safety are involved**
- **FDA requirements for storage conditions and product accountability remain (and must be documented)**
- **If home delivery is for only a limited number of trial participants, documenting this approach as a “protocol deviation” may be acceptable**
- **If the change to home delivery is more extensive, a protocol amendment would be required**

Q17. Investigational Products to Local Provider



- *[Inquiry regarding whether investigational product intended for infusion can be administered locally]*
- Specific situations will affect feasibility/appropriateness, but generally for documenting oversight:
 - investigators and sub-investigators → FDA Form 1572
 - local providers, nurses, phlebotomists → responsibility log, if product administration is within scope of practice
- Use procedures to assure product accountability and quality, including that the drug is kept under appropriate storage conditions during delivery

Q11. How do I obtain signed informed consent from a hospitalized patient who is in isolation when a COVID-19 infection control policy prevents us from entering the patient's room to collect a signed informed consent form?

- Use traditional methods or use electronic informed consent when feasible, or consider other procedures to satisfy FDA's informed consent documentation requirement (*described in guidance*)**

Method 1: A photograph of the signed informed consent document can be transmitted to the trial staff

Method 2: A witness can attest to the signature, but a photograph of the signed informed consent document cannot be transmitted

Q27. Certain clinical trial protocols have an exclusion criterion for receipt of another “investigational medical product.” If a participant receives a vaccine or other medical product for the prevention or treatment of COVID-19 authorized under an Emergency Use Authorization (EUA), would FDA consider this receipt of an investigational medical product?

- **A medical product under an EUA isn’t approved but is authorized for use in clinical care, and when used under EUA is *not* considered an investigational product**
- **If same product is used in a clinical investigation under an IND, receipt of the same product *is* considered investigational**
- **Scientific reasons may exist for specific exclusion or discontinuation criteria**

- **Sponsors should document COVID-19 contingency measures and how they affect the trial, as well as effects at the individual participant level**
- **FDA anticipates there will be many protocol deviations that may lead to missing data, capture of data outside of protocol defined windows, and other changes**
- **“Document now” so that clinical study reports can capture:**
 - **listing of all participants affected by the COVID-19 related study disruption, along with a description of how each participant’s experience was altered**

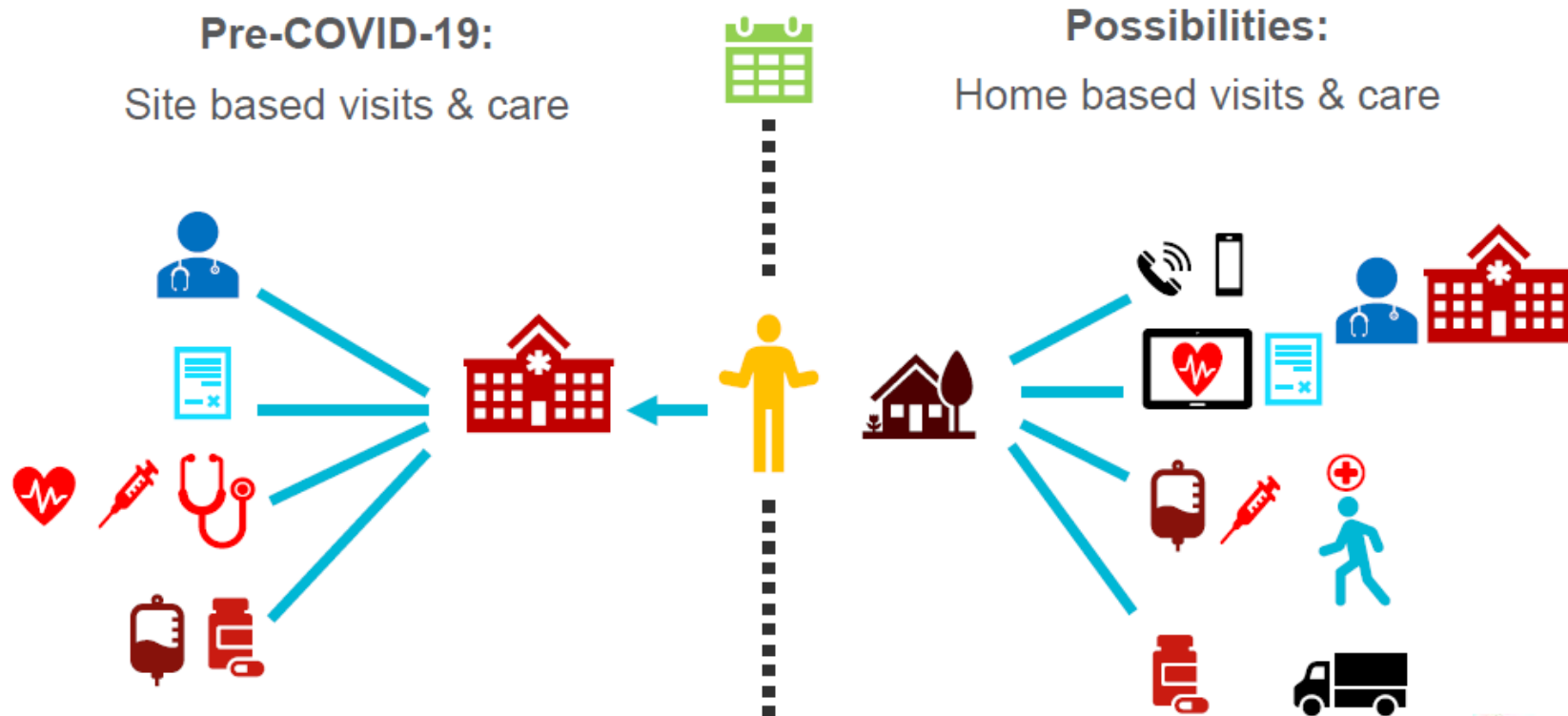
Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

Guidance for Industry

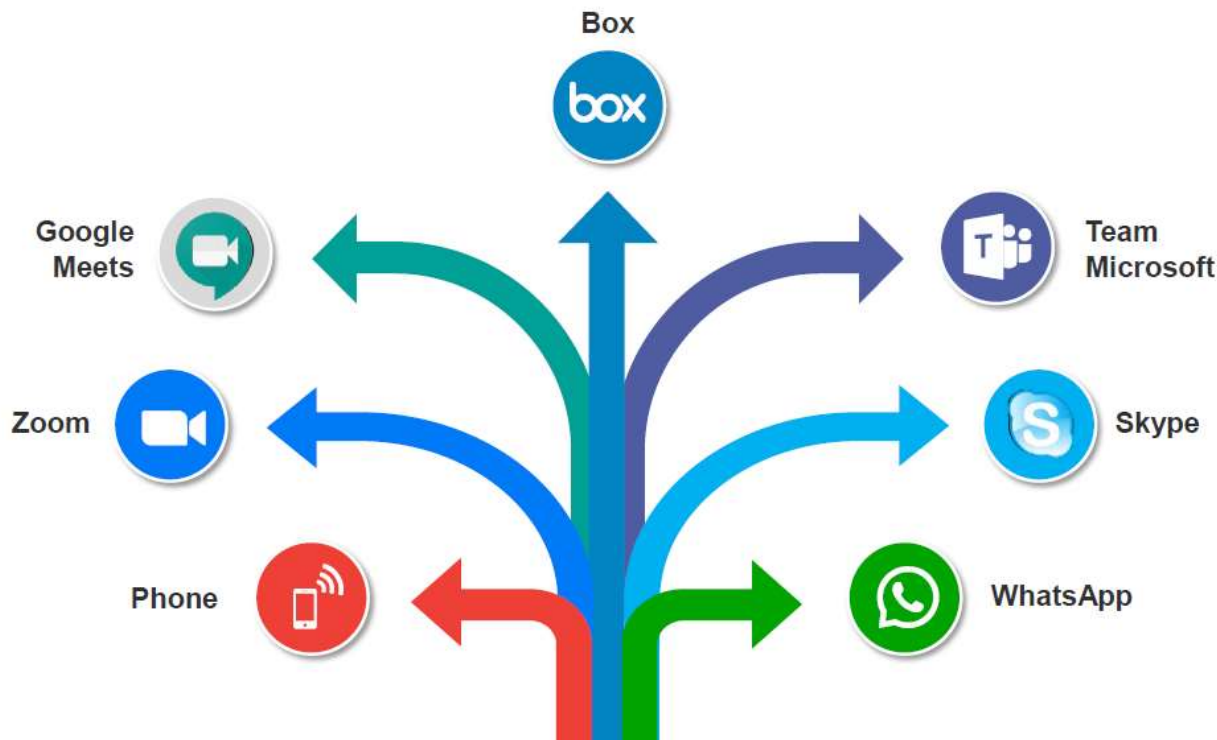
June 2020

“...to help ensure that the trial will provide interpretable findings with correct statistical quantification of uncertainty”

Clinical Trials Transformation Initiative (CTTI): Perspective on Clinical Trials - 20 May 2020



CTTI: Transition to Remote/Virtual Trial Visits



85% of respondents (n=62) to CTTI survey transitioned to remote/virtual visits in ≥ 1 ongoing trials

- Emergence of *digital health technologies* (e.g., sensors and software applications) is changing clinical research
- Digital health technologies have applications in settings involving clinical trials and observational studies
- *Decentralized clinical trials* involve decentralized trial operations and use technology to communicate with study participants and collect data; such trials provide opportunities for:
 - faster enrollment and sustained participation in trials
 - greater convenience for participants
 - potential for less missing data
 - increased participant diversity

Digital Health Technology and Clinical Trials

Continuous
glucose
monitor



Continuous
EKG
monitor



Continuous
blood
pressure
monitor



Fall
detector



Smart pills



Actigraphs

Patient
reported
outcome



Cellphone
camera



Specific
tests of
function



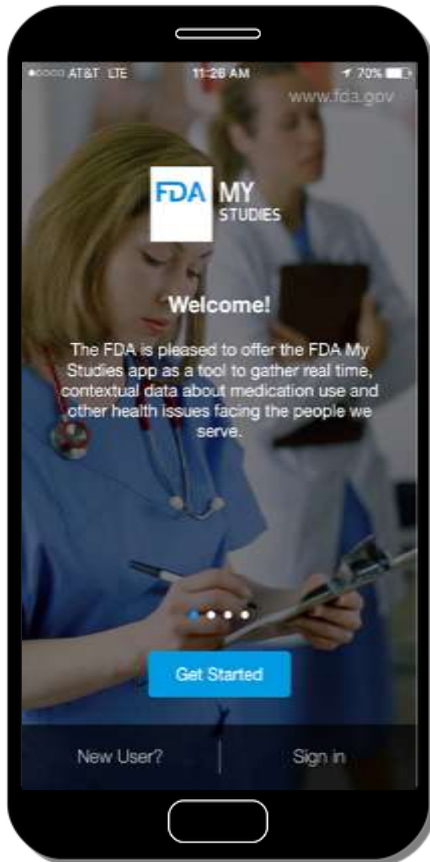
Potential Uses for DHTs in Clinical Trials



- **Screening, enrollment, and enrichment**
 - e.g., help determine disease severity, functional status at enrollment
- **Safety monitoring**
 - identification of rare adverse events, real-time access to safety data
- **Dose-effect evaluation**
 - visualize response over a dosing interval
- **Endpoint assessment**
 - *note: can be more compelling in superiority studies (vs. non-inferiority studies given challenges in interpretation)*

- **Appealing to the potential users?**
- **Easy to put on?**
- **Easy to operate?**
- **Feasible to wear for the required time period?**
- **Adequate battery life?**
- **Reliable syncing of data?**
- **What about “bring your own” device?**

FDA COVID MyStudies App

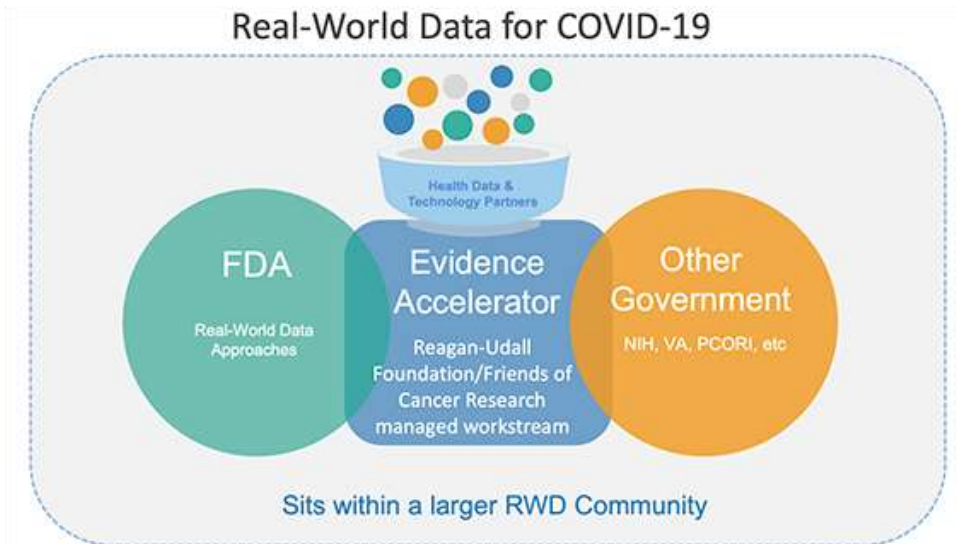


- **Mobile app – web-based configuration portal**
- **Secure storage environment**
 - **21 CFR Part 11 and FISMA compliant**
- **Deployed in several demonstration projects**
 - **collect RWD in randomized trial of patients with pediatric juvenile arthritis**
 - **collect RWD for registry of patients with inflammatory bowel disease**
- **Repurposed during COVID to facilitate enrollment in clinical trials** (<https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app>)

- **Real-world data continue to accumulate as the pandemic unfolds; valid real-world evidence to inform pandemic response would be beneficial; progress is made from “lessons learned”**
- **More data aren’t always better; challenges in diagnosing, treating, and reporting on a new disease can create methodological problems; our understanding of COVID-19 evolves over time**
- **COVID-19 presents an opportunity to leverage real-world data to inform clinical and regulatory decisions, but scientific rigor must be maintained**

'Evidence Accelerator' for COVID-19

- **FDA collaboration with Reagan-Udall Foundation & Friends of Cancer Research to accelerate better understanding of COVID-19**



- **'Parallel Analysis' activity: Data partners use a common protocol to conduct side-by-side analyses of real-world data on various COVID-19-related topics**



- Internet-based repository of RWD on novel uses of existing drugs
- Facilitates evaluation of FDA-approved treatments when used in clinical practice for unapproved uses
- Recently updated to include a focus on COVID-19
- See <https://cure.ncats.io/> or download “CURE ID” app

- From Guidance on COVID-19 Clinical Trial Conduct :

“FDA is issuing this guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency”

“This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2))”

Which of the following statements is false (*single best answer*)?

- a) Ensuring the safety of trial participants is a core focus of the FDA COVID-19 Clinical Trial guidance**
- b) The FDA COVID-19 Clinical Trial guidance has been updated several times based on inquiries “from the field”**
- c) Digital health technologies were being implemented before COVID-19 and increased in use during the pandemic**
- d) All processes described in FDA guidance on COVID-19 will be inappropriate when the public health emergency ends**

- **FDA is working closely with stakeholders to provide guidance on clinical trial conduct during the COVID-19 pandemic that protects patient safety and promotes trial integrity**
- **The COVID-19 pandemic has disrupted the conduct of clinical trials, such as increasing the use of remote trial procedures**
- **Digital technologies have the potential to change the way many clinical trials are conducted**



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Thank You