Clinical Cancer Research During the COVID-19 Pandemic: FDA Perspective

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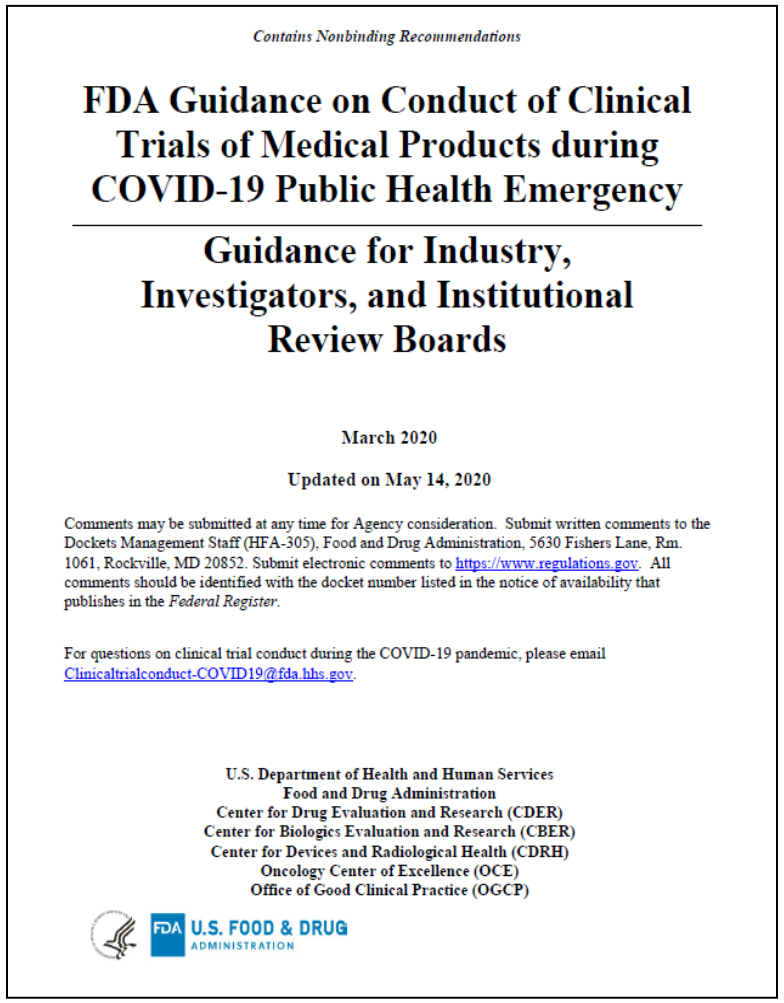
Regulatory Challenges to Trial Conduct During COVID

- Ensuring the safety of trial participants
  - Informing patients of changes and ensuring adequate consent
  - Evaluating safety using alternative methods (e.g., telemedicine)
  - Delays or omission of safety evaluations (e.g., labs, exams, etc.)
- Maintaining trial and data integrity
  - Changes to assessments that are basis of formal hypothesis testing
  - Interpreting missing data
  - Understanding reasons for protocol deviations

Trial Conduct during the COVID-19 Pandemic



Contains Nonbinding Recommendations

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on May 14, 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.

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)

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Guiding Principles

- "Ensuring the safety of trial participants is paramount."
- Provides guidance on most common issues
- Advises contacting FDA on certain issues

FDA Guidance: Common Issues

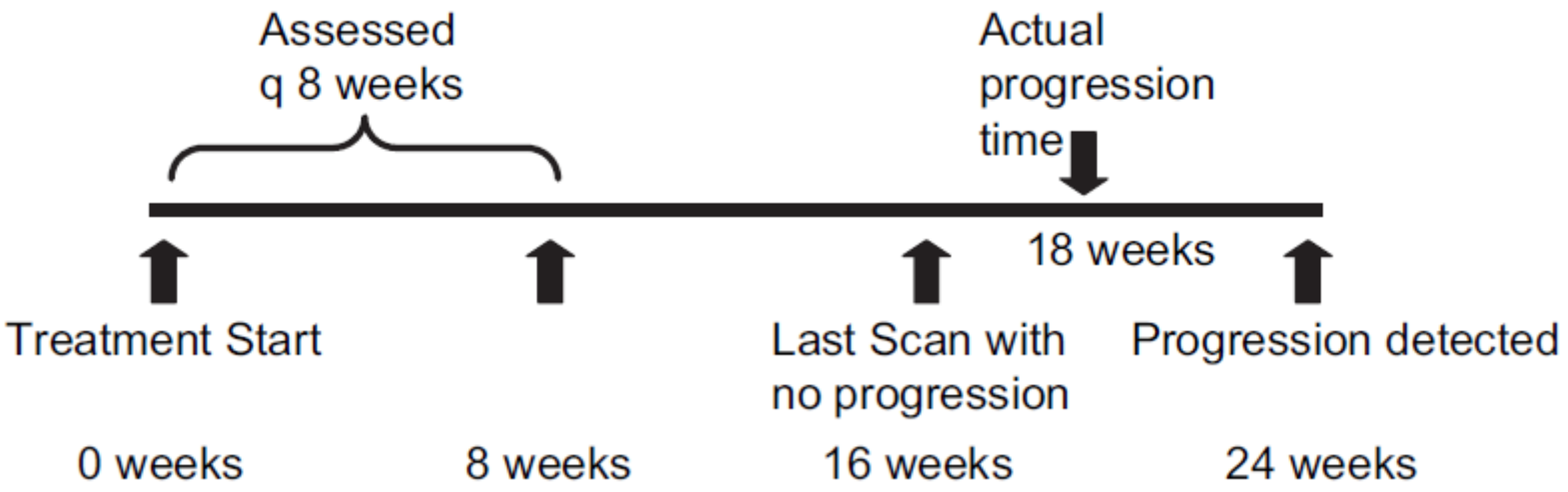
- Alternative offsite methods (i.e remote monitoring) may be used
- Changes to protect the life and well-being of patients (e.g. limit exposure to COVID-19) can be implemented without IRB/FDA approval but are required to be reported afterwards
- COVID therapy (vaccines, etc.) received under EUA should not necessarily exclude patients from trials
- Contingency measures should be documented
  - How restrictions led to changes, who was impacted, and how

Examples of When to Contact FDA Review Divisions

- Protocol modifications related to efficacy endpoints
  - Example: disparities in lab measurements or imaging protocols will introduce variability and can affect type I and type II error rates

- Changes to data management and/or statistical analysis plans
  - Example: Before locking database, address in SAP how protocol deviations related to COVID will be handled for the pre-specified analysis

Example: Assessment of PFS

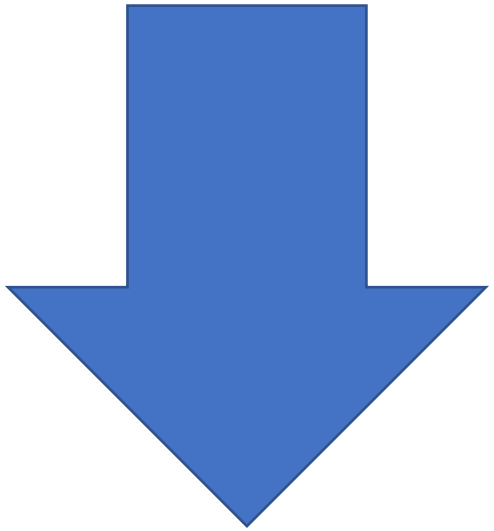


- Variability could include missing or out of window assessments
- May not affect PFS interpretation if well-balanced between arms
- Asymmetry between arms will introduce bias in assessment of PFS

Panageas et al. JNCI 2007

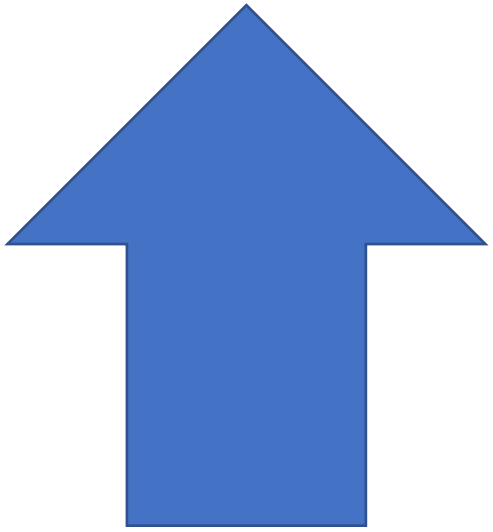
Assessing Safety via Telemedicine

Assessment without physical exam



DECREASED reporting?

Telemedicine may allow more caregivers to participate in visit



INCREASED reporting?

- Asymmetrical differences between arms can result in bias

Learning from COVID-19

- ALL stakeholders have a responsibility to evaluate data generated during COVID-19 to characterize effects of remote trial conduct on clinical trial data
- FDA'S OCE is dedicated to working with the broader community to generate insights to advancing trial modifications that can facilitate decentralized trials
- Trial initiation for COVID-related products was expedited and procedures used to achieve this speed should be reviewed and aspects carried forward where appropriate

Trial Modernization Post-COVID

- Trial modernization efforts were underway before the pandemic
- These efforts will be better informed by evaluating data generated during the COVID-19 pandemic
- Areas of interest include:
  - Incorporating technology to reduce patient burden
  - Using non-trial site labs, imaging centers, and drug administration
  - Minimizing collection of non-essential data
- Ability to incorporate these aspects will depend on their effect on patient safety and maintaining data and trial integrity

Broadening Inclusion and Addressing Disparities

- Healthcare disparities have been highlighted by COVID-19
- There is an under-representation of racial and ethnic minorities in oncology clinical trials used to support registration
- In promoting inclusion and reducing disparities
  - Representation should be addressed throughout a drug's development
  - Decentralized trials may expand access to broader patient populations
  - RWD may be useful to obtain additional information on under-represented populations

Credit: Nicole Gormley, M.D.; U.S Food and Drug Administration

Key Take Home Points

- FDA continues to promote flexibility in trial conduct if:
  - Safety of trial participants is maintained
  - Data and trial integrity are not compromised
- Broadening inclusion on clinical trials is a priority
- Efforts to learn from the pandemic are ongoing and will better inform trial modernization efforts
- In modernizing trials, must prioritize modifications that provide:
  - Biggest benefit to patients
  - Most efficiencies to investigators
  - Have the least effect on data quality