Coronavirus Disease 2019 (COVID-19): Risk Assessment and Mitigation Strategies for the Collection of Patient-Reported Outcome Data through Clinical Sites

Version 3.0
June 5, 2020

Table of Contents

Background

- Members of the Electronic Patient-Reported Outcome (ePRO) Consortium and the Patient-Reported Outcome (PRO) Consortium were invited to collaborate on a risk assessment and mitigation plan for clinical trials in response to the impact of COVID-19.
- Over a 4-week period beginning in March 2020, member representatives participated in a series of teleconferences in which they engaged with others to provide suggestions for the assessment of risk and mitigation strategies for their firms.
- This presentation is the result of this collaborative effort.

Objective and Scope

- Issue:
  - Due to concerns with COVID-19, many patients are either unable or unwilling to travel to sites for scheduled visits or sites have had to close due to social distancing measures.
- Objective:
  - Provide a selection of risk assessment and mitigation strategies for consideration by sponsors and electronic clinical outcome assessment (eCOA) providers to facilitate the continued collection of PRO data in clinical trials.
- Scope
  - This presentation focuses on the current challenges of capturing PRO data originally intended to be collected electronically (i.e., ePRO) from study participants during in-person visits to study sites.

Core Principles

The following are considered core principles and should be kept at the forefront of the decision-making process by sponsors and eCOA providers.

1. **Ensure Patient Safety**
   - Non-negotiable
   - To reduce risk of exposure, patients should visit clinics only if absolutely necessary for treatment reasons.
2. **Minimize Patient Burden**
3. **Ensure Transparency (i.e., changes to protocol and new processes are clearly documented)**
   - Non-negotiable
   - Transparency with respect to all aspects of changes to the protocol, new processes, and compliance with regulatory guidance and ethics board requirements
4. **Minimize Site Burden**
   - To the extent possible, there should not be a significant increase in site burden associated with the alternative approaches to the collection of PRO data.
5. **Maintain Data Integrity**
   - Integrity of data is of paramount importance; strategies should be employed to ensure data integrity to the greatest extent possible.

Core Principles - Summary

- Patient safety and transparency are non-negotiable. However, firms will likely need to make thoughtful compromises that may impact data integrity (e.g., if paper is used), completeness (e.g., increase of missing data), and quality (e.g., out of range responses).

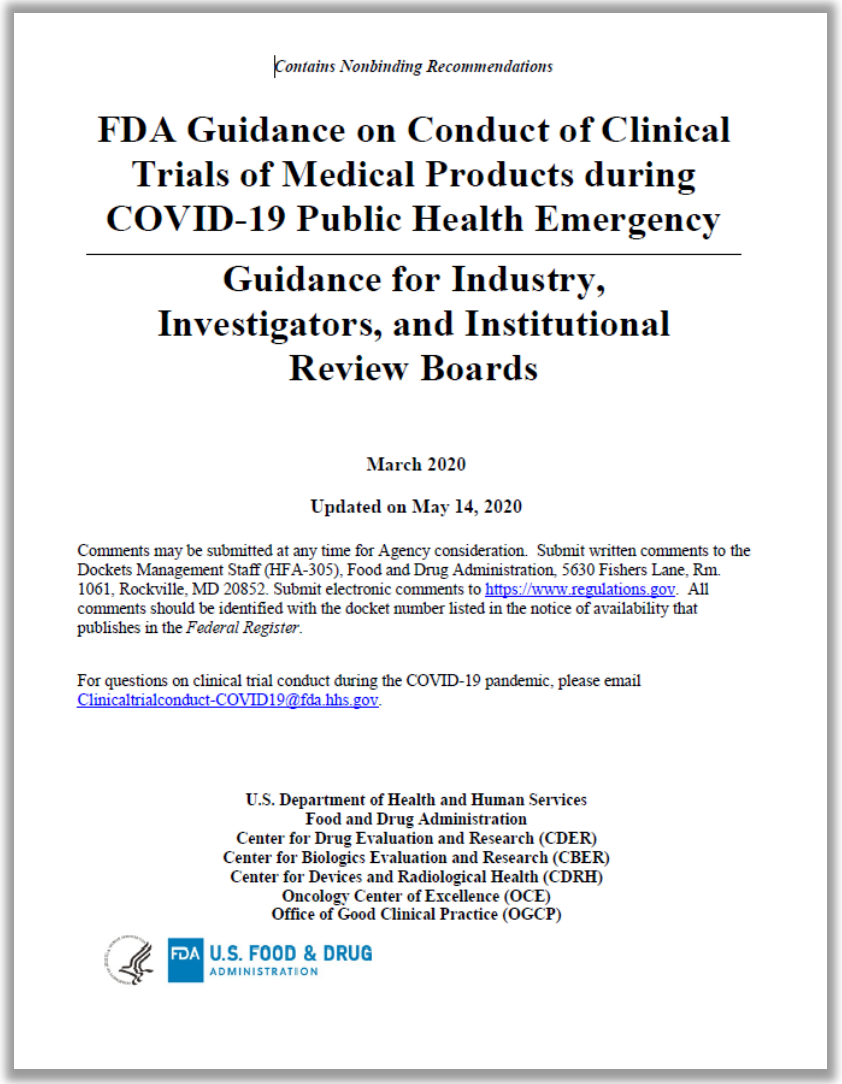
- In this challenging environment, it is unrealistic to expect perfection; in many cases, some data will be better than no data.

- The key takeaway is to be transparent about any deviations from the original protocol. Decisions can be made after the fact about how the data captured in these reactive ways should be used.

Regulatory Guidance:
U.S. Food and Drug Administration (FDA)

In March 2020, FDA issued guidance for industry, investigators, and institutional review boards conducting clinical trials during the COVID-19 pandemic.

Check the FDA website for current updates.



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.

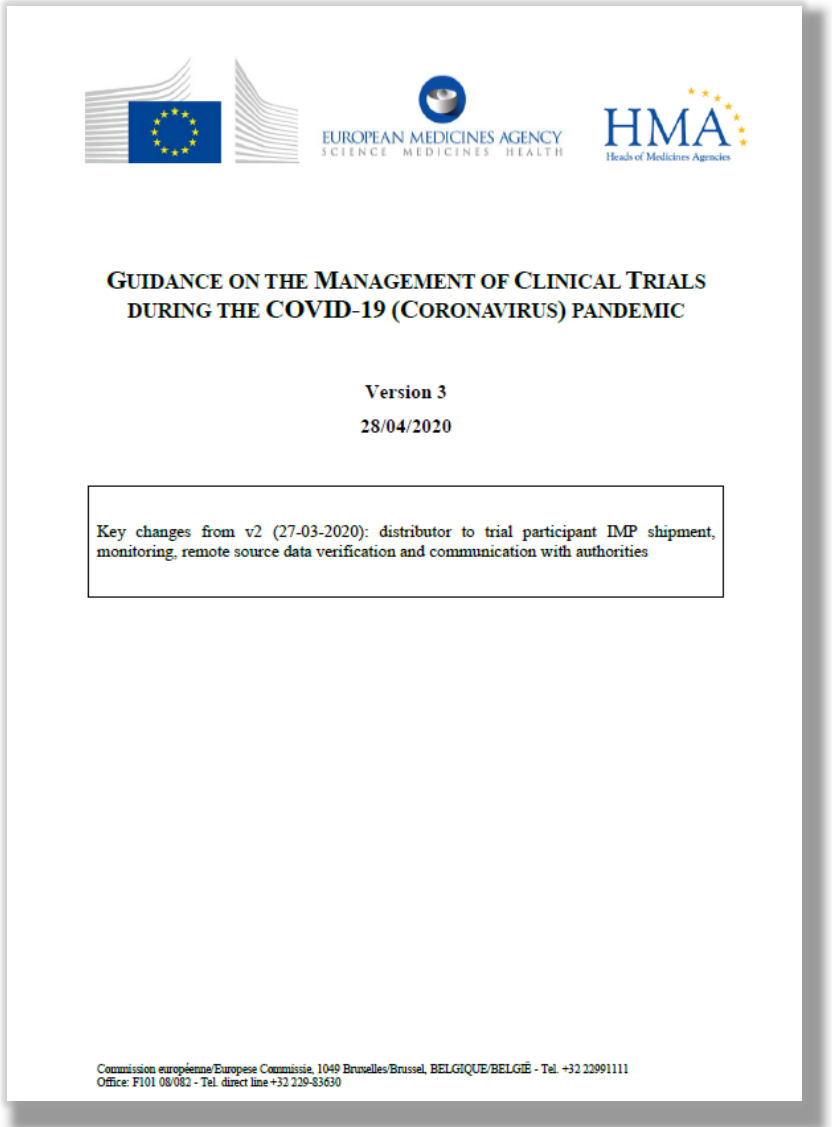
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

FDA U.S. FOOD & DRUG ADMINISTRATION

Regulatory Guidance: European Medicines Agency (EMA)

In March 2020, EMA issued guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic.

Check the EMA website for current updates.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

Version 3

28/04/2020

Key changes from v2 (27-03-2020): distributor to trial participant IMP shipment, monitoring, remote source data verification and communication with authorities

Commission européenne/Europese Commissie, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË - Tel. +32 22991111
Office: F101 08/082 - Tel. direct line +32 229-83630

Regulatory Guidance: United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA)

In March 2020, MHRA issued guidance on managing clinical trials during Coronavirus (COVID-19).

Check the MHRA website for current updates.

Guidance

Managing clinical trials during Coronavirus (COVID-19)

How investigators and sponsors should manage clinical trials during COVID-19

Published 19 March 2020
Last updated 22 April 2020 — see all updates
From: Medicines and Healthcare products Regulatory Agency

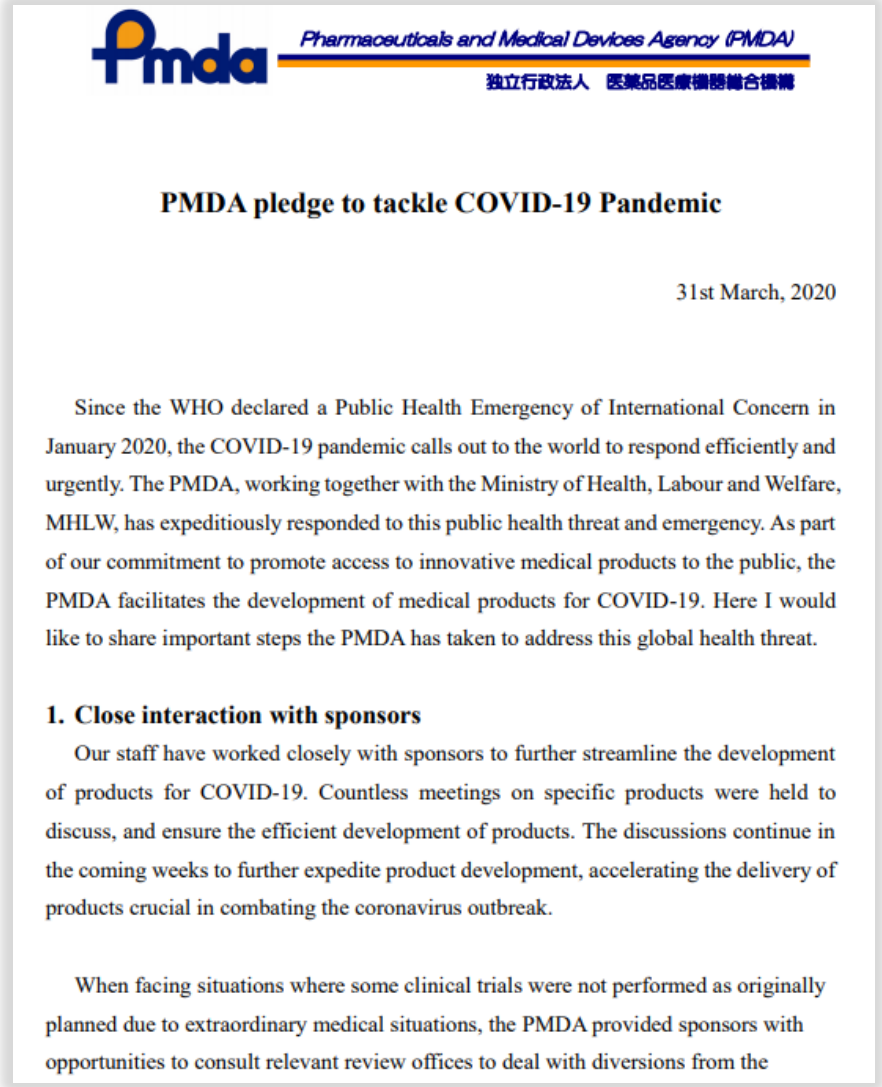
Contents

This guidance advises those involved in clinical trials on specific issues which may arise as a result of COVID-19, and what they are required to do.

Regulatory Guidance: Japan's Pharmaceuticals and Medical Devices Agency (PMDA)

In March 2020, PMDA issued its pledge to tackle COVID-19 Pandemic.

Check the PMDA website for current updates.



Pharmaceuticals and Medical Devices Agency (PMDA)
独立行政法人 医薬品医療機器総合機構

PMDA pledge to tackle COVID-19 Pandemic

31st March, 2020

Since the WHO declared a Public Health Emergency of International Concern in January 2020, the COVID-19 pandemic calls out to the world to respond efficiently and urgently. The PMDA, working together with the Ministry of Health, Labour and Welfare, MHLW, has expeditiously responded to this public health threat and emergency. As part of our commitment to promote access to innovative medical products to the public, the PMDA facilitates the development of medical products for COVID-19. Here I would like to share important steps the PMDA has taken to address this global health threat.

1. Close interaction with sponsors

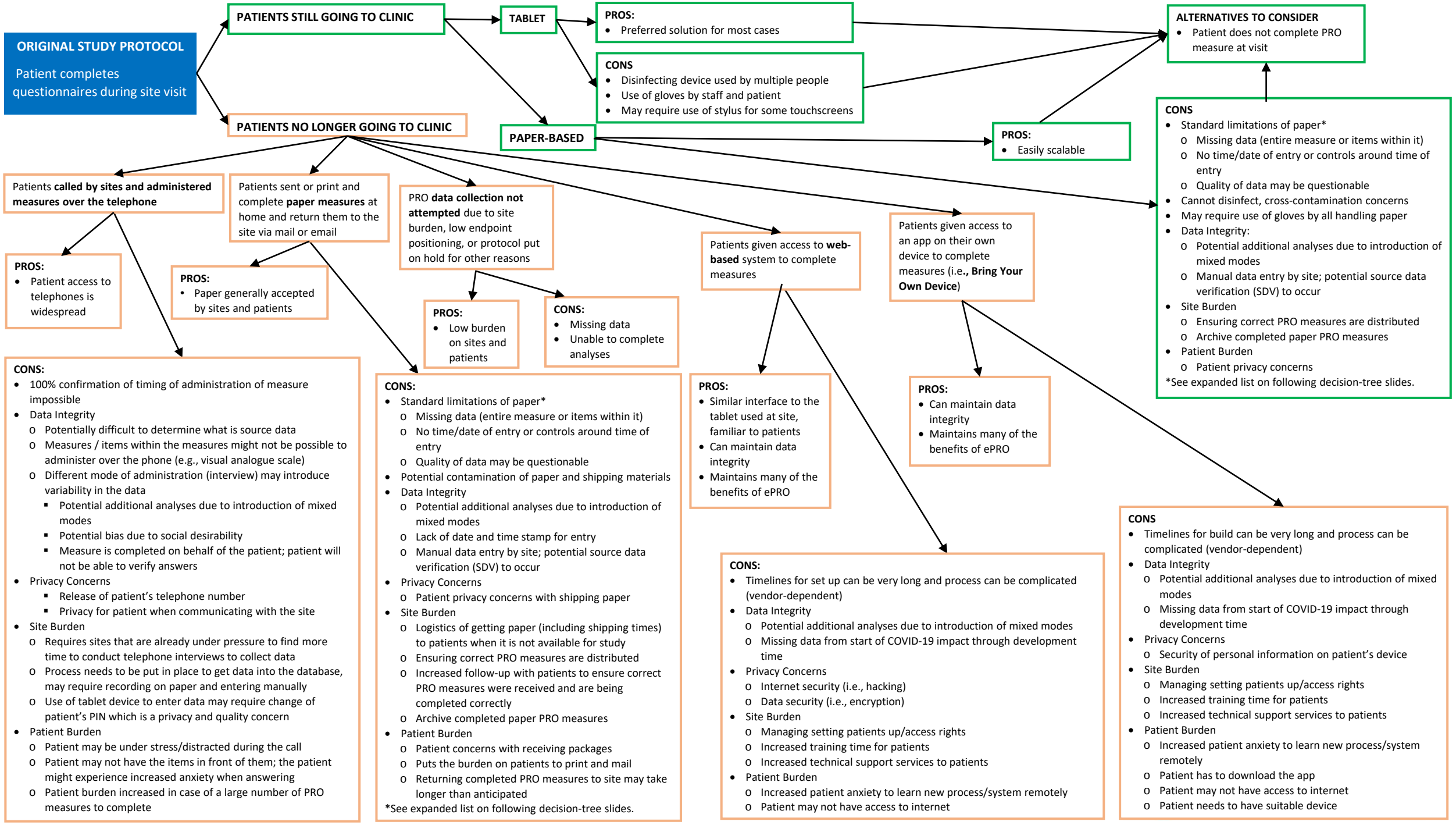
Our staff have worked closely with sponsors to further streamline the development of products for COVID-19. Countless meetings on specific products were held to discuss, and ensure the efficient development of products. The discussions continue in the coming weeks to further expedite product development, accelerating the delivery of products crucial in combating the coronavirus outbreak.

When facing situations where some clinical trials were not performed as originally planned due to extraordinary medical situations, the PMDA provided sponsors with opportunities to consult relevant review offices to deal with diversions from the

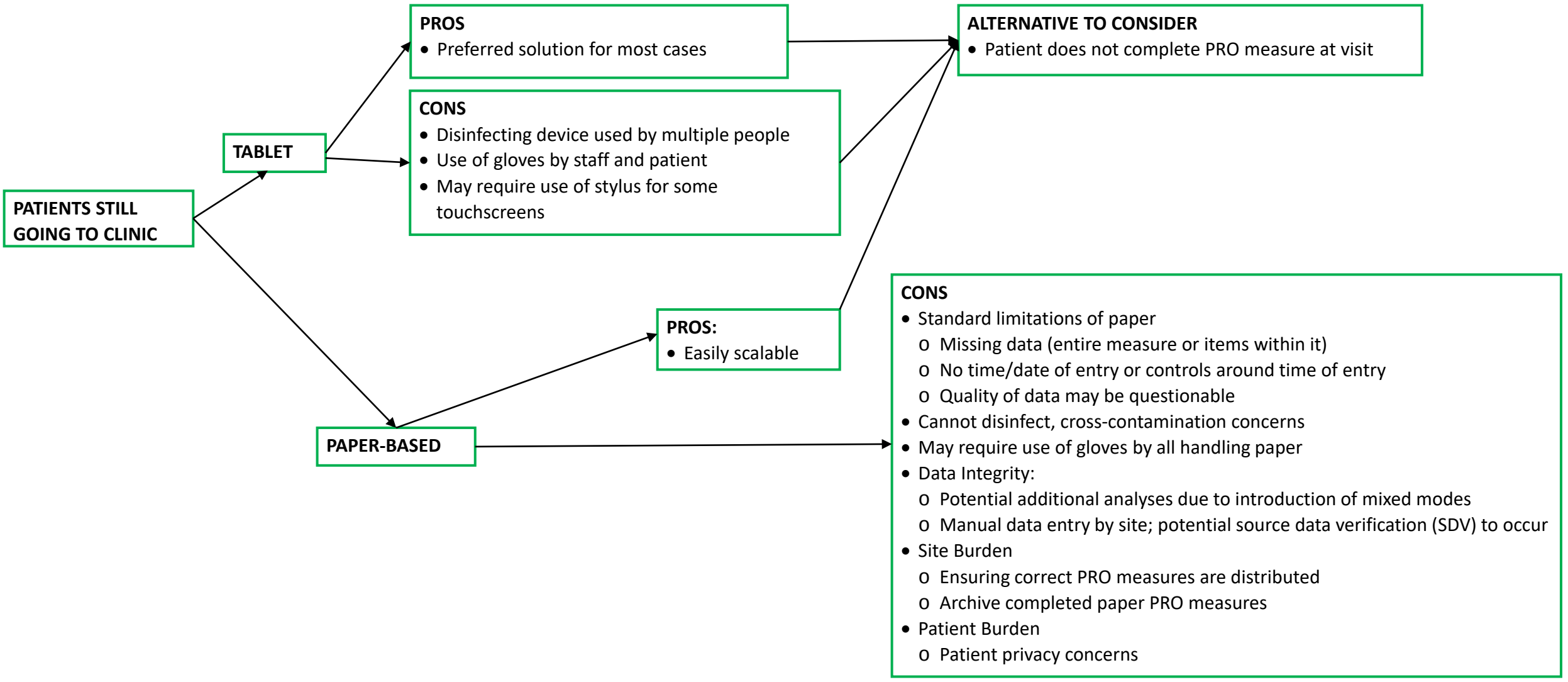
Decision Tree Diagram

- The following decision tree diagram assumes the original study protocol required patients to complete measures in person during a site visit.
- Two scenarios are provided:
  - Patients still going to clinic
  - Patients no longer going to clinic
- The diagram is also embedded here for download >>

Disclaimer: The material presented in the diagram is not necessarily in order of priority.


ORIGINAL STUDY PROTOCOL
Patient completes questionnaires during site visit
PATIENTS STILL GOING TO CLINIC
PATIENTS NO LONGER GOING TO CLINIC
TABLET
PAPER-BASED
PROS:
Preferred solution for most cases
CONS
Disinfecting device used by multiple people
Use of gloves by staff and patient
May require use of stylus for some touchscreens
ALTERNATIVES TO CONSIDER
Patient does not complete PRO measure at visit
PROS:
Easily scalable
CONS
Standard limitations of paper*
Missing data (entire measure or items within it)
No time/date of entry or controls around time of entry
Quality of data may be questionable
Cannot disinfect, cross-contamination concerns
May require use of gloves by all handling paper
Data Integrity:
Potential additional analyses due to introduction of mixed modes
Manual data entry by site; potential source data verification (SDV) to occur
Site Burden
Ensuring correct PRO measures are distributed
Archive completed paper PRO measures
Patient Burden
Patient privacy concerns
*See expanded list on following decision-tree slides.
Patients called by sites and administered measures over the telephone
PROS:
Patient access to telephones is widespread
CONS:
100% confirmation of timing of administration of measure impossible
Data Integrity
Potentially difficult to determine what is source data
Measures / items within the measures might not be possible to administer over the phone (e.g., visual analogue scale)
Different mode of administration (interview) may introduce variability in the data
Potential additional analyses due to introduction of mixed modes
Potential bias due to social desirability
Measure is completed on behalf of the patient; patient will not be able to verify answers
Privacy Concerns
Release of patient's telephone number
Privacy for patient when communicating with the site
Site Burden
Requires sites that are already under pressure to find more time to conduct telephone interviews to collect data
Process needs to be put in place to get data into the database, may require recording on paper and entering manually
Use of tablet device to enter data may require change of patient's PIN which is a privacy and quality concern
Patient Burden
Patient may be under stress/distracted during the call
Patient may not have the items in front of them; the patient might experience increased anxiety when answering
Patient burden increased in case of a large number of PRO measures to complete
Patients sent or print and complete paper measures at home and return them to the site via mail or email
PROS:
Paper generally accepted by sites and patients
CONS:
Standard limitations of paper*
Missing data (entire measure or items within it)
No time/date of entry or controls around time of entry
Quality of data may be questionable
Potential contamination of paper and shipping materials
Data Integrity
Potential additional analyses due to introduction of mixed modes
Lack of date and time stamp for entry
Manual data entry by site; potential source data verification (SDV) to occur
Privacy Concerns
Patient privacy concerns with shipping paper
Site Burden
Logistics of getting paper (including shipping times) to patients when it is not available for study
Ensuring correct PRO measures are distributed
Increased follow-up with patients to ensure correct PRO measures were received and are being completed correctly
Archive completed paper PRO measures
Patient Burden
Patient concerns with receiving packages
Puts the burden on patients to print and mail
Returning completed PRO measures to site may take longer than anticipated
*See expanded list on following decision-tree slides.
PRO data collection not attempted due to site burden, low endpoint positioning, or protocol put on hold for other reasons
PROS:
Low burden on sites and patients
CONS:
Missing data
Unable to complete analyses
Patients given access to web-based system to complete measures
PROS:
Similar interface to the tablet used at site, familiar to patients
Can maintain data integrity
Maintains many of the benefits of ePRO
CONS:
Timelines for set up can be very long and process can be complicated (vendor-dependent)
Data Integrity
Potential additional analyses due to introduction of mixed modes
Missing data from start of COVID-19 impact through development time
Privacy Concerns
Internet security (i.e., hacking)
Data security (i.e., encryption)
Site Burden
Managing setting patients up/access rights
Increased training time for patients
Increased technical support services to patients
Patient Burden
Increased patient anxiety to learn new process/system remotely
Patient may not have access to internet
Patients given access to an app on their own device to complete measures (i.e., Bring Your Own Device)
PROS:
Can maintain data integrity
Maintains many of the benefits of ePRO
CONS
Timelines for build can be very long and process can be complicated (vendor-dependent)
Data Integrity
Potential additional analyses due to introduction of mixed modes
Missing data from start of COVID-19 impact through development time
Privacy Concerns
Security of personal information on patient's device
Site Burden
Managing setting patients up/access rights
Increased training time for patients
Increased technical support services to patients
Patient Burden
Increased patient anxiety to learn new process/system remotely
Patient has to download the app
Patient may not have access to internet
Patient needs to have suitable device

Patients Still Going to Clinic: Tablet and Paper-based Approaches OR Alternative to Consider



Patients No Longer Going to Clinic: Telephone and Paper-based Approaches OR Data Collection Not Attempted

PATIENTS NO LONGER GOING TO CLINIC

Patients **called by sites and administered measures over the telephone**

PROS:
- Patient access to telephones is widespread

CONS:
- 100% confirmation of timing of administration of measure impossible
- Data Integrity
  - Potentially difficult to determine what is source data
  - Measures / items within the measures might not be possible to administer over the phone (e.g., visual analogue scale)
  - Different mode of administration (interview) may introduce variability in the data
    - Potential additional analyses due to introduction of mixed modes
    - Potential bias due to social desirability
    - Measure is completed on behalf of the patient; patient will not be able to verify answers
- Privacy Concerns
  - Release of patient's telephone number
  - Privacy for patient when communicating with the site
- Site Burden
  - Requires sites that are already under pressure to find more time to conduct telephone interviews to collect data
  - Process needs to be put in place to get data into the database, may require recording on paper and entering manually
  - Use of tablet device to enter data may require change of patient's PIN which is a privacy and quality concern
- Patient Burden
  - Patient may be under stress/distracted during the call
  - Patient may not have the items in front of them; the patient might experience increased anxiety when answering
  - Patient burden increased in case of a large number of PRO measures to complete

Patients sent or print and complete **paper measures** at home and return them to the site via mail or email

PROS:
- Paper generally accepted by sites and patients

CONS:
- Standard limitations of paper*
  - Missing data (entire measure or items within it)
  - No time/date of entry or controls around time of entry
  - Quality of data may be questionable
- Potential contamination of paper and shipping materials
- Data Integrity
  - Potential additional analyses due to introduction of mixed modes
  - Lack of date and time stamp for entry
  - Manual data entry by site; potential source data verification (SDV) to occur
- Privacy Concerns
  - Patient privacy concerns with shipping paper
- Site Burden
  - Logistics of getting paper (including shipping times) to patients when it is not available for study
  - Ensuring correct PRO measures are distributed
  - Increased follow-up with patients to ensure correct PRO measures were received and are being completed correctly
  - Archive completed paper PRO measures
- Patient Burden
  - Patient concerns with receiving packages
  - Puts the burden on patients to print and mail
  - Returning completed PRO measures to site may take longer than anticipated

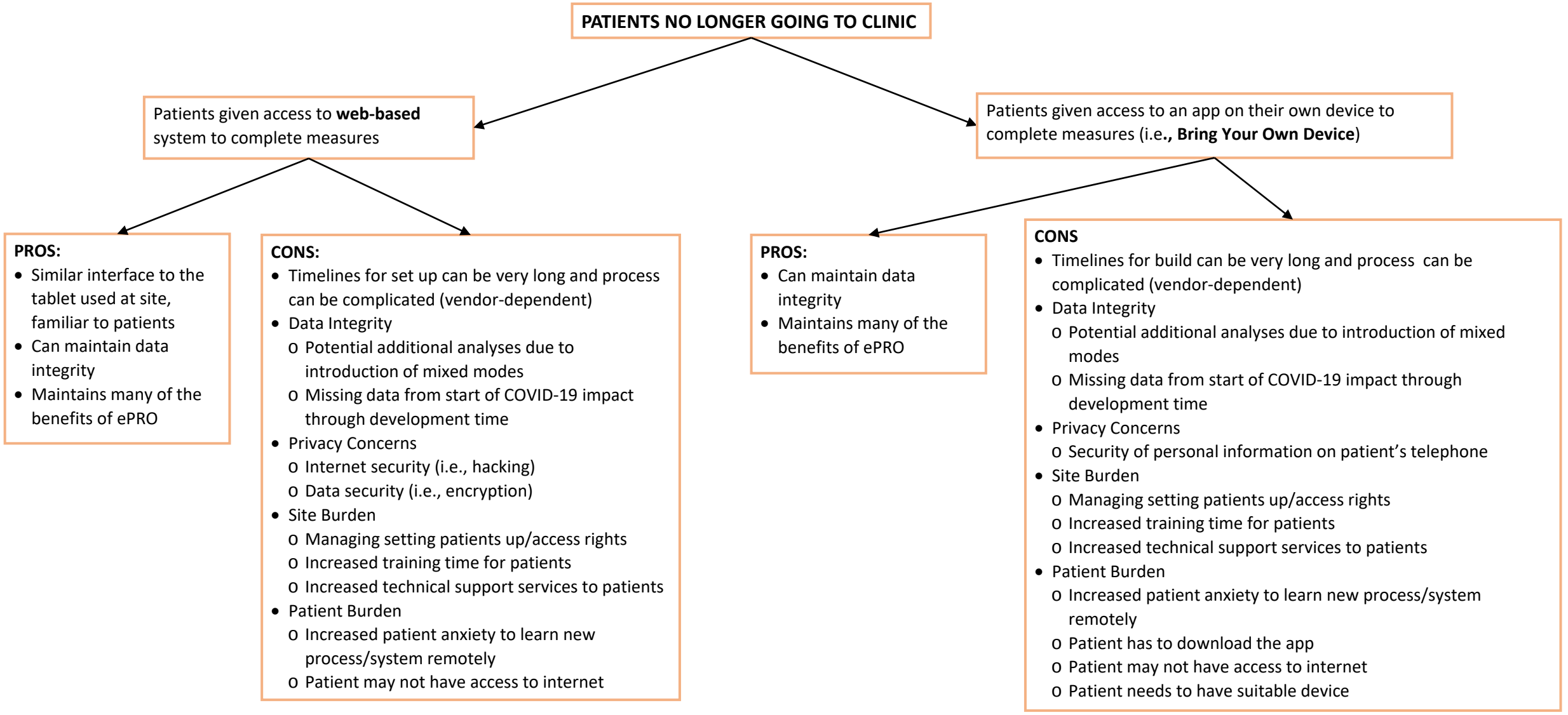
*See expanded list on following decision-tree slides.

PRO **data collection not attempted** due to site burden, low endpoint positioning, or protocol put on hold for other reasons

PROS:
- Low burden on sites and patients

CONS:
- Missing data
- Unable to complete analyses

Patients No Longer Going to Clinic: Web-based and BYOD Approaches



Other Considerations

- Although there are perceived advantages to taking a study-level approach (i.e., the same solution implemented for all sites across a study), we concur with FDA's position that "The need to put new processes into place or to modify existing processes will vary by the protocol and local situation."*
- Applicable solutions may depend on the endpoint hierarchy, trial phase, and where in the course of the trial (e.g., just about to begin, already begun but has a while until completion, or in the final stages).
- Timeline for development of the alternative solution will affect if some of these solutions can be implemented, especially if they weren't already in place as backup options.

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

Other Considerations - Continued

- Consider the clinical trial patient population when deciding what mode to use remotely.
  - For example, patients enrolled in trials may have varying access to needed technology or internet.
  - A poll of the patients enrolled currently, if it can be done expeditiously, may be helpful in decision making.
- When choosing electronic options, sponsors should consider providing the technology (e.g., devices, internet access) to those patients who do not have a device or data plan that would support the technology.
- Other possible solutions that have unique challenges*
  - Interactive voice response system (IVRS)
  - Telehealth/video conferencing
  - Home health visit/direct to patient

*This list is not meant to be exhaustive; other options may be available and useful.

Other Considerations: Telephone-based Approaches

- Bias
  - As many measures have not been designed to be administered in an interview setting there is a risk of systematic bias being introduced if patients are reluctant to answer sensitive questions over the phone
  - Use of third parties to administer measures by phone can reduce site burden and alleviate concerns that patients may try to please the site staff by offering ratings that might not truly reflect their experience
  - Interviewer training is key to avoid inadvertently leading the patient in either case
- Hybrid approach (i.e., measure is emailed to the subject to refer and read along during the phone interview) may support accurate administration of the interview
- Consider video-conferencing, which could be used as an additional verification of communication between the site and patient to confirm the timing and accuracy of patient responses.

Other Considerations: Bring Your Own Device (BYOD)

- Obviously requires patients to have a suitable device
- Pushes “tech support” onto sites and patients who now have to install and login to the study app themselves
- Regulators may have a concern about additional variance being introduced to the data with patients responding on a range of device types
- Resources to consider:
  - Gwaltney C, Coons SJ, O’Donohoe P, O’Gorman H, Denomey M, Howry C, Ross J. “Bring Your Own Device” (BYOD): The future of field-based patient-reported outcome data collection in clinical trials? *Therapeutic Innovation & Regulatory Science* 2015;49:783-791.
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4835151/
  - https://pubmed.ncbi.nlm.nih.gov/29753356/

Altering the Mode of Administration of a PRO Measure: Licensing Approval

Does a psychometrically validated version of your alternative mode of administration already exist?

- **If yes:** Utilize this version, confirm whether or not an amendment to the license agreement is needed.
- **If no:** Exercise due diligence and complete a literature review to determine if there is published precedence supporting administration of the alternative mode of administration. Consider using this published literature to document support of your decision and request license holder approval for use of this alternative method.

  Example: If moving from electronic to telephone administration of EQ-5D-5L, a validated EQ-5D-5L Phone Interview version exists and modification to the license agreement would be needed.

If no response to your request from the license holder: Document your rationale for proceeding with the chosen alternative method.

If license holder does not recommend your alternative method and missing data for this PRO measure is not an option: Document your rationale for proceeding with the alternative method available.

Example: Electronic mode is no longer available at site and the study team determines that telephone administration is the chosen alternative mode of administration. License holder recommends web-based back-up for collection, but this method is not available in time for collection of key treatment endpoint data. Document rationale for choosing to proceed with alternative method to avoid missing key endpoint data.

Sample Language: Approaching the License Holder

Dear Licensor:

I am contacting you concerning [study name] (license agreement attached). In the context of Coronavirus Disease 2019 (COVID-19) containment, *patients are unable to attend site visits to complete the [measure name] via [original mode of administration] as planned. Therefore, we request to modify the original mode of administration and instead use [proposed mode of administration].*

Please contact us as soon as possible if this modification is acceptable and inform us if an amendment to the license agreement is required. Could you please send any instructions that you have developed for this proposed mode of administration?

Suggestions to Licensors/Copyright Holders

- Proactively provide guidance to licensees related to how changes to the mode of administration should be addressed and what changes are acceptable.
  - Provide information on the instrument website regarding alternative approaches and whether a new license will be required.
- In this challenging environment, it is important to be flexible with respect to changing the mode of administration.

Institutional Review Board (IRB)

- According to FDA guidance, sponsors should take necessary measures to protect patient safety.
- Sponsors may make protocol changes without prior approval of the IRB if it is done to eliminate apparent immediate hazards to the human subjects.
- Protocol changes should be communicated to IRBs and ethical committees to ensure transparency.
- Protocol amendments may not be required for temporary solutions due to COVID-19.
- Protocol Deviations due to COVID-19: Consider these changes protocol deviations and follow the IRB's policy for protocol deviations (confirm by reaching out to the IRB directly).

What do you need to report to the IRB?

1. Does the change you are making to the research affect the documents that were originally submitted to the IRB for initial approval?
    - For example, if the IRB approval process did not include the methods by which monitoring was conducted (i.e., moving from site monitoring to remote monitoring), then making a change does not affect the IRB approval. Contact your IRB for guidance.

2. Changes to Research Made in Response to COVID-19
    - Some IRBs have received questions from several research sponsors about the appropriate process for making changes to clinical studies in response to the current COVID-19 pandemic. These changes may include things like:
        - Changing the mode of administration for PRO/observer-reported outcome (ObsRO) measures
        - Replacing protocol-mandated visits to healthcare facilities with home visits or telemedicine
        - Shipping investigational products directly to research patients
    - We want to provide information on the requirement for IRB review of changes in research made in response to this situation. FDA regulations require that:
        - 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).

What do you need to report to the IRB? Continued

3. If a sponsor or investigator needs to make a change to research plans in order to eliminate apparent immediate hazards to research patients, these changes can be made and then reported to the IRB per their reporting policies (e.g., WIRB-Copernicus IRB policy is within 5 days). Eliminating immediate hazards may include actions to reduce potential exposure to COVID-19, such as, changing mode of ePRO administration. Some IRBs encourage sponsors and investigators to take such steps as necessary to eliminate apparent immediate additional risks to patients.
4. The notification to the IRB may be a full protocol amendment, but it does not have to be. The notification of the change in research (CIR) plans may also be a memo, letter, or other document that explains the changes being made, and provides enough information for the IRB to assess the relative risks resulting from the changes. The amendment or CIR document will proceed through IRB review as per the usual process.
5. To make the process of defining and submitting COVID-19-related changes in research as easy as possible, check with your IRB to determine if there are special forms to use.
6. As an alternative to changes to research, consider whether they are protocol deviations. If so, follow the IRB's policy for reporting protocol deviations.

Risk Assessment and Mitigation Strategies

- The following template provides a mechanism for identifying the risks and impacts of COVID-19 to current projects. Awareness and/or mitigation strategies are also provided for each scenario.
- Project Impact Tracking (to be completed by each eCOA provider):
  - High – high probability of additional issues occurring
  - Moderate – medium probability of additional issues occurring
  - Low – low probability of additional issues occurring
- The template is also embedded here for download >> 

Disclaimer: The material in the table is not necessarily presented in order of priority.

Risk and Mitigation Template (1 of 3)

Risk	Project Impact	Awareness and/or Mitigation
Risk of COVID-19 contamination: • Patients • Devices • Adapters • Shipments • Returns		• Refer to provider's internal disinfection policies and guidance provided by CDC and WHO • Must ensure all devices and accessories are disinfected when packing for shipment to sites and/or patients • Must disinfect device and accessories when returned to eCOA provider • Warning to recipient to disinfect cardboard/paper packages when received or not touch package for certain amount of time (24 hours for cardboard) to prevent possible exposure
Provisioned Model (Tablet): If solution is for site-based data collection and site does not want to use one tablet for all patients due to risk of contamination/virus spread.		• Web-based backup solutions • BYOD • In-person administration to paper backup • In-person administration to tablet • Paper backup • Refer to provider's internal disinfection policies and guidance provided by CDC and WHO
Provisioned Model (Tablet): If study sites are closing and patients cannot go to clinical site for completion of site-based assessments OR patient cannot travel to the clinical sites.		• Web-based backup solutions • BYOD • Telephone/Interview • Paper backup via mail (includes printing and sending screenshots for completion)
Provisioned Model (eDiary): If patient's eDiary is lost, broken, or stolen, how does the eCOA provider replace the device.		• Plan for remote shipping departments so eDiaries can be replaced and sent directly to patient's preferred address (home or elsewhere).

Risk and Mitigation Template (2 of 3)

Risk	Project Impact	Awareness and/or Mitigation
Interruption of internet services due to overload		• Provisioned model: Retains data until device is able to transmit to central database. • Web-based model: Saves data as it is entered in case of system overload. • BYOD model: Retains data on device until device is able to transmit to central database. • Any functionality that relies on an active internet connection (e.g., calculations or installing apps) will not be available.
Interruption of cellular networks due to overload		• Provisioned model: Retains data until device is able to transmit to central database. • Web-based model: Saves data as it is entered in case of system overload. • BYOD model: Retains data on device until device is able to transmit to central database. • Any functionality that relies on an active cellular connection (e.g., calculations or installing apps) will not be available.
Recruitment efforts and screening of patients		• If studies rely on calculations on the site-based device to determine screen-fail or randomization, need to ensure this screening activity is handled if not using site-based device.
Contractual services interrupted		• eCOA provider manages with each sponsor/contract research organization (CRO) depending on services.

Risk and Mitigation Template (3 of 3)

Risk	Project Impact	Awareness and/or Mitigation
Options for back-up system		• Web-based solution • BYOD • Telephone administration and entry into the tablet at site • Telephone administration, collection to paper and entry via data change form (DCF) • Paper backup option (not ideal) • IVRS (for assessments with 8 or less questions) • Video conferencing • Visiting patients at home
Missingness of data could vary by mode		• When migrating to a different mode, reconsider the risks of missing data and try match original implementation aimed at avoiding missing data. • Web-based systems: Edit checks must be performed to ensure that questions were not skipped, accidentally, if this solution is offered as a backup to provisioned model. • Paper backup option: Must ensure patient does not skip questions.
eCOA providers' internal systems having interruption of services		• Refer to eCOA providers' business continuity plan.

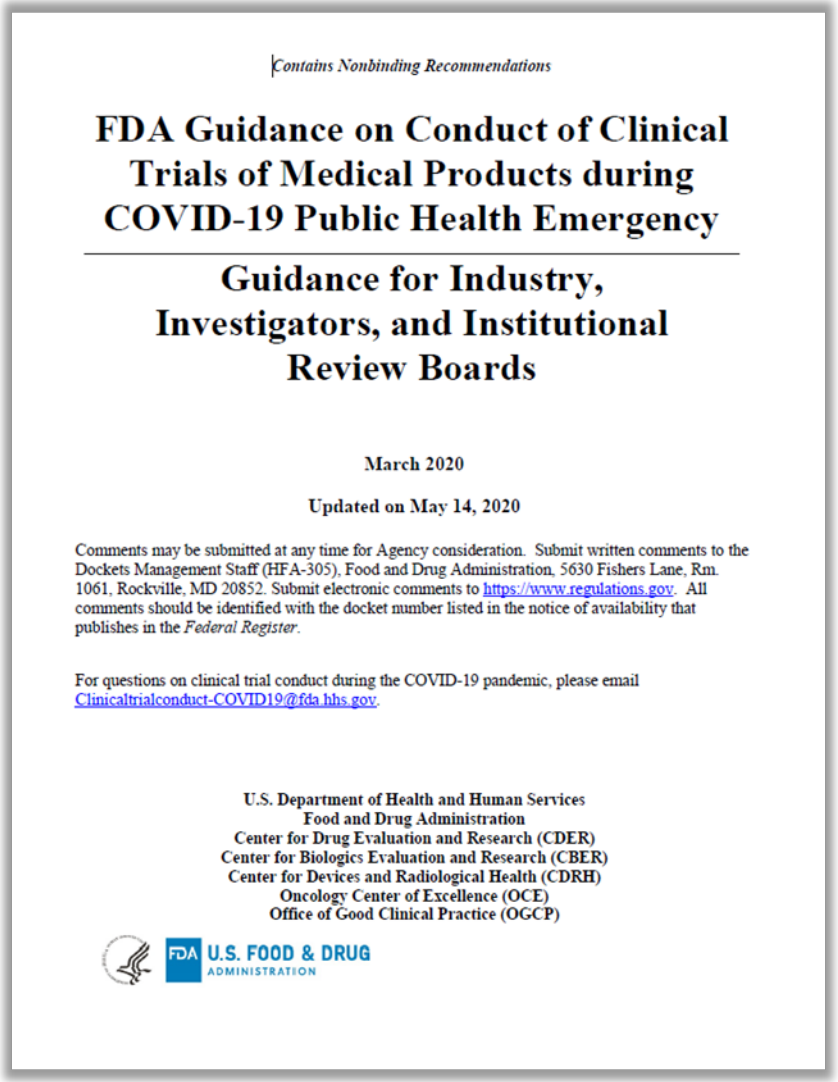
Regulatory Considerations

- Ensuring patient safety is paramount
  - Consider each decision to modify trial procedures in terms of how it affects patient safety
  - Consult with investigators and IRBs
  - Inform patients of procedural changes
- COVID-19-related procedural changes must be documented in the Clinical Study Report, reported to IRB and updated in IND
  - Prospective reporting is preferred, but changes made immediately to ensure patient safety may be reported retrospectively:
    - Duration of those changes
    - Which patients were impacted
    - How those patients were impacted
- FDA has indicated that for a study-wide change in protocol conduct, protocol amendments that are necessary to prevent imminent hazards to patients can generally be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND or IDE.

Regulatory Considerations - Continued

"To facilitate FDA's review of the data, …investigators should document, and sponsors should report in the clinical trial datasets, whether the assessment was conducted in-person or remotely (including the type of technology used), as well as the date of the assessment and the person conducting the assessment."

ePRO Consortium and PRO Consortium recommend documenting whether the patient was impacted by COVID-19 and if so, what mode of administration was used to collect the source data. This will ensure transparency and facilitate sensitivity analyses that may be required.



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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)

FDA U.S. FOOD & DRUG ADMINISTRATION

Resources

- EMA COVID-19 Guidance
- FDA COVID-19 Guidance
- MHRA COVID-19 Guidance
- PMDA COVID-19 Guidance
- WCG IRB COVID-19 Guidance
- CDC Public Resources
- WHO Public Advice