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

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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, 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).

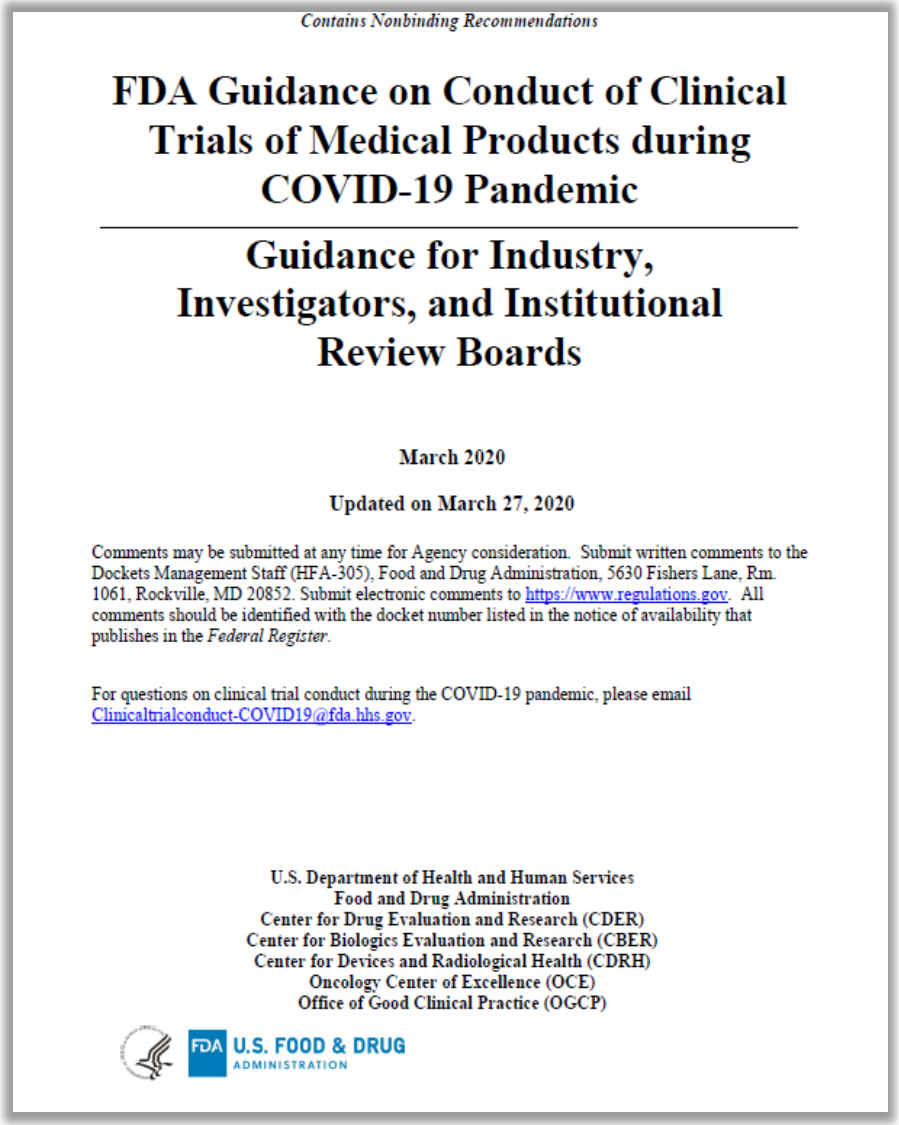
- In this challenging environment, it is unrealistic to expect perfection; in many cases, some data will be better than no data.

- 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 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.

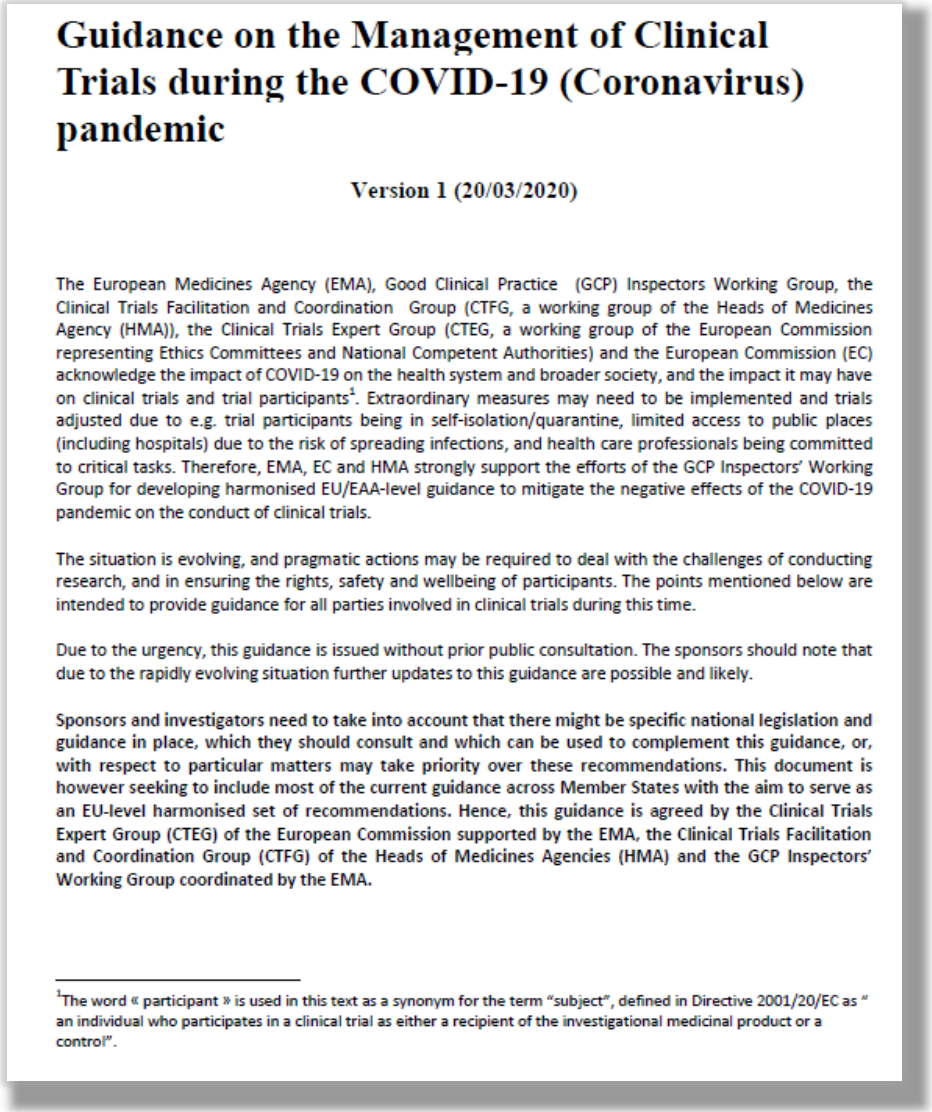
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

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.



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

Version 1 (20/03/2020)

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[1]. 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 harmonised EU/EAA-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.

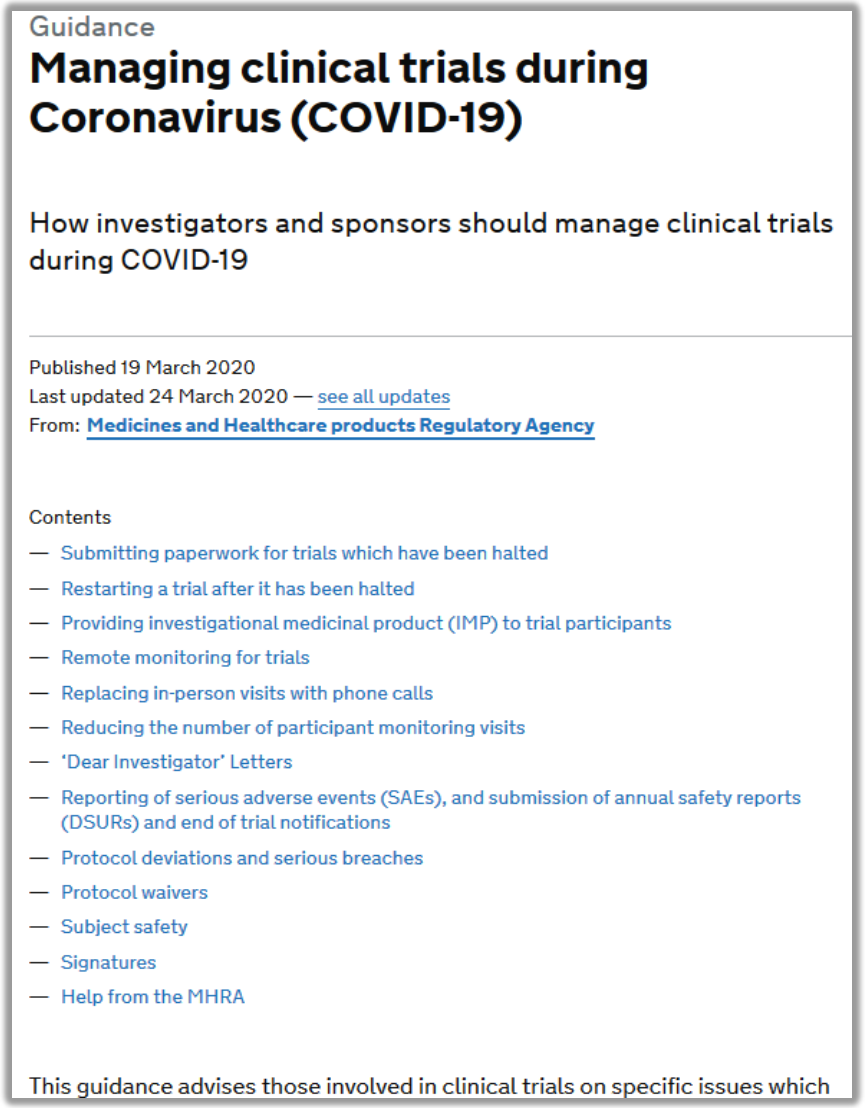
Sponsors and investigators need to take into account that there might be specific national legislation and guidance in place, which they should consult and which can be used to complement this guidance, or, with respect to particular matters may take priority over these recommendations. This document 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.

[1]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 either a recipient of the investigational medicinal product or a control".

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 24 March 2020 — see all updates
From: Medicines and Healthcare products Regulatory Agency

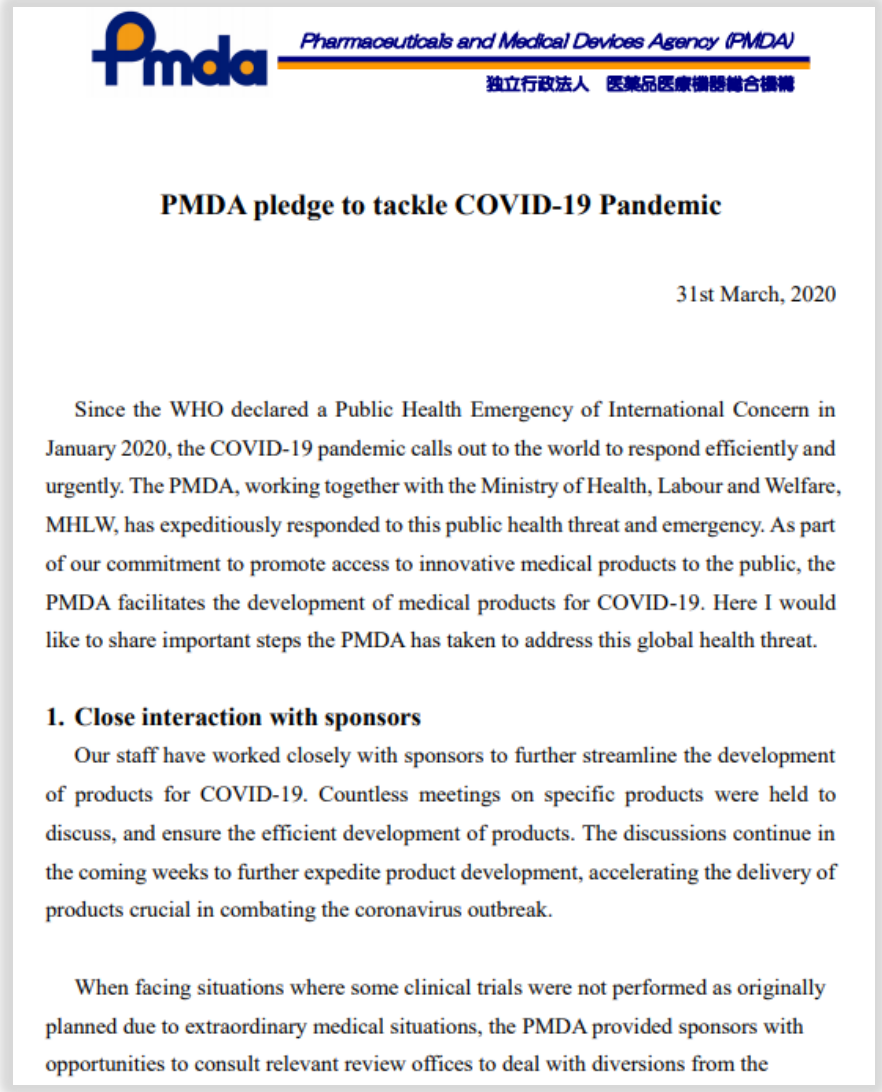
Contents

This guidance advises those involved in clinical trials on specific issues which

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

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?

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.

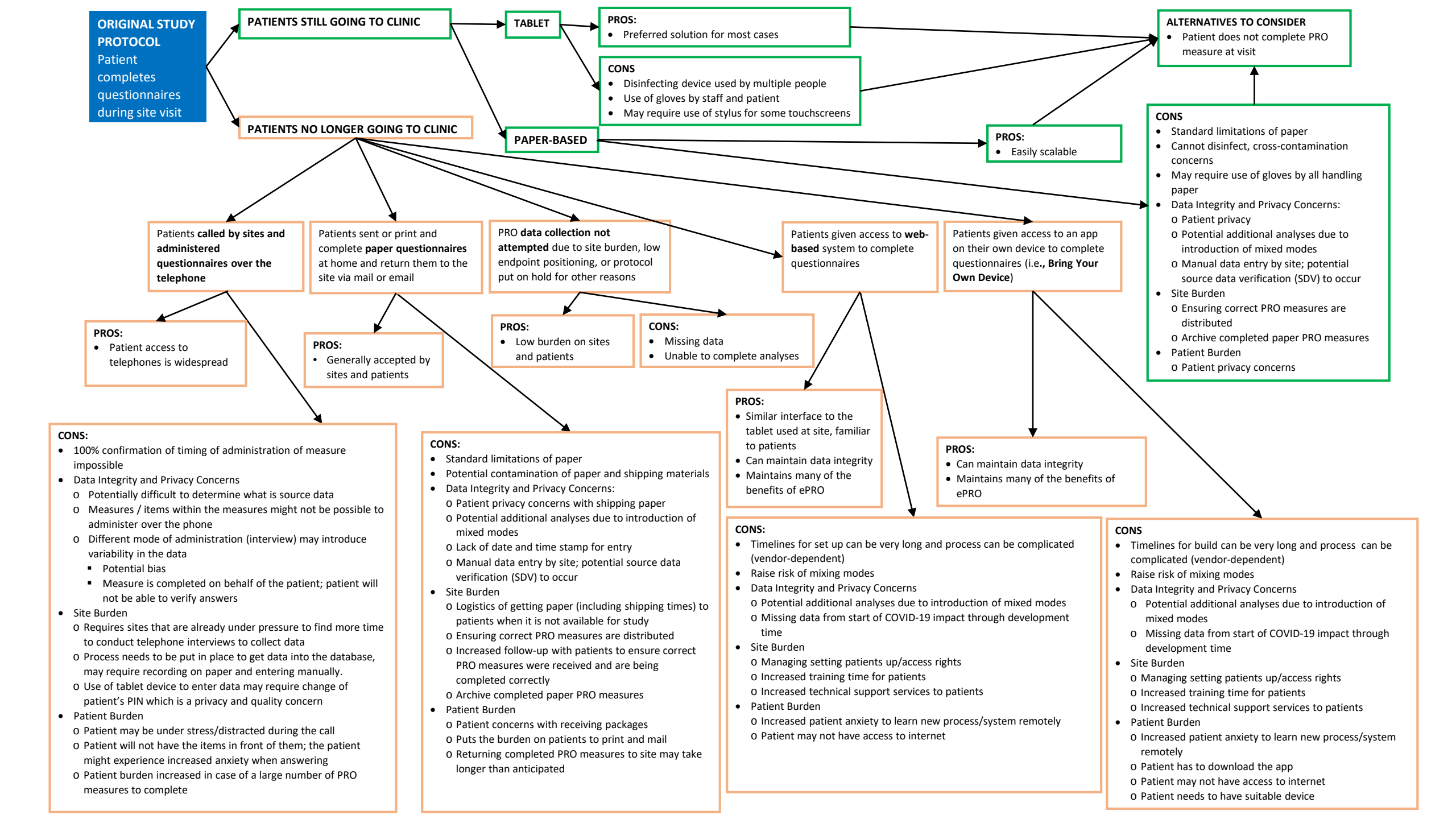
5. To make the process of defining and submitting COVID-19-related changes in research as easy as possible, check with your IRB to determine if there are special forms to use.

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.

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 in the diagram is not necessarily presented 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
Cannot disinfect, cross-contamination concerns
May require use of gloves by all handling paper
Data Integrity and Privacy Concerns:
o Patient privacy
o Potential additional analyses due to introduction of mixed modes
o Manual data entry by site; potential source data verification (SDV) to occur
Site Burden
o Ensuring correct PRO measures are distributed
o Archive completed paper PRO measures
Patient Burden
o Patient privacy concerns
Patients called by sites and administered questionnaires over the telephone
Patients sent or print and complete paper questionnaires at home and return them to the site via mail or email
PRO data collection not attempted due to site burden, low endpoint positioning, or protocol put on hold for other reasons
Patients given access to web-based system to complete questionnaires
Patients given access to an app on their own device to complete questionnaires (i.e., Bring Your Own Device)
PROS:
Patient access to telephones is widespread
PROS:
Generally accepted by sites and patients
PROS:
Low burden on sites and patients
CONS:
Missing data
Unable to complete analyses
PROS:
Similar interface to the tablet used at site, familiar to patients
Can maintain data integrity
Maintains many of the benefits of ePRO
PROS:
Can maintain data integrity
Maintains many of the benefits of ePRO
CONS:
100% confirmation of timing of administration of measure impossible
Data Integrity and Privacy Concerns
o Potentially difficult to determine what is source data
o Measures / items within the measures might not be possible to administer over the phone
o Different mode of administration (interview) may introduce variability in the data
Potential bias
Measure is completed on behalf of the patient; patient will not be able to verify answers
Site Burden
o Requires sites that are already under pressure to find more time to conduct telephone interviews to collect data
o Process needs to be put in place to get data into the database, may require recording on paper and entering manually.
o Use of tablet device to enter data may require change of patient's PIN which is a privacy and quality concern
Patient Burden
o Patient may be under stress/distracted during the call
o Patient will not have the items in front of them; the patient might experience increased anxiety when answering
o Patient burden increased in case of a large number of PRO measures to complete
CONS:
Standard limitations of paper
Potential contamination of paper and shipping materials
Data Integrity and Privacy Concerns:
o Patient privacy concerns with shipping paper
o Potential additional analyses due to introduction of mixed modes
o Lack of date and time stamp for entry
o Manual data entry by site; potential source data verification (SDV) to occur
Site Burden
o Logistics of getting paper (including shipping times) to patients when it is not available for study
o Ensuring correct PRO measures are distributed
o Increased follow-up with patients to ensure correct PRO measures were received and are being completed correctly
o Archive completed paper PRO measures
Patient Burden
o Patient concerns with receiving packages
o Puts the burden on patients to print and mail
o Returning completed PRO measures to site may take longer than anticipated
CONS:
Timelines for set up can be very long and process can be complicated (vendor-dependent)
Raise risk of mixing modes
Data Integrity and Privacy Concerns
o Potential additional analyses due to introduction of mixed modes
o Missing data from start of COVID-19 impact through development time
Site Burden
o Managing setting patients up/access rights
o Increased training time for patients
o Increased technical support services to patients
Patient Burden
o Increased patient anxiety to learn new process/system remotely
o Patient may not have access to internet
CONS
Timelines for build can be very long and process can be complicated (vendor-dependent)
Raise risk of mixing modes
Data Integrity and Privacy Concerns
o Potential additional analyses due to introduction of mixed modes
o Missing data from start of COVID-19 impact through development time
Site Burden
o Managing setting patients up/access rights
o Increased training time for patients
o Increased technical support services to patients
Patient Burden
o Increased patient anxiety to learn new process/system remotely
o Patient has to download the app
o Patient may not have access to internet
o Patient needs to have suitable device

Other Considerations

- We recommend a study-level approach (i.e., the same solution implemented for all sites across a study) but recognize some sites may need accommodation.
- Applicable solutions may depend on the endpoint hierarchy, trial phase, 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.
- Other possible solutions that have unique challenges:
  - Interactive voice response system (IVRS)
  - Telehealth/video conferencing
  - Home health visit/direct to patient

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 template 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
- 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.
- 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

Resources

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