Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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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)

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Table of Contents

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Guidance for Industry[1]

I. INTRODUCTION

This guidance provides sponsors and investigators with considerations for approaches on how common symptoms related to the Coronavirus Disease 2019 (COVID-19) can be measured and analyzed in clinical trials evaluating drugs or biological products[2] for the prevention or treatment of COVID-19 in outpatient adult and adolescent[3] subjects.[4] This guidance is not intended for development programs evaluating products to treat or prevent postinfectious COVID-19 conditions (e.g., long COVID, multisystem inflammatory syndrome) in children and adults, or development programs for preventative vaccines. This guidance does not address considerations for clinical trial design other than those pertaining to the measurement and analysis of COVID-19-related symptoms among outpatients. Considerations for patients with COVID-19 who require hospitalization are out of scope for this guidance.

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see 21 CFR 10.115(g)(2)

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] For the purposes of this guidance, adolescents are defined as 12 years of age to younger than 18 years of age.

[4] For treatment trials, sponsors should document diagnosis of laboratory-confirmed SARS-CoV-2, as well as the duration of symptoms before treatment. Sponsors of clinical trials to evaluate drugs and biological products to treat or prevent COVID-19 should see the guidance for industry, investigators, and institutional review boards *Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due To Disasters and Public Health Emergencies* (September 2023) and the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (November 2023). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

and (g)(3). FDA made this determination because although the COVID-19-related public health emergency under section 319 of the Public Health Services Act has expired, SARS-CoV-2 continues to circulate, COVID-19 remains a serious health risk for some individuals, and there is a need to ensure that sponsors are aware of FDA's recommendations to facilitate timely development of drugs and biological products for treatment and prevention of COVID-19. This guidance supersedes the guidance of the same name issued on September 29, 2020.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Sponsors continue to conduct outpatient prevention or treatment clinical trials in adult and adolescent subjects that incorporate assessments of COVID-19-related symptoms; however, challenges persist. These challenges include but are not limited to the identification of methods to assess the numerous and heterogenous symptoms across subjects, patient burden, poor compliance with diary completion, and potential missing data. To address these challenges, sponsors should identify key common symptoms for daily assessments based on the program-specific context of use (e.g., target population, mechanism of action of the investigational product, underlying pathophysiology of COVID-19, symptomatology associated with the currently circulating variants) to optimize the measurement strategy for symptoms most likely to change while lessening the burden on trial subjects.[5] To assist sponsors, this guidance provides an exemplary set of common COVID-19-related symptoms as well as an approach to their measurement for use in clinical trials (see Table 1). The symptom items are derived from existing literature, the Centers for Disease Control and Prevention (CDC),[6] and clinical research.

[5] See the FDA Patient-Focused Drug Development (PFDD) Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making, available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical. The guidance series is part of FDA's PFDD efforts in accordance with the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act of 2017 Title I. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. When final, the PFDD guidance series will replace the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

[6] For detailed information, see the CDC's COVID-19 Symptoms of Coronavirus web page, available at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fabout%2Fsymptoms.html.

III. DISCUSSION

A. General Recommendations

FDA recommends the following for sponsors initiating clinical trials evaluating drugs for the prevention or treatment of COVID-19 in outpatient adult and adolescent subjects:

- Use patient-reported outcome (PRO) instruments[7] to assess COVID-19-related symptoms; the use of PRO instruments is advised when measuring signs and symptoms best known by the patient or best measured from the patient perspective.

- Consult with the appropriate FDA review division regarding PRO instruments proposed for use.

- Conduct PRO assessments of COVID-19-related symptoms at least every 24 hours and conduct assessments at the same time each day.

- Use electronic data collection systems with reminders to trial subjects to complete the PRO instrument to minimize missing data and provide time stamps of completion. Alternatively, if a paper-based diary is used, sponsors should send reminders (e.g., phone calls, text messages, email) to trial subjects.

- Include a set of common COVID-19-related symptoms (for an example, see Table 1) in the daily PRO assessments of all trial subjects regardless of which symptoms a subject had at baseline, as new symptoms may appear following the baseline assessment.

- Consider whether a comprehensive set of COVID-19-related symptoms, beyond the set of common COVID-19-related symptoms assessed in the daily PRO instrument, is useful when collected at study baseline and again at landmark time points[8] and also whether a transition to weekly PRO assessments later in the study period would be useful, depending on the program-specific context of use (e.g., study duration).

[7] See the FDA PFDD Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making, available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[8] Landmark times are predefined fixed time points after baseline.

- Conduct an evaluation to ensure the PRO instrument's comprehensibility and usability before implementation in a trial to mitigate the risk of poor instrument performance.[9,10] Such an evaluation should be conducted even if the sponsor chooses to use an approach similar to the example approach shown in Table 1.

B. Example Assessment of Key COVID-19-Related Symptoms

Given the heterogeneous nature of COVID-19-related symptoms, key COVID-19-related symptoms should be assessed systematically to provide an accurate evaluation of benefit in outpatients. In this guidance we provide an exemplary set of 14 common COVID-19-related symptoms to consider in Table 1 (as described below). Although we recommend assessing these items to capture change in common COVID-19-related symptoms (e.g., emergence, improvement, or worsening) during the clinical trials, a subset of key COVID-19-related symptoms can be used to derive symptom-based efficacy endpoints. Determination of which subset to investigate will depend on what aspect(s) of the condition the study drug is expected to improve as well as symptomatology associated with the currently circulating COVID-19 variant(s) of concern. The final assessment plan should be informed by qualitative evidence from patient interviews and/or the literature.

- In the example in Table 1, the following applies for rating each symptom:
  - Items 1 to 10, 13, and 14: Trial subjects rate symptom severity at its worst over a specified recall period (e.g., 24 hours) using a verbal rating scale for severity.
  - Items 11 (vomiting) and 12 (diarrhea) are each recorded promptly after a vomiting or diarrhea episode occurs.
- In the example in Table 1, there is no total score. Each symptom is scored individually using the following response options and/or scoring values:
  - Items 1 to 10: None = 0, Mild = 1, Moderate = 2, and Severe = 3.
  - Items 11 and 12: Record the time of event occurrence.
  - Items 13 and 14: Sense of smell/taste same as usual = 0, Sense of smell/taste less than usual = 1, No sense of smell/taste = 2.

[9] See the guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (February 2022).

[10] See the draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* (June 2022). When final, this guidance will represent the FDA's current thinking on this topic.

Table 1. Example Assessment of 14 Common COVID-19-Related Symptoms: Sample of Items and Response Options

Example of items *For items 1–10, sample item wording could be "What was the severity of your [**insert symptom**] at its worst over the past 24 hours?"*	**Example of response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. If you had vomiting (throwing up)**	Record each episode of vomiting

Example of items *For items 1–10, sample item wording could be "What was the severity of your [**insert symptom**] at its worst over the past 24 hours?"*	**Example of response options and scoring***
12. If you had diarrhea (loose or watery stools) **	Record each episode of diarrhea
13. Rate your sense of **smell** in the past **24 hours**†	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of **taste** in the past **24 hours**†	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the verbal rating scale response options presented to trial subjects because these values may distract subjects with unnecessary information.

** The statements shown for items 11 and 12 are intended for documentation in real-time. For frequent events or episodes, the sponsor should consider an event-driven electronic diary rather than a diary completed once daily with a 24-hour recall.[11]

† In lieu of items 13 and 14, sponsors may include optional questions on severity of loss and/or alteration of smell/taste based on the program-specific context of use. The item descriptions should include sufficient detail for the respondent to understand the concept being asked (e.g., loss of smell versus parosmia and/or phantosmia-like alteration of smell). The same recommendation applies to item 14. Understandability of the response options should be supported by qualitative evidence from patient interviews and/or the literature.

- Sponsors can consider using alternative items and response options for assessment of common COVID-19-related symptoms. For example, a sponsor can consider using a 4-point (none/mild/moderate/severe) or binary response (yes/no) scale for assessment of patient-reported loss and/or alteration of smell and taste; vomiting and diarrhea might also be rated on a verbal rating frequency scale with a 24-hour recall period.

[11] See the draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making* (April 2023). When final, this guidance will represent the FDA's current thinking on this topic.

- According to the mechanism of action of the investigational product and the underlying pathophysiology of COVID-19, clinical manifestations of the currently circulating COVID-19 variant(s) of concern, and program-specific study design, sponsors can also assess additional emerging symptoms (e.g., cognitive dysfunction) if appropriate.

When designing and implementing PRO instruments, sponsors should consider the following recommendations:

- FDA recommends using response scales that include verbal descriptors (e.g., none, mild, moderate, severe) because the absence of verbal descriptors may create difficulty in interpretation. Accordingly, response scales such as visual analog scales and 0-to-10 numeric rating scales are not directly interpretable and may result in interpretation difficulties in this context.

- FDA recommends avoiding an excessively large number of items in the PRO instrument(s), which may lead to unnecessary patient burden, poor compliance with diary completion, and missing data.

C. Considerations for Outpatient Clinical Trial Endpoint Selection

1. Endpoint Selection

Sponsors should consider the following:

- The selection of time point(s) for clinical endpoint assessments in prevention or treatment trials in outpatient adult and adolescent subjects is dependent on up-to-date knowledge of the time course of COVID-19-related symptom onset or resolution. For example, clinical findings show that certain symptoms (e.g., cough, fatigue, or alterations in taste and smell) may take longer to resolve in comparison to other symptoms.[12,13] Furthermore, the CDC has reported findings of COVID-19 rebound, which may be part of the natural history of SARS-CoV-2 infection in some individuals. The rebound included a recurrence of COVID-19 symptoms, but the severity of the illness was mild.[14]

[12] Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, Huet K, Plzak J, Horoi M, Hans S, Barillari MR, Cammaroto G, Fakhry N, Martiny D, Ayad T, Jouffe L, Hopkins C, and Saussez S, 2020, Clinical and Epidemiological Characteristics of 1420 European Patients With Mild-to-Moderate Coronavirus Disease 2019, J Intern Med, 288(3):335–344.

[13] Boscolo-Rizzo P, Borsetto D, Fabbris C, Spinato G, Frezza D, Menegaldo A, Mularoni F, Gaudioso P, Cazzador D, Marciani S, Frasconi S, Ferraro M, Berro C, Varago C, Micolai P, Tirelli G, Da Mosto MC, Obholzer R, Rigoli R, Polesel J, and Hopkins C, 2020, Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19, JAMA Otolaryngol Head Neck Surg, 146(8):729–732.

[14] See the CDC Health Alert Network's Covid 19 Rebound After Paxlovid Treatment, available at https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_467.pdf.

- Sponsors can use early phase trials in the target patient population to examine the effect of an investigational drug on the time course of symptoms to inform endpoint development for pivotal trials. Sponsors can consider a variety of endpoint definitions to evaluate the effect of a drug on common COVID-19-related symptoms.

- FDA encourages sponsors to provide a rationale to support their proposed endpoints, taking into account relevant information from literature sources and any relevant clinical trials.

2. Trials of Drugs for Treatment of COVID-19

Sponsors should consider the following:

- As described in the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention*, an appropriate endpoint could be the time to sustained symptom alleviation or resolution assessed over an appropriate duration.

- Sustained symptom alleviation or resolution can be defined as occurring when no key COVID-19-related symptom scored higher than a prespecified threshold over a clinically meaningful time period (as documented using a PRO instrument).

- To evaluate clinical benefit, sponsors should include trial entry criteria defining the minimal baseline severity score for COVID-19-related symptoms (e.g., at least two symptoms with a score of 2 or higher using the scoring system shown in Table 1[15]).

FDA does not recommend the following:

- Defining endpoints based on adding scores of the items within a set of common COVID-19-related symptoms to form an aggregate score. Given the heterogeneity of COVID-19-related symptoms, any single trial subject may only experience a small subset of the common COVID-19-related symptoms described in this guidance.

- Calculating an area under the curve of COVID-19-related symptoms, as this metric is not easily interpretable in this context of use.

3. Trials of Drugs for Prevention of COVID-19

Sponsors should consider the following:

- As described in the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention*, there is interest in ascertaining whether the severity of COVID-19-related symptoms is milder in trial subjects receiving prophylaxis compared with subjects not receiving prophylaxis.

[15] Note that the example relates to the items using verbal rating scale. For event-driven symptoms, consider a baseline threshold frequency to reflect moderate to severe severity in the target patient population.

- Sponsors should collect data on COVID-19-related symptoms and other endpoints to characterize levels of severity for prevention trials.[16] Sponsors can consider using the set of 14 common COVID-19-related symptoms, as described in Table 1, in such data collection.

D. Handling Data

Sponsors developing drugs for the prevention or treatment of COVID-19 and investigators conducting related clinical trials should consider the following regarding missing data and other related issues for clinical trials:

- Sponsors and investigators should make efforts to minimize the amount of missing data. These efforts should generally include providing reminders (e.g., phone calls, text messages, email) to trial subjects to complete PRO instruments, monitoring adherence with PRO instrument completion throughout the assessment period, following up with trial subjects who are not successfully completing PRO instruments (and, where permissible, close contacts if the trial subject is not responding), supplemental training of trial subjects, and recording verbal responses for those who are unable to self-record because of illness or other circumstances. FDA recommends obtaining contact information for close contacts of trial subjects for use in case of nonresponse. If the investigator or a member of the study team plans to contact a family member or other close contact when subjects do not respond to follow-up, this should be described in the informed consent document approved by the institutional review board. The reasons for missing data should be documented. We recommend employing risk-based approaches, including centralized monitoring in clinical trials, to ensure data quality and integrity.[17]

- The informed consent process[18] and informed consent document should include information to educate prospective subjects about the continued scientific importance of their follow-up data even if they choose to discontinue treatment.

- The sponsor should prospectively plan appropriate methods for handling missing data in the development of endpoints and conduct of analyses, considering the reason for the

[16] See the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention*.

[17] For additional information, see the guidance for industry *A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers* (April 2023).

[18] For information about the informed consent process, see FDA's proposed recommendations in the guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (August 2023). For information about use of electronic systems and processes that may employ multiple electronic media to obtain informed consent, see the guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (December 2016). See also the guidance for industry, investigators, and institutional review boards *Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due To Disasters and Public Health Emergencies,* and the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention*.

missing data.[19] Sensitivity analyses considering different approaches to account for the missing data should be specified in the statistical analysis plan.[20]

- Sponsors should prospectively specify how intercurrent events, including hospitalization and death, will be handled in the statistical analysis.

- The aim should be to ascertain vital status for all COVID-19 trial subjects even after a subject decides to discontinue treatment or discontinue participation in the trial, including follow-up for key outcomes, while adhering to informed consent requirements.[21]

E. Additional COVID-19-Related Assessments

In addition to assessment of key COVID-19-related symptoms, such as by using the assessments provided as an example in Table 1, FDA recommends that sponsors standardize the collection and reporting of other clinical trial assessments for trial subjects. Additional assessments and their associated methods that sponsors can consider include the following:

- Use of any medications to treat some of the COVID-19-related symptoms (e.g., analgesics, antipyretics): The name of medication, dose, dosage form, and date and time(s) of administration should be reported.

- Body temperature: The timing and the route of the body temperature assessment method (e.g., oral) should be specified in the protocol, and sponsors should provide thermometers to trial subjects.

- Oxygen saturation: Pulse oximetry data should be collected, and the sponsor should provide that equipment and provide training or instruction on its use to subjects.

- Patient-reported global impression items assessing a) return to usual health, b) return to usual activities, c) overall COVID-19-related symptoms, and d) cluster of COVID-19-related symptom (e.g., respiratory, digestive): examples of patient-reported global impression item(s) can include the following:

[19] For additional information, see the draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making.*

[20] For additional information on sensitivity analysis, see the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[21] For example, if a subject withdraws from the interventional portion of a clinical investigation and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access the subject's medical record or other confidential records that would require additional consent from the subject to obtain the continued follow-up information (21 CFR 50.20 and 50.25(a)(1)). However, an investigator may consult publicly available sources of information to determine a subject's vital status after a subject withdraws from a clinical trial.

- In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? Yes or No

- In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? Yes or No

- In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst? None, Mild, Moderate, or Severe

- In the past 24 hours, what was the severity of your (cluster name: e.g., respiratory) COVID-19-related symptoms at their worst? None, Mild, Moderate, or Severe

Further considerations include the frequency of patient-reported global impression items which may be less frequent (i.e., weekly) with differing recall periods including now, past 24 hours, or past week depending on the intent of the assessment.