
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

**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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Clinical/Medical**

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Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

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 FDA-2020-D-1824 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA web page titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders> and the FDA web page titled "Search for FDA Guidance Documents," *available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. You may also send an e-mail request to COVID19-productdevelopment@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1824 and complete title of the guidance in the request.

Questions

For questions about this document, contact (CDER) Elektra Papadopoulos at 301-796-0967 or email elektra.papadopoulos@fda.hhs.gov; or (CBER) Office of Communication, Outreach, and Development at 1-800-835-4709 or 240-402-8010 or email ocod@fda.hhs.gov.

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**Assessing COVID-19-Related Symptoms
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Guidance for Industry¹**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide sponsors and investigators with considerations for approaches on how common COVID-19-related symptoms can be measured and analyzed in clinical trials evaluating drugs or biological products² for the prevention or treatment of COVID-19 in outpatient adult and adolescent³ subjects.⁴ This guidance is not intended for development programs evaluating products to treat or prevent postinfectious COVID-19 conditions such as multisystem inflammatory syndrome in children or to 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.

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 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 *FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency* (March 2020, updated July 2020) and the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (May 2020). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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This guidance is intended to remain in effect for the duration of the public health emergency related to COVID-19 declared by the Department of Health and Human Services (HHS), including any renewals made by the Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)). However, the recommendations and processes described in the guidance are expected to assist the Agency more broadly in its efforts to provide sponsors with considerations for the measurement and analysis of COVID-19-related symptoms in clinical trials evaluating drugs to prevent or treat COVID-19 in outpatient adult and adolescent subjects beyond the termination of the COVID-19 public health emergency and reflect the Agency's current thinking on this issue. Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

Given this public health emergency, and as discussed in the Notice in the Federal Register of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents, including this guidance, 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

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named *SARS-CoV-2* and the disease it causes has been named *Coronavirus Disease 2019 (COVID-19)*. On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.⁵ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.⁶

Sponsors may encounter challenges in identifying methods to assess the numerous and heterogeneous COVID-19-related symptoms across subjects when designing clinical trials of

⁵ Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 2020, and July 23, 2020), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

⁶ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

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drugs to treat or prevent COVID-19 in adult and adolescent outpatient subjects. In many instances, daily assessment of all COVID-19-related symptoms may not be feasible. Sponsors should identify a minimum number of key symptoms for daily assessments to lessen burden on trial subjects. To assist sponsors, this guidance provides an example with a set of common COVID-19-related symptoms as well as an approach to their measurement for use in clinical trials. The symptom items used in the example are derived from information provided by the Centers for Disease Control and Prevention (CDC)⁷ as of August 28, 2020.

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) instruments⁸ 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.
- Conduct an evaluation to ensure the PRO instrument's basic comprehensibility and usability before implementation in a trial to mitigate risk of poor instrument performance.

⁷ 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.

⁸ For detailed information on the use of PRO instruments intended to support labeling claims, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

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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 of an Assessment of Key COVID-19-Related Symptoms

Given the heterogeneous nature of COVID-19-related symptoms in outpatients, key COVID-19-related symptoms should be assessed systematically to provide an accurate evaluation of benefit. We provide one option to consider in Table 1 of this guidance, which summarizes (as described below) how a set of 14 common COVID-19-related symptoms can be assessed.

- In the example in Table 1, the following applies for rating each symptom:
 - Items 1–10, trial subjects rate symptom severity at its worst over a specified recall period (e.g., 12 or 24 hours) using a 4-point scale for severity.
 - Items 11 (vomiting) and 12 (diarrhea) are each rated on a 4-point frequency scale.
 - Items 13 (sense of smell) and 14 (sense of taste) are each rated on a 3-point scale.
- In the example in Table 1, there is no total score. Each symptom is scored individually using the following response options and scoring values:
 - Items 1–10: None = 0; Mild = 1; Moderate = 2; and Severe = 3
 - Items 11 and 12: Not at all = 0; 1–2 times = 1; 3–4 times = 2; 5 or more times = 3
 - 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

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

Example items	Example response options and scoring*
<p><i>For items 1–10, sample item wording could be: “What was the severity of your [insert symptom] at its worst over the last 24 hours?”</i></p>	
1. Stuffy or runny nose	<p>None = 0</p> <p>Mild = 1</p> <p>Moderate = 2</p> <p>Severe = 3</p>
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. How many times did you vomit (throw up) in the last 24 hours ?**	<p>I did not vomit at all = 0</p> <p>1–2 times = 1</p> <p>3–4 times = 2</p> <p>5 or more times = 3</p>

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Table 1, continued

<p>12. How many times did you have diarrhea (loose or watery stools) in the last 24 hours?**</p>	<p>I did not have diarrhea at all = 0</p> <p>1–2 times = 1</p> <p>3–4 times = 2</p> <p>5 or more times = 3</p>
<p>13. Rate your sense of smell in the last 24 hours</p>	<p>My sense of smell is THE SAME AS usual = 0</p> <p>My sense of smell is LESS THAN usual = 1</p> <p>I have NO sense of smell = 2</p>
<p>14. Rate your sense of taste in the last 24 hours</p>	<p>My sense of taste is THE SAME AS usual = 0</p> <p>My sense of taste is LESS THAN usual = 1</p> <p>I have NO sense of taste = 2</p>

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the response options presented to trial subjects to avoid confusing subjects.

** The response options shown for items 11 and 12 are intended only for use with a 24-hour recall period.

- 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 binary response scale for assessment of patient-reported alteration of taste and smell; vomiting and diarrhea might also be assessed by asking a trial subject to rate the symptom severity at its worst, similar to items 1–10 in Table 1. Sponsors can also consider including additional symptoms, 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 in this context of use. Accordingly, using response scales such as visual analogue scales and 0–10 numeric rating scales may result in interpretation difficulties in this context.

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- FDA recommends avoiding an excessively large number of items in the PRO instrument(s), which can result in subject burden 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 knowledge of the time course of COVID-19-related symptom onset or resolution, which is still evolving. For example, clinical findings show that certain symptoms (e.g., cough, fatigue, decreased sense of taste and sense of smell) may take longer to resolve in comparison to other symptoms.^{9, 10}
- Sponsors can use early phase trials to examine the effect of an investigational drug on the time course of symptoms to inform endpoint development for confirmatory 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* (May 2020), an appropriate endpoint could be the time to sustained clinical recovery assessed over an appropriate duration.
- Sustained clinical recovery 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).

⁹ Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al., 2020, Clinical and Epidemiological Characteristics of 1,420 European Patients with Mild-to-Moderate Coronavirus Disease 2019, *J Intern Med*, epub ahead of print April 30, 2020, doi: 10.1111/joim.13089.

¹⁰ Boscolo-Rizzo P, Borsetto D, Fabbris C, et al., 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.

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- To accurately 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, with the exception of taste and smell where subjects may enter with a score of 1 or higher).
- Sponsors should define screening criteria that exclude trial subjects who require hospitalization.

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.
- Sponsors should collect data on COVID-19-related symptoms to define their levels of severity for prevention trials. 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 treatment or prevention of COVID-19 and investigators conducting related clinical trials should consider the following regarding missing data 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 compliance 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), 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

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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.

- The informed consent process¹¹ 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 analyses, considering the reason for the missing data.
- Sponsors should prospectively specify how 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.¹²

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.

¹¹ For information about the informed consent process, see FDA's proposed recommendations in the draft guidance for institutional review boards (IRBs), clinical investigators, and sponsors *Informed Consent Information Sheet* (July 2014). When final, this guidance will represent FDA's current thinking on this topic. For information about use of electronic systems and processes that may employ multiple electronic media to obtain informed consent, see the guidance for IRBs, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (December 2016). See also the guidance for industry, investigators, and institutional review boards *FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency* and the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention*.

¹² 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.

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- Body temperature: the timing and the route of 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 with specific equipment, and the sponsor should provide that equipment to subjects and provide training or instruction on its use.
- Patient-reported global impression items assessing a) return to usual health; b) return to usual activities; and c) overall COVID-19-related symptoms: examples of patient-reported global impression item(s) can include the following:
 - 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