COVID-19: Developing Drugs and Biological Products for Treatment or Prevention

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)

May 2020
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 the 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) 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-1370 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "Coronavirus Disease 2019 (COVID-19)," *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 webpage 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-1370 and complete title of the guidance in the request.

Questions

For questions about this document, contact Eithu Lwin, 301-796-0728, Eithu.Lwin@fda.hhs.gov.

Contains Nonbinding Recommendations

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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 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 assist sponsors in the clinical development of drugs[2] for the treatment or prevention of COVID-19. Preventative vaccines[3] and convalescent plasma[4] are not within the scope of this guidance.

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 HHS Secretary in accordance with section 319(a)(2) of the Public Health Service (PHS) Act. However, the recommendations described in the guidance are expected to assist the Agency more broadly in its continued efforts to assist sponsors in the clinical development of drugs for the treatment of COVID-19 beyond the termination of the

[1] This guidance has been prepared by the Office of New Drugs and the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) 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] Clinical trials of preventative vaccines raise different and additional considerations, including those pertaining to subject selection, safety monitoring, and effectiveness evaluation. We encourage developers of preventative vaccines to contact the Office of Vaccines Research and Review in CBER.

[4] FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma.

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 related to COVID-19 declared by HHS, 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 (FD&C Act) 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, effective January 27, 2020, 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]

COVID-19 can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death. The incubation period for SARS-CoV-2 is thought to be as long as 14 days, with a median time of 4 to 5 days from exposure to symptom onset.[7] There are currently no FDA-approved drugs to treat COVID-19. Clinical management includes symptomatic and supportive care, such as supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) when indicated.

[5] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 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 (March 13, 2020), available at https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

[7] See the Centers for Disease Control and Prevention Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.

This guidance describes FDA's current recommendations regarding phase 2 or phase 3 trials for drugs under development to treat or prevent COVID-19.[8] This guidance focuses on the population, trial design, efficacy endpoints, safety considerations, and statistical considerations for such clinical trials. This guidance does not provide general recommendations on early drug development in COVID-19, such as use of animal models. Drugs should have undergone sufficient development before their evaluation in phase 2 or phase 3. FDA is committed to supporting all scientifically sound approaches to attenuating the clinical impact of COVID-19. Sponsors engaged in the development of drugs for COVID-19 should also see the guidance for industry and investigators *COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products* (May 2020).[9]

This guidance focuses on the development of drugs with direct antiviral activity or immunomodulatory activity. However, the recommendations in this guidance may be applicable to development plans for drugs for COVID-19 with other mechanisms of action. The mechanism of action of the drug may impact key study design elements (e.g., population, endpoints, safety assessments, duration of follow-up). Additionally, for some biological products (e.g., cellular and gene therapies and blood products) there may be additional considerations and we encourage you to reach out to the applicable review division as appropriate.

III. DISCUSSION

A. Population

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- A range of populations is appropriate for evaluation and may include outpatient, inpatient, or inpatient on mechanical ventilation populations.

- For treatment trials, sponsors should document diagnosis of COVID-19. Laboratory-confirmed disease is preferred.

- For treatment trials, FDA recommends that sponsors categorize the baseline severity of the enrolled population. The criteria used to describe baseline severity should incorporate objective measures. Examples of severity criteria are provided in the Appendix.

- For prevention trials, sponsors should conduct trials in communities with documentation of circulating SARS-CoV-2 infection.[10] Populations including the following may be considered:

[8] Phase 2 and phase 3 trials need to be registered at www.ClinicalTrials.gov as required by 42 CFR part 11.

[9] 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/RegulatoryInformation/Guidances/default.htm.

[10] Subjects in prophylaxis trials may be either SARS-CoV-2 negative or have an unknown SARS-CoV-2 status.

105
106 – Pre-exposure prophylaxis trials in persons at high risk for SARS-CoV-2 exposure
107 with no symptoms (e.g., health care workers and first responders)
108
109 – Post-exposure prophylaxis trials in health care workers or household contacts with no
110 symptoms and with a documented exposure to a definite or clinically presumed case
111
112 • Given the expected fluctuation in regions in the frequency of SARS-CoV-2 infection,
113 sponsors should address the need to open new sites and potentially suspend existing sites.
114
115 • Clinical trials should include persons at high risk of complications such as the elderly,
116 persons with underlying cardiovascular or respiratory disease, diabetes, chronic kidney
117 disease, or other comorbidities, and immunocompromised persons (e.g., HIV-infected
118 patients, organ transplant recipients, or patients receiving cancer chemotherapy).[11]
119
120 • COVID-19 disproportionately affects adults, including older individuals. The geriatric
121 population should be appropriately represented in clinical trials.[12] Sponsors should
122 consider conducting trials in nursing homes or other elder care facilities.
123
124 • Racial and ethnic minority persons should be represented in clinical trials. Sponsors
125 should ensure that clinical trial sites include geographic locations with a higher
126 concentration of racial and ethnic minorities to recruit a diverse study population.[13]
127
128 • Patients with renal or hepatic impairment should be enrolled in clinical trials provided the
129 pharmacokinetics of the drug have been evaluated in these patients and appropriate
130 dosing regimens have been identified.
131
132 • The principles outlined in this document can be used to guide drug development for
133 children and pregnant and lactating individuals. There is a need to generate clinical trial
134 data to inform the use of drugs in these populations.
135

[11] See the Centers for Disease Control and Prevention Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html, and the web page Information for People who are at Higher Risk for Severe Illness, available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.

[12] See the draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Design* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic. 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.

[13] Ibid.

- FDA encourages the enrollment of pregnant and lactating individuals in the phase 3 (efficacy) clinical trials if appropriate.[14]

- Children should not be categorically excluded from clinical trials of investigational COVID-19 products in which there is a prospect for direct benefit.[15]

  - Sponsors are encouraged to discuss pediatric drug development with FDA early in the course of clinical development, including the potential for extrapolation of adult efficacy data, appropriate pharmacokinetic trials in pediatric subjects to support dose selection, and the recommended size of the preapproval safety database in children. In addition, disease severity classification should reflect age-appropriate norms, as applicable. Decisions on the timing of initiating pediatric studies depend on several factors, including but not limited to the amount of available clinical and/or nonclinical safety data for the drug. For example, if dosing recommendations for a drug are the same for adults and adolescents[16] and there is sufficient prospect of benefit to justify the risks, then it may be appropriate to include adolescents in the initial phase 3 clinical trials.

  - Sponsors are encouraged to submit an initial pediatric study plan as soon as practicable.[17]

  - Under the Pediatric Research Equity Act, all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication or indications in pediatric populations unless this requirement is waived, deferred, or inapplicable.[18] FDA intends to work with sponsors to reach agreement on the initial pediatric study plan and any pediatric trial protocols as quickly as possible to avoid any unnecessary delays in the initiation of trials or submission of any marketing application.

[14] FDA has proposed relevant recommendations in the draft guidance to industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[15] See 21 CFR part 50, subpart D.

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

[17] See 505B(e) of the FD&C Act. Additionally, FDA has proposed relevant recommendations in the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[18] See 21 U.S.C 355c.

B. Trial Design

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- FDA strongly recommends that drugs to treat or prevent COVID-19 be evaluated in randomized, placebo-controlled, double-blind clinical trials using a superiority design.[19]

  – Background standard of care should be maintained in all treatment arms. Sponsors should address anticipated off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19.

  – The standard of care is expected to change as additional information, such as from randomized controlled trials, emerges. Where treatments become standard of care for specific COVID-19 populations (e.g., severely ill hospitalized patients), trials in these populations should generally be designed as placebo-controlled superiority studies with an add-on design (i.e., the investigational agent or placebo added on to the standard of care agent). For agents with a similar mechanism of action as the standard of care (e.g., direct antiviral agent as the investigational agent when the new standard of care is also a direct antiviral agent), an active-comparator controlled study design may be considered if there is sufficient preclinical and initial clinical evidence of activity of the investigational agent. Sponsors should plan early discussion with the appropriate clinical division.

- Under certain circumstances it may be appropriate to conduct decentralized and/or platform clinical trials. Sponsors considering these approaches should discuss their plans with the Agency. FDA recognizes the potential of, and significant interest in, such approaches, and may provide additional recommendations as we gain more experience regarding their use in this context.

- Given the infection control concerns associated with COVID-19, sponsors should limit in-person data collection to those measurements intended to ensure safety and establish effectiveness or influence the benefit-risk assessment.

- The trial should be of sufficient duration to evaluate safety and effectiveness reliably (i.e., the duration should be adequate to capture the vast majority of COVID-19-related outcomes that are relevant for the population under study). For example, a 4-week duration would likely be sufficient to capture most important outcomes (e.g., mortality) in a trial of mechanically ventilated patients. Longer durations would potentially be appropriate for trials of patients who are less ill at baseline and for trials of preventive treatments. In some cases, longer follow-up should be considered to assess safety.

[19] FDA has proposed relevant recommendations in the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

- When there is compelling preclinical or preliminary clinical evidence, it may be appropriate to move directly to conduct a trial of sufficient size and appropriate design to provide substantial evidence of effectiveness and adequate characterization of safety.

- In instances where there is some but limited information supporting the potential for efficacy,[20] approaches where an initial assessment of potential benefit can be made before enrolling a large number of subjects are appropriate. These approaches may include the following:

  – Conducting an initial small, controlled trial to assess for drug activity (proof-of-concept) that suggests the potential for clinical benefit.

  – Conducting a trial that incorporates prospectively planned criteria to stop the trial for futility (i.e., with the prospect of expanding from a proof-of-concept phase to a larger confirmatory trial). Such a trial might also incorporate additional prospectively planned adaptations (see additional comments on adaptive design proposals below).

- FDA encourages sponsors to use an independent data monitoring committee (DMC) to ensure subject safety and trial integrity.

  – Sponsors should submit the DMC charter as early as possible.

  – Sponsors should ensure there will be appropriate DMC monitoring to safeguard the welfare of subjects, accounting for important factors such as the expected enrollment rate, the expected lag time to analyze interim data for DMC meetings, and the frequency of DMC meetings.[21]

  – If enrollment is anticipated to be rapid, but additional safety data are needed before dosing a large number of subjects, an enrollment pause could be built into the trial. In this case, enrollment would be temporarily halted, and the DMC would assess the data and then recommend that the trial or dosing group either terminate or resume enrollment.

- FDA encourages sponsors to incorporate prospectively planned criteria to stop the trial for futility (lack of efficacy) or harm in any confirmatory trial. The stopping criteria should aim to ensure a high probability of halting the trial if the drug is harmful (e.g., associated with a higher risk of death), a reasonable probability of halting the trial if the

[20] See the guidance for industry and investigators *COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products*, which describes the information and data recommended to support FDA's review for the initiation of clinical trials during the COVID-19 public health emergency.

[21] FDA has proposed relevant recommendations in the draft guidances for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006) and *Safety Assessment for IND Safety Reporting* (December 2015). When final, these guidances will represent the FDA's current thinking on these topics.

drug is ineffective, and a high probability of continuing the trial if the drug is effective. If accrual in such a trial is expected to be rapid, an enrollment pause may be considered to support stopping for futility.

- If a trial incorporates the possibility of early stopping for evidence of benefit or any adaptations to the sample size, dosing arms, or other design features, sponsors should prospectively plan the design in a manner to ensure control of the type I error rate and reliable treatment effect estimation.[22] An independent committee, such as a DMC, should be tasked with providing any recommendations for early termination or design adaptations based on unblinded interim data.

- FDA anticipates events that occur outside of an ongoing trial may provide important new information relevant to the ongoing trial (e.g., changes to the standard of care) and may motivate revisions to the trial design. Well-motivated changes based on information external to the trial can be acceptable and sponsors are encouraged to discuss these changes with the FDA.

C. Efficacy Endpoints

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- The drug development program should evaluate the effect of the investigational drug relative to placebo on clinically meaningful aspects of the disease. The relevance and appropriateness of measures may depend on the population studied, the clinical setting, and/or baseline disease severity (see Appendix).

- Examples of important clinical outcome measures in treatment trials include the following:

  – All-cause mortality

  – Respiratory failure (i.e., need for mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery)

  – Need for invasive mechanical ventilation

  – Need for intensive care unit (ICU) level care based on clear definitions and specific clinical criteria

  – Need for hospitalization based on clear definitions and specific clinical criteria

  – Objective measures of sustained improvement (e.g., return to room air or baseline oxygen requirement)

[22] See the guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (November 2019).

- Sustained clinical recovery (e.g., resolution of symptoms)

- The choice, time frame, and interpretation of endpoints may differ depending on the population evaluated in the trial. For example,

  - In a trial in severe and/or critical patients, examples of appropriate endpoints could be

    - All-cause mortality at an appropriate time point (e.g., at least 28 days)

    - Proportion of patients alive and free of respiratory failure at an appropriate time point (e.g., at least 28 days)

    - Clinical status at an appropriate time point assessed using an ordinal scale[23] that incorporates multiple clinical outcomes of interest (e.g., death, mechanical ventilation) ordered by their clinical importance[24]

    - Time to sustained recovery assessed over an appropriate duration

  - In an outpatient treatment trial, examples of appropriate endpoints could be

    - Proportion of patients hospitalized by an appropriate time point (e.g., at least 28 days)

    - Time to sustained clinical recovery assessed over an appropriate duration

- Sponsors should address potential relapses in their endpoint definitions to ensure adequate assessment of the durability of response.

- In phase 2 treatment trials, a virologic measure may be acceptable as a primary endpoint to support a phase 3 clinical endpoint study. However, virologic endpoints are not appropriate as primary endpoints in a phase 3 trial because there is no established predictive relationship between magnitude and timing of viral reductions and the extent of clinical benefit of how a patient feels, functions, or survives. Additionally, the optimal sample size, timing, methods for collection procedures, and assays for clinically relevant virologic measurements have not been established. In phase 3 treatment trials, virologic endpoints may be assessed as secondary endpoints. Collection of virologic data and evaluation of antiviral resistance are important components of drug development for COVID-19.

- For endpoints defined by events through or at a prespecified time point, the time point should be defined as number of days after randomization. The time window should be

[23] An example can be found at WHO R&D Blueprint novel Coronavirus, available at https://apps.who.int/iris/handle/10665/330695.

[24] Ordinal data should be collected daily to inform analyses.

sufficiently long to ensure capture of important events related to patient status, treatment, and COVID-19 progression.

- In prevention trials, the primary endpoint should be the occurrence of laboratory-confirmed SARS-CoV-2 infection (with or without symptoms) or SARS-CoV-2 infection with symptoms (i.e., COVID-19) through a prespecified time point.

  – Sponsors are encouraged to evaluate both laboratory-confirmed SARS-CoV-2 infections (with or without symptoms) and SARS-CoV-2 with symptoms (i.e., COVID-19) when possible.

  – Ascertaining whether COVID-19 is milder in persons receiving prophylaxis compared with persons not receiving prophylaxis is of interest. Sponsors should collect clinical outcome data (e.g., hospitalization) and data on symptoms to support such analyses.

D. Safety Considerations

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

- It is important to include a broad population of subjects in adequate and well-controlled clinical trials to generate a safety database that will best inform the safe use of the drug.

- The size and composition of the safety database needed to support an indication for COVID-19 depends on factors such as the proposed population, the treatment effect, the drug's toxicity, and the extent of the prior clinical experience with the drug (and possibly with related drugs).

- Sponsors may provide a standardized toxicity grading scale for clinical trials in patients with severe COVID-19 or patients with serious comorbidities. Examples of toxicity grading scales include those published by the National Institutes of Health's Division of AIDS[25] and the National Cancer Institute (NCI).[26]

- Sponsors should address the potential for drug-drug interactions that could increase the risk for toxicities (caused by increased exposures of the drug or the drug that it interacts with) and propose mitigation strategies.

[25] See the National Institutes of Health's Division of AIDS Adverse Event Grading Tables, available at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

[26] See the National Cancer Institute's Common Terminology Criteria for Adverse Events, available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- Safety assessments (e.g., vital signs, laboratory studies, electrocardiograms) should be performed on a schedule commensurate with severity of illness and the identified potential risk of the study drug.

- Sponsors should conduct safety reporting as outlined in FDA regulations[27] and relevant guidance.[28]

E. Statistical Considerations

Sponsors of drugs to treat or prevent COVID-19 should consider the following statistical considerations:

- The primary efficacy analysis should be conducted in an intention-to-treat population, defined as all randomized subjects.

- The primary efficacy analysis should be prespecified in the protocol.

- To the extent possible, sponsors should justify their assumptions in sample size calculations. The sample size should be large enough to provide a reliable answer to the safety and efficacy questions the trial is meant to address.

- Examples of analytic approaches for the primary efficacy analysis include:

  – Binary outcome analysis: each person is classified as having a successful or an unsuccessful outcome, with a difference in proportions used to compare treatment arms.

  – Ordinal outcome analysis: options include a proportional odds approach, a rank-based approach, and an approach to compare means with a score or weight assigned to each category. Any of these approaches should be supplemented by analyses communicating how treatment impacts different categories of the scale.

  – Time-to-event analysis: use of a proportional hazards model or log-rank test should be supplemented by a display of Kaplan-Meier curves in each treatment group.

- To improve the precision of treatment effect estimation and inference, sponsors should consider adjusting for prespecified prognostic baseline covariates (e.g., age, baseline severity, comorbidities) in the primary efficacy analysis and should propose methods of

[27] See 21 CFR 312.32.

[28] See the guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012). In addition, FDA has proposed relevant recommendations in the draft guidance for industry *Safety Assessment for IND Safety Reporting*. When final, this guidance will represent the FDA's current thinking on this topic.

covariate adjustment. For example, for a binary endpoint, methods can be used to gain precision in the evaluation of the difference in proportions.[29]

- If a treatment trial enrolls a mixture of patients with different baseline severity levels, sponsors should conduct subgroup or interaction analyses by baseline severity to assess for differential treatment effects.

- The trial should aim to minimize missing data. The protocol should distinguish between discontinuation from the study drug and withdrawal from study assessments. Sponsors should encourage subjects who discontinue therapy to remain in the study and to continue follow-up for key outcomes. Virtual follow-up is acceptable if appropriate, and the aim should be to record vital status for all subjects.

- For the primary analyses, death should not be considered a form of missing data or censoring. Death should be incorporated into the endpoint as a highly unfavorable possible outcome. For primary endpoints other than all-cause mortality, a treatment effect could be driven by non-mortality components (e.g., hospitalization) despite increased mortality on drug. Therefore, analyses of all-cause mortality will be important regardless of the selected primary endpoint.

[29] Ge M, Durham LK, Meyer RD, Xie W, and Thomas N, 2011, Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences, Drug Inf J, 45:481–493.

APPENDIX

EXAMPLES OF BASELINE SEVERITY CATEGORIZATION

SARS-CoV-2 infection without symptoms

- Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test
- No symptoms

Mild COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO_2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute
- No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19

- Positive testing by standard RT-PCR assay or an equivalent test
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$
- No criteria for Critical Severity

Critical COVID-19

- Positive testing by standard RT-PCR assay or equivalent test

- Evidence of critical illness, defined by at least one of the following:

  – Respiratory failure defined based on resource utilization requiring at least one of the following:

    ▪ Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)

  – Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)

  – Multi-organ dysfunction/failure

NOTE: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection.