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

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*.

For questions regarding this document, contact (CDER) Maria Clary 240-402-8615, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

November 2023
Clinical/Medical

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

Guidance for Industry

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Contains Nonbinding Recommendations

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Guidance for Industry[1]

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

The purpose of this guidance is to assist sponsors in the clinical development of drugs[2] for the treatment or prevention of COVID-19. This guidance describes FDA's current recommendations for phase 2 and phase 3 trials with a focus on trial population, trial design, efficacy endpoints, safety considerations, and statistical considerations. There may be additional considerations for some biological products (e.g., cellular and gene therapies and blood products), so FDA encourages sponsors to reach out to the applicable review division as appropriate.

The development of drugs for the treatment of Long COVID-19, preventative vaccines[3] and convalescent plasma[4] is not within the scope of 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 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 and to see the guidance for industry *Development and Licensure of Vaccines to Prevent COVID-19* (October 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.

[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). See the guidance for industry *Investigational COVID-19 Convalescent Plasma* (October 2023).

and (g)(3). FDA made this determination because although the COVID-19-related public health emergency under section 319 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 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 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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

COVID-19, the disease caused by the SARS-CoV-2 virus, can range from mild to severe or critical disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death. Additionally, the SARS-CoV-2 virus can cause asymptomatic infection.[5] Clinical management includes the use of preventative vaccines and therapeutic agents (e.g., direct antivirals, immunomodulators) and supportive care, such as supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation.[6]

III. DISCUSSION

A. Treatment Trials

1. Population

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

- The enrolled population should reflect the intended use of the product. For example:
  - Non-hospitalized individuals at standard risk of progression to serious disease
  - Non-hospitalized individuals at high risk of progression to serious disease
  - Hospitalized individuals requiring supplemental oxygen
  - Hospitalized individuals with respiratory failure

[5] 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.

[6] See the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, available at https://www.covid19treatmentguidelines.nih.gov/management/.

- For treatment trials, sponsors should document diagnosis of laboratory-confirmed SARS-CoV-2 as well as the duration of symptoms before treatment.

- For treatment trials, FDA recommends that sponsors categorize the baseline severity of COVID-19 in the enrolled population. The criteria used to describe baseline disease severity should incorporate objective measures. Examples of disease severity criteria are provided in Appendix A.

- Clinical trials intended to demonstrate prevention of serious outcomes, including hospitalization or death, should include groups of persons at high risk of progression to severe disease.[7]

- Age is one of the strongest risk factors for severe COVID-19 outcomes. To the fullest extent possible, older adults, including individuals 75 years of age and older, should be represented in relevant clinical trials.[8] Sponsors should consider conducting trials in nursing homes or other eldercare facilities.

- Individuals from underrepresented racial and ethnic groups should be represented in clinical trials. Sponsors should select clinical study site locations to facilitate enrollment of a diverse study population.[9]

- Studies to characterize the effect of extrinsic factors (e.g., drug-drug interactions) and intrinsic factors (e.g., renal impairment or hepatic impairment) on the pharmacokinetics of a drug should be conducted early in development to inform the management of drug-drug interactions and inclusion of individuals with renal and/or hepatic impairment in clinical trials as appropriate. Sponsors should consider recommendations in relevant guidances for industry.[10]

- The principles outlined in this document can be used to guide drug development for children and for pregnant and lactating individuals. There is a need to generate clinical trial data to inform the use of drugs in these populations.

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[7] See the NIH COVID-19 Treatment Guidelines Overview of COVID-19, available at https://www.covid19treatmentguidelines.nih.gov/overview/overview-of-covid-19/.

[8] See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

[9] Ibid.

[10] See the guidances for industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020), *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020), *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003), and the draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* (September 2020). 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.

- Because COVID-19 during pregnancy may increase the risk of severe symptoms and preterm birth, sponsors should ensure that adequate nonclinical studies have been completed so that pregnant individuals can be enrolled in phase 3 (efficacy) clinical trials.[11]

- FDA encourages enrolling lactating individuals in phase 3 (efficacy) clinical trials.

- Children should not be categorically excluded from clinical trials of investigational COVID-19 products in which there is a prospect for direct benefit.[12]

  - Sponsors are encouraged to discuss pediatric drug development with FDA early in the course of clinical development, including the potential for extrapolation of efficacy data from studies in adults, 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[13] and there is a prospect of direct benefit, then adolescents should be included in the initial phase 3 clinical trials.

  - Sponsors are encouraged to submit an initial pediatric study plan as soon as practicable.[14]

  - Under the Pediatric Research Equity Act, all applications for new active ingredients (which include 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.[15] 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

[11] FDA has proposed relevant recommendations in the draft guidance for 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.

[12] For additional safeguards for children in clinical investigations, see 21 CFR part 50, subpart D.

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

[14] See 505B(e) of the FD&C Act. Additionally, FDA has proposed relevant recommendations in the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

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

unnecessary delays in the initiation of trials or submission of any marketing application.

2. Trial Design and Conduct

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

- FDA strongly recommends that drugs to treat COVID-19 be evaluated in randomized, controlled, double-blind clinical trials.
  - Typically, trials should be designed as placebo-controlled superiority studies. An add-on placebo design (i.e., the investigational agent or placebo added on to standard of care) may be necessary to maintain equipoise.
  - For agents with a similar mechanism of action as the background standard of care (e.g., direct antiviral agent as the investigational agent when the standard of care is also a direct antiviral agent), an active-comparator controlled study design may be considered. A superiority trial design or noninferiority design[16] may be appropriate.
- Sponsors are encouraged to use quantitative clinical pharmacology approaches that leverage all available information for selection of dosing regimen(s) to be evaluated in clinical trials.[17]
- Sponsors should plan to collect baseline vaccination status, changes in vaccination status during the trial, and baseline and concomitant medication use, including COVID-19 standard of care therapies.
- Sponsors should address the possibility of drug and COVID-19 vaccine interactions for drugs that may interfere with vaccine effectiveness (i.e., monoclonal antibodies targeting the vaccine antigen). Sponsors should consult with the Agency early in the development program for such drugs.
- SARS-CoV-2 has and continues to evolve, resulting in the emergence of SARS-CoV-2 with genetic changes that may impact the effectiveness of antiviral drugs. Sponsors should determine the antiviral activity (EC_{50} and EC_{90} values) of their drug against currently predominant and emerging U.S. variants.
- Using an antiviral drug to treat COVID-19 may contribute to the emergence of viruses with reduced susceptibility to the drug or to other approved or investigational drugs. Sponsors should characterize drug resistance pathways and the potential for cross-

[16] The noninferiority margin must be sufficiently supported to conduct a noninferiority trial and the justification should be discussed with FDA. See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

[17] See the guidances for industry *Population Pharmacokinetics* (February 2022) and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (May 2003).

resistance to other drugs using both nonclinical and clinical studies. Details regarding drug resistance analysis are provided in Appendix B. Sponsors should also refer to the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency* (June 2006).

- Clinical trial protocols should include plans to characterize the impact of drugs on viral shedding and immune responses as described in Appendix C.

- Decentralized clinical trials (DCTs) may play a role in COVID-19 drug development programs. Sponsors considering a DCT should plan early discussions with the appropriate review division, as a DCT may introduce additional complexities related to feasibility, design, implementation, and analysis of the data.[18,19]

  – Sponsors should consider several factors when determining if conducting a DCT is appropriate, selecting the location of a trial visit, and/or selecting personnel performing an assessment. These factors include the following:

    - The severity of COVID-19

    - The nature of the investigational product (e.g., ease of administration, safety profile, stability profile, storage conditions)

    - The type of trial procedure or assessment (e.g., administration of investigational product, clinical laboratory assessment, clinical outcome assessment, or adverse event assessment/follow-up)

- Sponsors considering the use of adaptive design elements in their clinical trial should review the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019). If a trial incorporates 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.

- FDA strongly discourages disseminating data from ongoing trials. Knowledge of accumulating data by trial investigators and subjects can adversely affect subject accrual, adherence, and retention, as well as endpoint assessment, compromising the ability of the trial to reliably achieve its objective in a timely manner. Issues with trial conduct caused by knowledge of interim results are difficult to predict and generally impossible to adjust for in statistical analyses. Therefore, releasing interim results could have ramifications on the integrity of the ongoing trial and the ability to collect reliable and interpretable data

[18] See the draft guidance for industry *Decentralized Clinical Trials for Drugs, Biological Products, and Devices* (May 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[19] See the draft guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2021). When final, this guidance will represent the FDA's current thinking on this topic.

needed to support regulatory decision-making. If sponsors intend to conduct interim analyses, FDA recommends they prospectively plan these analyses and incorporate processes to maintain the integrity of the trial (e.g., using an independent DMC).[20] FDA recognizes there may be exceptional circumstances in which a sponsor determines it needs to disseminate results for safety or other reasons. In such situations, the sponsor is strongly encouraged to discuss with FDA before releasing such results.

- 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 drug is ineffective, and a high probability of continuing the trial if the drug is effective.

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

  – Sponsors should submit the DMC charter to FDA before enrolling subjects.

  – 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]

- The trial should aim to minimize missing data. The protocol should distinguish between discontinuation from the study drug and withdrawal from study assessments. Trial subjects may choose to discontinue treatment during the trial for various reasons, such as experiencing adverse events or perceived lack of efficacy. Unless the subject withdraws consent,[22] sponsors should encourage subjects who discontinue therapy to remain in the study and to continue follow-up for key safety and efficacy assessments. Virtual follow-up is acceptable, if appropriate, and the aim should be to record vital status for all subjects.

- Applicable clinical trials need to be registered at www.ClinicalTrials.gov as required by 42 CFR part 11. FDA encourages responsible parties to promptly update www.clinicaltrial.gov with the results of completed trials given their public health importance.

[20] See guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics*.

[21] See the guidance for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

[22] Withdrawal of consent refers to a subject's voluntary termination of participation in the clinical trial during the course of the trial. The reason for withdrawal of consent should be captured in a case report form.

3. Efficacy Endpoints

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

- The drug development program should evaluate the effect of the investigational drug relative to placebo or an active comparator on clinically meaningful aspects of the disease. The relevance and appropriateness of measures may depend on factors such as the mechanism of action of the drug, the population studied, the clinical setting, the phase of drug development, and/or baseline disease severity (see Appendix A).

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

  – All-cause mortality.

  – Respiratory failure (i.e., need for mechanical ventilation, extracorporeal membrane oxygenation, noninvasive positive pressure ventilation, or high-flow nasal cannula oxygen delivery).

  – Need for invasive mechanical ventilation.

  – Need for hospitalization.

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

  – Sustained symptom alleviation or resolution. For trials evaluating non-hospitalized patients, this 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 patient-reported outcome instrument).[23]

  – Clinical status using an ordinal scale that incorporates multiple clinical outcomes of interest ordered by their clinical importance.

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

[23] See the guidances for industry *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* (September 2020) and *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) for additional information on using patient-reported outcome measures to define clinical recovery. Also see FDA Patient-Focused Drug Development Guidance Series which can be found at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

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

    - All-cause mortality at an appropriate time point (e.g., at least 28 days for hospitalized noncritically ill patients,[24] 60 days for critically ill patients[25])

    - Proportion of patients alive and free of respiratory failure at an appropriate time point (e.g., at least 28 days for hospitalized noncritically ill patients, 60 days for critically ill patients)

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

    - Proportion of patients progressing to hospitalization or death by an appropriate time point (e.g., at least 28 days).

    - Time to sustained symptom alleviation or resolution assessed over an appropriate duration.

- For primary endpoints other than all-cause mortality, a treatment effect could be driven by nonmortality components (e.g., hospitalization) despite increased mortality while on the investigational drug. Therefore, analyses of all-cause mortality will be important regardless of the selected primary endpoint. Additionally, powering the trial based on other endpoints, such as time to sustained recovery, may result in less precision in the assessment of all-cause mortality attributable to a smaller patient sample size. Depending on the population and mechanism of action of the investigational drug(s), additional consideration may be needed to determine if the sample size is sufficient to provide an adequate assessment of mortality.

- In their endpoint definition, sponsors should address the occurrence of relapses 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 progression to a phase 3 clinical endpoint trial. 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 reductions in viral RNA shedding and the extent of clinical benefit of how a patient feels, functions, or survives. Additionally, the optimal sample size, timing, and methods for collection procedures have not been established and assays for clinically relevant virologic measurements have not been validated. In phase 3 treatment trials, virologic endpoints may be assessed as

[24] See 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.

[25] C Karagiannidis, C Mostert, C Hentschker, T Voshaar, J Malzahn, G Schillinger, J Klauber, U Janssens, G Marx, S Weber-Carstens, S Kluge, M Pfeifer, L Grabenhenrich, T Welte, and R Busse, 2020, Case Characteristics, Resource Use, and Outcomes of 10021 Patients with COVID-19 Admitted to 920 German Hospitals: an Observational Study, Lancet Respir Med, 8(9):853–862.

secondary endpoints. Collection of virologic data and evaluation of activity against circulating variants and treatment-emergent resistance are important components of drug development for COVID-19 (see Appendix B and Appendix C).

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

4. Safety Considerations

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

- 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). For example, for drugs with a well-characterized safety profile with low toxicity, a more streamlined approach to data collection may be appropriate (e.g., limiting adverse event collection to serious adverse events, adverse events leading to discontinuation, and grade 3 and grade 4 adverse events).[26] Conversely, for drugs that are less well characterized or repurposed agents known to be highly toxic (e.g., some oncologic drugs), a more detailed collection of safety data would be warranted. Sponsors are encouraged to discuss their proposed safety database with FDA early in the course of clinical development.

- Sponsors may provide a standardized toxicity grading scale. For clinical trials in subjects with severe COVID-19 or subjects with serious comorbidities, examples of toxicity grading scales include those published by the National Institutes of Health's Division of AIDS[27] and the National Cancer Institute.[28] For trials evaluating mild-to-moderate COVID-19, an example grade scale can be found in the guidance for industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (September 2007).

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

[26] See the guidance for industry *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-approval or Post-Approval Clinical Trials* (December 2022).

[27] 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.

[28] 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[29] and relevant guidance.[30]

5. Statistical Considerations

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

- 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.

- Sponsors are encouraged to consider the estimands[31] of interest and to adequately define those estimands in both the protocol and the statistical analysis plan.

  - The primary efficacy analysis should be conducted in all randomized subjects.

  - For key efficacy endpoints in treatment trials, FDA generally recommends the following approaches for handling intercurrent events.[32] For any alternative strategies, sponsors should justify that the estimand addresses a meaningful clinical question of interest and can be estimated with plausible assumptions.

    - Sponsors should use a composite variable strategy[33] to handle death, with death taking a sufficiently unfavorable value. Death should not be considered a form of missing data.

    - Sponsors should also use the composite variable strategy for handling hospitalization in the outpatient population.

[29] See 21 CFR 312.32.

[30] 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*.

[31] See the guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[32] Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. See ICH E9(R1).

[33] Ibid.

396 ▪ Sponsors should use a treatment policy strategy[34] for other intercurrent events.
397
398 • To improve the precision of treatment effect estimation and inference, sponsors should
399 consider adjusting for prespecified prognostic baseline covariates (e.g., age, baseline
400 severity, comorbidities, baseline medications, and COVID-19 vaccination status) in the
401 primary efficacy analysis and should propose methods of covariate adjustment. For
402 example, for a binary endpoint, methods can be used to gain precision in the evaluation
403 of the difference in proportions.[35,36]
404
405 • Restricting analyses to a subset of patients defined by a post-randomization variable (e.g.,
406 intensive care unit admission, ventilator use) can lead to results that are difficult to
407 interpret. The analysis set or sets to be used in the statistical analyses for any key efficacy
408 endpoint should be defined according to measurements and characteristics that can be
409 observed at baseline.
410
411 • If a treatment trial enrolls a mixture of subjects with different baseline severity levels,
412 baseline medication use, and/or vaccination statuses, sponsors should conduct subgroup
413 or interaction analyses to assess for differential treatment effects. Sponsors should also
414 provide analyses describing concomitant medication use and changes in vaccination
415 status during the trial overall and by treatment arm.
416
417 • Sponsors should submit a statistical analysis plan for review before any unblinding of
418 data. In addition to the statistical methods provided in the protocol, the statistical analysis
419 plan for a trial should contain detailed information on each primary and secondary
420 endpoint; the main, supplemental, and sensitivity analysis methods of key efficacy
421 endpoints; the multiple testing procedure for controlling the overall type I error rate, if
422 applicable; and methods for handling missing data. If applicable, sponsors should
423 prespecify the interim analysis procedures (e.g., statistical methods, boundaries) and
424 should provide in a DMC charter detailed procedures and discussions of methods to
425 maintain trial integrity (e.g., unblinded personnel, firewalls).
426
427 **B. Prevention Trials**
428
429 • The availability of vaccines and timing of vaccine administration to prevent COVID-19
430 has implications for the design and conduct of trials evaluating drugs for the prevention
431 of COVID-19. FDA recommends that sponsors contact the Agency early on in the
432 planning of such trials.
433

[34] Ibid.

[35] JA Steingrimsson, DF Hanley, and M Rosenblum, 2017, Improving Precision by Adjusting for Prognostic Baseline Variables in Randomized Trials With Binary Outcomes, Without Regression Model Assumptions, Contemp Clin Trials, 54:18–24.

[36] T Ye, M Bannick, Y Yi, and J Shao, 2023, Robust Variance Estimation for Covariate-Adjusted Unconditional Treatment Effect in Randomized Clinical Trials With Binary Outcomes, Stat Theory and Relat Fields, 7(2):159–163.

- 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 infection (with or without symptoms) and SARS-CoV-2 infection with symptoms (i.e., COVID-19) when possible.

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

- Sponsors should also conduct SARS-CoV-2 antibody testing at baseline and at later time points to detect serologic evidence of infection in prevention trials, which may identify cases of asymptomatic infection or infections that were otherwise undetected by virologic testing.

- For pre- or post-exposure prevention trials, protocols should include clear plans and testing algorithms for detecting SARS-CoV-2 infection. Protocols should indicate the specific viral assay(s) to be used and should describe assay performance characteristics, including any known or predicted impact of emerging SARS-CoV-2 variants on assay performance.

APPENDIX A

EXAMPLES OF BASELINE SEVERITY CATEGORIZATION

SARS-CoV-2 infection without symptoms

- Positive testing by virologic test (i.e., a nucleic acid amplification test or an antigen test)
- No symptoms

Mild COVID-19

- Positive testing by virologic test (i.e., a nucleic acid amplification test or an antigen test)
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste or smell, without shortness of breath or dyspnea
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19

- Positive testing by virologic test (i.e., a nucleic acid amplification test or an antigen test)
- 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, heart rate ≥ 90 beats per minute; with saturation of oxygen (SpO_2) > 93% on room air at sea level[1]
- No clinical signs indicative of Severe or Critical Severity

Severe COVID-19

- Positive testing by virologic test (i.e., a nucleic acid amplification test or an antigen 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

[1] Although pulse oximetry is useful for estimating blood oxygen levels, pulse oximeters have limitations and a risk of inaccuracy under certain circumstances that should be considered. See FDA's Pulse Oximeter Accuracy and Limitations: FDA Safety Communication, 2022, available at https://www.fda.gov/medical-devices/safety-communications/pulse-oximeter-accuracy-and-limitations-fda-safety-communication.

- 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 clinical criteria for Critical Severity

Critical COVID-19

- Positive testing by virologic test (i.e., a nucleic acid amplification test or an antigen test)

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

  – Respiratory failure defined as 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, extracorporeal membrane oxygenation

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

  – Multi-organ dysfunction/failure

APPENDIX B

DRUG RESISTANCE ANALYSIS

The drug resistance analysis plan should include the following:

- Characterize the antiviral activity of the drug in cell culture assays against a panel of geographically, temporally, and phylogenetically distinct SARS-CoV-2 isolates, including isolates representative of the most common variants currently circulating globally.

- Evaluate combination antiviral activity relationships in cell culture assays between candidate drugs planned for use in a combination regimen, or between the candidate drug(s) and any other authorized or approved drugs if they are anticipated to be used in combination.

- Select for viruses resistant to the drug in cell culture assays and characterize drug-resistant viruses genotypically and phenotypically to support drug resistance and cross-resistance analyses. These studies should be conducted under appropriate biocontainment[1] or consider using a surrogate or recombinant virus expressing the SARS-CoV-2 target protein.

- Identify reported SARS-CoV-2 amino acid polymorphisms in the drug target and describe their prevalence and rates of emergence in publicly available viral sequence databases. If the drug has been co-crystalized with the viral target protein, identify polymorphisms in the viral target at amino acid positions that are within 5 angstroms of the drug structure.

- Include detailed plans in clinical protocols to (a) characterize the impact of SARS-CoV-2 genetic variability on clinical and virologic outcomes (i.e., baseline resistance analyses) and (b) identify SARS-CoV-2 genetic changes associated with treatment (i.e., treatment-emergent resistance analyses).

- Characterize the impact of specific amino acid variants in the drug target on drug activity using cell culture phenotype assays. If a pseudotyped virus-like particle assay or other surrogate assay is used, conduct validation studies showing that the surrogate assay yields results that are consistent with those obtained with authentic virus regarding the relative impact of different variants.

[1] For biosafety considerations from the National Institutes of Health, see the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules and the FAQs — Interim Laboratory Biosafety Guidance for Research with SARS-CoV-2 and IBC Requirements under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, available at https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf. See also the Centers for Disease Control and Prevention's guideline Biosafety in Microbiological and Biomedical Laboratories, available at https://www.cdc.gov/labs/BMBL.html. Studies should also follow applicable federal policies and guidelines related to dual use research of concern, available at https://www.phe.gov/s3/dualuse/Pages/default.aspx.

- Assess the potential for cross-resistance with other drugs with the same target or similar mechanism of action based on results of genotypic and phenotypic assays.

- Monitor continuously for emerging SARS-CoV-2 variants and evaluate phenotypically any specific variants in the drug target that are becoming prevalent or could potentially impact drug activity.

- Conduct proof of principle studies in small animal models given the limited availability of nonhuman primates.

- Identify known human genetic polymorphisms and characterize their potential impact on drug activity in nonclinical and/or clinical studies if the drug targets a host factor. The types and frequencies of polymorphisms in different racial/ethnic groups should be provided to FDA. Samples for resistance assessments should be collected in clinical trials for host targeting antivirals as resistance can occur with these drugs.

- Follow established FDA guidance for submission of next generation sequencing data generated from clinical trials.[2] Consult with the appropriate review division for additional advice on collection and submission of drug resistance data.

[2] See the guidance for industry *Submitting Next Generation Sequencing Data to the Division of Antiviral Products* (July 2019). 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.

APPENDIX C

IMPACT OF DRUGS ON VIRAL SHEDDING AND IMMUNE RESPONSES

Clinical trial protocols should include plans to characterize the impact of drugs on viral shedding and immune responses as follows:

- Indicate specific time points and clinical specimens to be collected and analyzed.

- Describe the specific types of respiratory samples to be collected (e.g., nasopharyngeal swabs, nasal mid-turbinate swab, saliva) and the collection procedures. Refer to current Centers for Disease Control and Prevention guidelines for specific definitions of specimen types and additional recommendations.[1]

- Collect and analyze the same specimen type(s) for baseline and subsequent time points when assessing the impact of treatment on viral shedding as assays may have varying sensitivity or performance for different respiratory specimen types.

- Collect nonrespiratory specimens (e.g., blood, bronchoalveolar lavage fluid) for virologic analyses when feasible to assess the impact of antiviral treatment on virus replication in other compartments, which may play a role in disease pathogenesis.

- Include an assessment of viral RNA levels (e.g., quantitative RT-PCR) for viral shedding analyses. Sponsors are encouraged to assess viral RNA shedding both quantitatively (e.g., $\log_{10}$ decline from baseline at a specific time point) and qualitatively (e.g., detected or not detected at a specific time point). Indicate the specific viral RNA assay(s) to be used and whether they have received FDA emergency use authorization or approval.

- Consider conducting virus infectivity assays to characterize the impact of treatment on shedding of cell culture infectious virus. Such assays should be conducted under appropriate biocontainment.[2]

- Describe assay performance characteristics, including any known or predicted impact of emerging SARS-CoV-2 variants on assay performance.

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[1] See the Centers for Disease Control and Prevention Interim Guidelines for Collecting and Handling of Clinical Specimens for COVID-19 Testing, available at https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html.

[2] For biosafety considerations from the National Institutes of Health, see the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules and the FAQs — Interim Laboratory Biosafety Guidance for Research with SARS-CoV-2 and IBC Requirements under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, available at https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf. See also the Centers for Disease Control and Prevention's and the National Institutes of Health's guideline Biosafety in Microbiological and Biomedical Laboratories, available at https://www.cdc.gov/labs/BMBL.html. Studies should also follow applicable federal policies and guidelines related to dual use research of concern, available at https://www.phe.gov/s3/dualuse/Pages/default.aspx.

- Characterize the impact of treatments on markers of inflammation (e.g., pro-inflammatory cytokines) and on the development of anti-SARS-CoV-2 immune responses when possible.

- Consider conducting these laboratory assessments in central laboratories or include internal assay references to minimize the potential introduction of variability attributable to assessments being conducted in different laboratories.