Summary Document

Topic: COVID-19 Efficacy Endpoints in Interventional Trials: What Constitutes an Incident Clinical Disease Case and What Triggers Diagnostic Work-Up

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Disclaimer: This document provides a summary of key points from the literature, guidelines or other documents from experts on the subject matter, including from national and multilateral organizations and authorities. This document does not aim to be exhaustive. Due to the rapidly evolving situation, this summary document may not include latest evidence and updates are likely. New versions will be issued when significant new information becomes available. Its purpose is to support organizations and institutions involved in the development of COVID-19 vaccines. It is the responsibility of each vaccine developer to review available evidence, take into account relevant guidance and recommendations, and to seek scientific advice from regulatory agencies as appropriate.

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Overview:

This Summary Document discusses the endpoint of clinically symptomatic COVID-19 in the context of trials assessing vaccine efficacy (VE). During the COVID-19 pandemic, clinical development of COVID-19 vaccines should focus on demonstrating VE against clinically symptomatic COVID-19 in the quickest possible way. Historically, vaccines for respiratory and other mucosal viruses have greater efficacy against severe disease than against mild disease, and greater efficacy against symptomatic disease than against asymptomatic infection.

The endpoints of clinically symptomatic COVID-19 have been aligned with the WHO COVID-19 severity grading. COVID-19 with signs and symptoms of pneumonia, defined in Box 1, should be considered for the primary efficacy assessment depending on the background incidence rate. In WHO's severity grading, COVID-19 pneumonia is defined as fever or signs and symptoms of lower respiratory tract disease, corresponding with moderate, severe, or critical disease. The prevention of moderate to severe disease provides individual benefit and is likely to significantly reduce healthcare utilization. All clinically symptomatic COVID-19, irrespective of severity grade, may be considered for secondary or primary VE assessment, depending on the incidence rate of SARS-CoV-2 infection. Efficacy against severe disease should be considered as a secondary endpoint. The NEWS-2 severity score should be considered to define severe disease. SARS-CoV-2 infection capturing both symptomatic and asymptomatic disease merits consideration as an additional endpoint.

COVID-19 vaccines, like influenza vaccines may reduce the risk of disease and severity of symptoms following infection. If this is the case, the endpoint of clinically symptomatic COVID-19 of any severity grade, risks the inclusion in efficacy analysis of cases of vaccine-induced attenuated COVID-19 defined as mild, residual COVID-19 upon infection in a vaccinated person. This lowers the VE estimate and reduce its precision. The use of the COVID-19 with signs or symptoms of pneumonia as the primary efficacy endpoint may result in earlier demonstration of VE by limiting the number of vaccine-induced attenuated COVID-19 included in the primary efficacy analysis despite there being fewer overall cases.

All programs assessing VE in preventing COVID-19 clinical *disease* should consider implementing a committee for clinical endpoint adjudication, and to assess the severity of COVID-19 in a standardized manner. All COVID-19 vaccine interventional trials, starting with early-stage clinical development trials should prospectively collect data on incident COVID-19 cases. Standardized consistent endpoint definitions for clinical disease may facilitate pooled analysis of early and advanced stage trials.

COVID-19 efficacy endpoints in interventional trials: clinically symptomatic COVID-19

Incident clinically symptomatic COVID-19 represents the main clinical endpoint for vaccine efficacy (VE) trials. The demonstration of VE depends on the difference in the ratio of incident COVID-19 cases between the vaccine and the control arm. The definition of a COVID-19 incident case (clinical endpoint) in vaccine trials differs from a case definition for public health purposes. A COVID-19 clinical endpoint for vaccine trials describes the clinical features of COVID-19 at the individual level.

The two endpoints most commonly considered for the assessment of VE are RT-PCR confirmed clinically symptomatic COVID-19 of any severity grade, and RT-PCR confirmed COVID-19 requiring signs or symptoms of pneumonia. The former includes all symptomatic COVID-19, including mild, moderate, severe and critical disease as defined by WHO, whereas the latter is defined by WHO as moderate, severe, or critical COVID-19, but excluding mild disease [1].

Typically, vaccines for respiratory and other mucosal viruses have greater efficacy against severe disease than against mild disease. COVID-19 with signs and symptoms of pneumonia (defined in Box 1) should be considered for the primary efficacy endpoint, providing individual benefit and impact on reducing healthcare utilization.

Box 1: COVID-19 requiring signs and symptoms of pneumonia.

(WHO COVID-19 disease severity: moderate, severe, or critical [1]

RT-PCR confirmed acute illness that is clinically consistent with COVID-19 pneumonia based on presence of at least one sign or symptom from category 1, *with or without* symptoms from category 2:

1. New onset *lower* respiratory tract disease (pneumonia) as diagnosed by any one or more of the following signs and symptoms: a) Fever or history of new-onset fever (defined as body temperature of ≥ 37.8°C irrespective of method) b) persistent dry (non-productive) cough, c) dyspnoea or tachypnoea (RR > 20/min), d) low peripheral capillary oxygen saturation (SpO_2 < 95% on room air) as measured by pulse-oximetry, e) chest pain, f) radiographic findings consistent with LRTD.
2. New onset systemic viral illness as diagnosed by any one or more of the following symptoms: a) myalgia, b) chills, c) loss of smell or taste, d) headache, e) sore throat, f) diarrhoea.

Alternatively, when the number of endpoints is a major concern (e.g. low incidence of COVID-19) all symptomatic COVID-19 (Box 2) could be considered. A COVID-19 clinical endpoint allowing symptoms of systemic viral illness without signs and symptoms of pneumonia will lead to a higher number of COVID-19 cases by including mild disease but may also lead to inclusion of vaccine-induced attenuated COVID-19 that lower the VE estimate. Thus, the use of the COVID-19 clinical endpoint requiring signs or symptoms of pneumonia can result in earlier demonstration of VE and possibly establish a higher VE point estimate by limiting the number of vaccine-induced attenuated COVID-19 included in the primary efficacy analysis despite there being fewer cases overall.

The presence of any of the clinical signs or symptoms included Box 2 should trigger key protocol-defined case-detection procedures, including nasopharyngeal swabs for PCR testing and the completion of diary cards for solicited symptoms of COVID-19.

Box 2: clinically symptomatic COVID-19 of any severity grade

(WHO COVID-19 disease severity: mild, moderate, severe, or critical [1])

RT-PCR confirmed an acute illness that is clinically consistent with COVID-19 based on presence of at least one ***new-onset*** symptom:

a) persistent cough, b) dyspnea or tachypnea (RR >20/min), c) Low peripheral capillary oxygen saturation (SpO_2 < 95% on room air) as measured by pulse-oximetry, d) chest pain, e) Radiographic findings consistent with LRTD, f) fever (defined as body temperature of ≥ 37.8°C, irrespective of method), g) myalgia, h) chills, i) loss of smell or taste, j) headache, k) sore throat, l) diarrhea

If participants experience any of the symptoms described in Box 2, they should be instructed to contact their local healthcare provider and inform the study site. In addition to symptom-directed case-detection, active case-finding through regular telephone assessments should be considered

throughout the post-vaccination follow-up period. Symptoms of COVID-19 may be assessed during these calls using a standard script. Regular site visits should be performed in addition to the telephone contact. Other differential diagnoses (e.g. influenza or other viral illnesses) should be sought in any suspected COVID-19 with negative laboratory confirmation.

Severe COVID-19 should also be considered as a secondary VE endpoint. Severe COVID-19 is defined as a virologically-confirmed COVID-19 with a National Early Warning-2 (NEWS-2) score of >6 [See Box 3 for NEWS2 scoring system]. The NEWS-2 severity score of >6 corresponds with the WHO definition of severe disease.

Box 3: NEWS2 Scoring system

Refer to: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2 [2]

Physiological parameter	Score						
	3	**2**	**1**	**0**	**1**	**2**	**3**
Respiratory rate (/min)	≤ 8		9-11	12-20		21-24	≥ 25
SpO2, Scale 1 (%)	≤ 91	92-93	94-95	≥ 96			
SpO2, Scale 2 (%)	≤ 83	84-85	86-87	88-92 ≥ 93 on air	93-94 on oxygen	95-96 on oxygen	≥ 97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic BP (mm Hg)	≤ 90	91-100	101-110	111-219			≥ 220
Pulse (/min)	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Consciousness				Alert			CVPU
Temperature (^{0}C)	≤ 35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	

BP = Blood pressure; NEWS = National Early Warning Score; SpO2 = Oxygen saturation

All programs assessing VE in preventing clinically symptomatic COVID-19 should consider implementing a committee for clinical endpoint adjudication and assessing the severity of COVID-19 in a standardized manner. All COVID-19 vaccine interventional trials, starting with early-stage clinical development trials should prospectively collect data on incident COVID-19 cases. Standardized consistent endpoint definitions for COVID-19 may facilitate pooled analysis of early and advanced stage trials.

Additional efficacy [objectives] and endpoints for consideration may include but are not limited to

- [VE in preventing] all COVID-19 clinical illness cases irrespective of RT-PCR confirmation
- [VE in preventing] any virologically confirmed COVID-19 including asymptomatic persons
- [VE in preventing] hospitalization due to virologically confirmed COVID-19
- [VE in preventing] death associated with virologically-confirmed COVID-19
- [VE in preventing] supplemental oxygenation
- [VE in preventing] mechanical ventilation
- [VE in preventing] multi-organ dysfunction syndrome (MODS)
- [VE in preventing] all-cause mortality
- [VE in preventing] any hospitalization

Additional Resources:

1. Clinical Management of COVID-19 (WHO interim guidance): https:// www.who.int/publications/i/item/clinical-management-of-covid-19
2. For NEWS-2 severity scoring system: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2
3. For laboratory testing: https://www.finddx.org/covid-19/pipeline/?section=immunoassays#diag_tab