Summary Document

Topic: Long COVID: Implications for Clinical Development

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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 focusses on Long COVID, also known as post-COVID syndrome or post-acute COVID-19, in the context of clinical development and vaccine efficacy trials. Long COVID is typically assessed in observational cohort studies. However, an assessment for Long COVID can be included as an exploratory objective in randomized clinical trials following an amendment to the study protocol. Long COVID is of public health relevance, and vaccine developers can consider implementing a more robust prospective, periodic assessment of solicited symptoms or a less robust but less expensive nested retrospective cohort study within efficacy clinical trials.

Prospective observational cohort studies have been widely used to assess different signs and symptoms of Long COVID and their duration post-acute COVID-19. In a randomized clinical trial, a vaccine effect on Long COVID can be explored by comparing the incidence and duration of Long COVID signs and symptoms. Long COVID is associated with COVID-19 severity. However, because very few clinically symptomatic breakthrough COVID-19 cases in vaccinees are severe or critical, a meaningful comparison between treatment arms will be restricted to mild to moderate severity graded COVID-19 cases, which will likely occur in both the vaccine and the control groups. Study sponsors should consider the follow up of study subjects with PCR-confirmed COVID-19 beyond 12 weeks after diagnosis for as long as is feasible and preferably at study conclusion.

There is no global consensus on the definition of Long COVID or the definitive symptoms. The National Institute for Health and Care Excellence describes Long COVID as signs and symptoms that develop or continue after acute COVID-19 and continue for more than 12 weeks and are not explained by an alternative diagnosis. In addition, the term Long COVID has been used to address both ongoing / post-acute symptomatic COVID-19 (from four to 12 weeks) and long-term post-COVID-19 syndrome (12 weeks or more). Long COVID can affect all age groups from children to older adults.

The Post COVID-19 Functional Status Scale can be considered as a general status functioning scale applicable for use after confirmed COVID-19 to assess changes in physical, mental, and social health status functionality. A baseline reference grading of functionality can be considered prior to SARS CoV-2 infection in study subjects. However, the PFCS scale should not replace but rather supplement assessment of any solicited and unsolicited adverse events during follow up visits.

Feasibility of assessing for Long COVID in clinical trials

Randomized controlled trials focus on demonstrating vaccine efficacy against COVID-19 of variable severity. None of the publicly available advanced stage clinical trial protocols consider assessment of Long COVID as an objective. Prospective assessment of solicited Long COVID symptoms triggered following a positive RT-PCR for COVID-19 is the most robust way of periodic symptom assessment. However, this study design may result in additional cost adjustments associated with data collection, particularly in ongoing studies. Alternatively, study sponsors can employ a nested retrospective cohort study with a questionnaire administered at the end of the study. This alternative is methodologically less robust; however, only requires a non-substantial amendment to the trial protocol and reconsent of subjects with confirmed COVID-19 for the additional research.

Describing the incidence of Long COVID as an exploratory objective within an efficacy trial is feasible through a protocol amendment. However, determining which endpoints are primary, secondary, or exploratory in a clinical trial, regardless of reasons, should always be made prospectively [1]. Exploratory endpoints often include important events expected to occur too infrequently to show a treatment effect or those less likely to show an effect for other reasons [1]. A comparison of symptom duration between subjects in the interventional and control arms must be conducted particularly for adverse events of mild to moderate severity grading. This provides an opportunity to accept or reject a hypothesis that vaccination against COVID-19 has a positive effect on the duration of COVID-19 symptoms.

Solicited and unsolicited systemic adverse events in Long COVID

There is no consensus on the definitive symptoms of Long COVID. The National Institute for Health and Care Excellence (NICE) describes Long COVID as signs and symptoms that develop or continue after acute COVID-19. It includes both ongoing symptomatic COVID-19 from four weeks to 12 weeks, and post COVID-19 syndrome with signs and symptoms that continue for >12 weeks [2]. Prospective observational cohort studies are the most commonly used study type for capturing signs and symptoms of Long COVID in subjects following acute episodes of COVID-19.

Ongoing or new symptoms following acute COVID-19 are highly variable and wide ranging. When Long COVID is prospectively assessed as an exploratory objective in a clinical trial, the corresponding exploratory endpoints should include all signs and symptoms that have been associated with Long COVID. Assessment of solicited and unsolicited adverse events following an acute episode of COVID-19 can be considered through to study completion in both the vaccinated and control groups within the trial. Various signs and symptoms (**Table 1**) have been identified as characteristic of Long COVID.

Table 1. Multisystemic symptoms of Long COVID[3,4,5,6]

Fatigue	Delirium	Tinnitus
Fever	Difficulty with concentration	Earache
Pain	Loss of memory	Hearing loss
Shortness of breath	Anxiety	Vertigo
Cough	Mood changes	Sore throat
Cognitive impairment (Brain fog)	Abdominal pain	Anosmia
Headache	Nausea	Ageusia
Insomnia	Diarrhea	Hoarse voice
Peripheral neuropathy	Loss of appetite	Acute kidney injury
Dizziness	Arthralgia	Skin rash
Depression	Myalgia	Hair loss
		Menstrual cycle changes

The symptom list displayed in **Table 1** is not exhaustive and there is lack of robust evidence on the prevalence of signs and symptoms with which to inform policy and treatment of Long COVID [7]. However, treatment should be tailored to individual symptoms based on their severity and duration in children and adult subjects affected by Long COVID.

Follow up

Follow up of clinical trial participants should be ideally for one to two years. Adverse events that could be characteristic of Long COVID should be followed up beyond 12 weeks after PCR confirmed COVID-19, for as long as is feasible with a final follow up visit at study conclusion [7]. Follow up should be considered even following the availability of a safe and effective vaccine.

Post-COVID-19 Functional Status (PCFS) scale

Given the heterogeneity of COVID-19 in terms of clinical and radiological presentation, the PCFS scale (**Table 2**) is to be considered when assessing the physical, mental, and social health functional limitations of subjects after confirmed COVID-19 [8]. The scale should be considered as a supplementary assessment tool and should not replace the regular assessment of solicited symptoms severity grading post-vaccination. The PCFS scale can be used to monitor the impact of Long COVID symptoms on the functional status of subjects during the assessment of subjects beyond 12 weeks from COVID-19 diagnosis, through to study conclusion. The PCFS scale will identify subjects suffering from a slow or incomplete recovery and help guide their management. The inclusion of pre-COVID-19 functional status at baseline or one month prior to infection as a reference value is optional and allows a change in status to be measured. The overall rating is equivalent to the poorest functional status indicated by the patients' responses [8].

Table 2. Post-COVID Functional Status Scale grading

Grade	Description
0	No functional limitations
1	Negligible functional limitations (All usual activities done at same level of intensity despite symptoms)
2	Slight functional limitations (Usual activities done at same level of intensity or sometimes avoided due to symptoms)
3	Moderate functional limitations (Usual activities structurally modified/reduced due to symptoms)
4	Severe functional limitations (Assistance needed in daily living activities due to symptoms). Nursing care required.
D	Death

Additional resources

1. FDA, 2017. Multiple endpoints in clinical trials- Guidance for Industry. January 2017. https://www.fda.gov/media/102657/download
2. COVID-19 rapid guideline: managing the long-term effects of COVID-19, National Institute for Health and Care Excellence guideline, 18 December 2020. https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-66142028400325
3. CDC (2020) Long term effects of COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html
4. Sudre, C. et al (2020) Attributes and predictors of Long COVID: Analysis of covid cases and their symptoms collected by the covid symptoms study app. https://www.medrxiv.org/content/10.1101/2020.10.19.20214494v1.full.pdf
5. The Prevalence of long COVID symptoms and COVID-19 complications, Office of National Statistics, 16 Dec 2020 https://www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications
6. Almufarrij I, Munro K. (2021) One year on: an updated systemic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms, International Journal of Audiology, 22 March 2021 https://www.tandfonline.com/doi/full/10.1080/14992027.2021.1896793
7. Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry, Food and Drug Administration, June 2020. https://www.fda.gov/media/139638/download
8. Klok FA, Boon GJAM, Barco S, et al. (2020) The Post-COVID-19 Functional Status (PCFS) Scale: a tool to measure functional status over time after COVID-19. Eur Respir J 2020; in press https://doi.org/10.1183/13993003.01494-2020) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7236834/pdf/ERJ-01494-2020.pdf