Summary Document

Topic: General Core Elements for Early Phase Clinical Trials of COVID-19 Vaccine Candidates: Aspects to Consider

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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 sets out general core clinical trial elements to be considered when designing Early-Phase clinical trials of COVID-19 vaccine candidates. Early-Phase trials are typically dose-finding and may include First-In-Human, Phase 1, and/or Phase 2a design aspects.

The sponsor is responsible for the clinical development of the COVID-19 vaccine candidate and will include construct- and platform-specific elements in the trial design, whilst complying with the competent authorities. However, additional elements including potential pathogen-specific elements should be considered in light of the accelerated development timelines in this pandemic. For example, the risk for potential vaccine-related disease enhancement described previously with SARS- and MERS vaccine candidates needs to be carefully considered and monitored.

As SARS-CoV-2 transmission emerges rapidly, the baseline serostatus in participants should be evaluated or – if respective assays are not yet available – samples collected for future evaluation. Prospective collection of data on confirmed COVID-19 cases in trial participants should be considered during the trial period as any data supporting vaccine efficacy may be relevant before large scale vaccine efficacy trials are conducted.

General Core Elements of Early Phase clinical trials of COVID-19 Vaccine Candidate:

Section	Element	Consideration	Rationale
Study population	Health Status	Should be performed in healthy* adults (* Individuals that are free of relevant acute or chronic medical disorders and are determined as healthy by medical history, physical examination, laboratory assessment and clinical judgment of the investigator)	• *To allow safety assessment without interference of underlying medical disorders e.g. compromised immunity, chronic diseases* • *To allow rapid recruitment* • *To minimize the risk of including subjects with conditions that may predispose them to vaccine-mediated enhanced disease (VMED) (e.g. SARS-CoV-2 infection)* • *To exclude subjects on concomitant medication associated with hACE-2 receptor upregulation (e.g. ACE-inhibitors, ibuprofen)*
	Age	Include healthy adults	• *Older adults are at increased risk of severe COVID-19 and COVID-19 related deaths* • *To minimize the influence of immunosenescence in FIH trials* • *Risk populations including older adults should be considered as early as possible after FIH*
	Gender	Adequate representation of both genders; strive for gender equality	• *Severe COVID-19 is reported more commonly in males than in females* • *To identify gender dependent safety risks or immune signals including VMED*
Study Design	Control Group	Include a control group (placebo or active)	• *To compare the vaccine safety, particularly any cases of VMED* • *To generate early vaccine efficacy data if COIVD-19 cases are detected during the trial*
	Dose levels	Preferably, 3 dose levels should be evaluated	• *To allow the generation of dose response curve and inform dose selection*
	Sample size	Sufficiently sized treatment arms	• *To minimize the risk of results being influenced by single extreme values* • *The sample size of early phase trials is selected to obtain descriptive estimates of reactogenicity and safety data and not calculated formally. A statement to that effect should be included*
Study Conduct	Nasopharyngeal and/or blood sampling for SARS-CoV-2	Pre- & post vaccination assessment of a) SARS-CoV-2 infection & b) anti-SARS-CoV-2 antibodies (binding or neutralizing)	• *To confirm post- vaccination SARS-CoV-2 infection (preferably through PCR) among symptomatic participants which may contribute to early efficacy data* • *To assess and characterize immune responses in baseline seropositives and seronegatives and its possible impact on VMED, if any (since enrolment of baseline seropositives cannot be completely*

Section	Element	Consideration	Rationale
			ruled out)[1]
	Other laboratory analyses	Pre- and post-immunization T-cell responses (Th1/Th2) and COVID-19 antigen-specific IgE[1]	• *To characterize the cell mediated immune (CMI) response* • *To assess CMI in the context of potential VMED* • *To detect anti-SARS-CoV-2 IgE which may have a role in VMED*
	Follow up duration	Safety follow up (SAEs, AESIs only) of preferably 12 months post vaccination	• *To allow reporting of delayed VMED* • *AESIs have been defined by Safety Platform for Emergency Vaccines (SPEAC)*[2]
Endpoints	Safety	Primary	• *In line with regulatory guidance and conventional clinical development pathway*
	Immunogenicity	Key immunogenicity endpoints (preferably at 2 or more weeks post last vaccination) defined for dose selection should be co-primary or secondary. Additional immunogenicity endpoints may be considered as exploratory. Considering construct-specific characteristics both humoral and CMI endpoints should be included	• *To gather early immune response information for vaccine* • *To support dose selection* • *To generate/ confirm hypothesis for subsequent clinical trials* • *Uniformity in the endpoints will allow comparisons across various CEPI programs and to historic data, if any*
	Efficacy	Confirmed COVID-19 cases during the entire follow up period (preferably 12 months) should be considered as an exploratory endpoint	• *To generate early efficacy data that may support rapid clinical development (Case definitions (CD) may not yet be in place but should be implemented as early as possible to allow for example integrated/prospective Bayesian analyses)*
Safety oversight	Halting rules	Define clearly in the protocol especially for safety occurrences	• *To allow objective monitoring of study progress and any safety concerns arising during the trial*
	Vaccine mediated ED	VMED should be monitored clinically throughout the trial period (e.g. more severe lung disease)	• *To detect presence of VMED early on in the program* • *CD of VMED is being defined by SPEAC and should be implemented when available*
	DSMB	An independent program DSMB should be established as early as possible to monitor program safety data as they accrue	• *To ensure independent review of data and to place program-specific data in the context of growing evidence from the current epidemic* • *To familiarize the DSMB as early as possible with the pathogen, the vaccine construct and platform*

1 - Consensus considerations on the assessment of the risk of disease enhancement with COVID-19 vaccines: Outcome of a Coalition for Epidemic Preparedness Innovations (CEPI)/Brighton Collaboration (BC) scientific working meeting, March 12-13, 2020.

2 - D2.3 Priority List of Adverse Events of Special Interest: COVID-19. V1.1 Date 05 March 2020.