Summary Document

Topic: Core Elements for Advanced Stage 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 core elements to be considered when designing advanced stage clinical trials of COVID-19 vaccine candidates. Advanced stage clinical trials (Phase 2b to 3) are typically conducted to evaluate the efficacy (or immunogenicity, where applicable) including in special populations (e.g. paediatric, geriatric, co-morbidities), and expand the safety database. This development pathway should allow rapid regulatory licensure (or other equivalent). Additional trials for special objectives (e.g. lot to lot consistency) may be considered separately from this pathway.

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, within the regulatory framework. However, some elements should be considered specifically in the light of need for accelerated development in the pandemic situation. An event driven trial with periodic interim endpoints and dynamic sample size may, for example, allow early determination of vaccine efficacy (VE) through pre-defined interim analysis (IA).

The control measures in community in light of COVID outbreaks may disturb trial continuity at one or multiple sites and there should be contingency plans to deal with the same. Vaccine-mediated enhanced disease (VMED) should be monitored but put in the context of data coming from early stage trials as well as animal studies. Standardization of diagnostic criteria, efficacy endpoints, follow up duration, immunogenicity testing will allow comparisons across programs.

Core Elements of Advanced Stage clinical trials of COVID-19 Vaccine Candidate:

Section	Element	Consideration	Rationale
Study population	Health Status	Individuals at risk of contracting SARS-CoV-2 infection and COVID-19. Certain underlying medical conditions should be allowed but chosen on construct specific considerations and trial objectives.	• *To allow enrollment of population that is representative of target population for eventual use of vaccine*
	Age	Enroll adult population, including a pre-defined minimal proportion of older adults. Consider defining a minimum proportion of subjects to be recruited in the older age population. An age based stratified randomization and/or analysis must be considered.	• *Older adults are at increased risk of severe and fatal COVID-19* • *Pediatric enrolment may not be possible in trials being done for initial licensure (or other equivalent), but may be enrolled in a separate trial to allow extension of indication* • *Consider a separate paediatric investigation plan in agreement with regulators*
	Pregnant and nursing women	May be enrolled as a subset in pivotal study or as part of a specifically focused study. Requirement for data will depend on the vaccine construct.	• *To allow inclusion of pregnant and nursing females in vaccine target population during post licensure use* • *Maintain a pregnancy register for inadvertent pregnancies*. • *Most clinical development programs will not consider enrolling pregnant women for an initial licensure (or other equivalent)*
	COVID-19 clinical illness	Screen for and exclude baseline acute COVID-19 cases. Serostatus at baseline needs to be established.	• *To avoid any interference with efficacy analysis* • *Baseline seropositives can be excluded from primary efficacy analysis, however a separate analysis based on serostatus may be considered*
Study Design	Vaccine efficacy (VE) as primary endpoint	Adaptive event-driven design: continue enrolment till there is a pre-defined degree of certainty that the true VE exceeds a pre-defined minimum VE as defined in the protocol or SAP for the study. [1]	• *To allow rapid study conduct and meet efficacy endpoint early* • *In the absence of a predictable incidence rate that can give a reliable sample size estimate, enrolment may continue till a fixed ratio of events across the treatment arms is achieved* • *Consider multiple interim analyses to detect early VE estimates*
	Vaccine safety as primary endpoint	Conventional RCT with fixed sample size calculated to establish vaccine safety.	• *To build a safety database as per regulatory requirements* • *In case vaccine efficacy is not being assessed as primary endpoint*
	Control Group	Trial should be controlled by having a placebo or active control arm. Active control may be considered as appropriate but corresponding vaccination regimen should be matched.	• *To allow assessment of vaccine efficacy and reactogenicity/safety* • *Use of placebo is justified in absence of existing standard of care. An end of study offer of a safe and effective vaccine (preferably licensed) may be considered among placebo recipients*
	Special objectives	Lot to lot (LTL) consistency; Feasibility of co-administration with other vaccines. (Either in separate trials or nested within a pivotal trial in subgroup). In absence of LTL consistency trial, include 2 separate lots of if available.	• *To allow expansion of indication (e.g. co-administration with flu vaccine)* • *To meet certain regulatory requirements (e.g LTL consistency)* • *A separate bridging trial may be considered in case vaccine efficacy is not established via the use of validated/commercial grade material*

Section	Element	Consideration	Rationale
Study Conduct	Study sites	Multiple sites with geographical diversity should be considered especially for efficacy trials. Recruitment may be started or halted at sites based on the outbreak situation in the region.	• *A large number of sites (catchment areas) increases the probability of exposure to SARS-CoV-2* • *To account for changing hot spots of the epidemic and for public-health interventions in different geographical locations* • *Take into account epidemiologic surveillance to identify sites with likely ongoing transmission when the efficacy trial is to be started*
	Follow up duration	A minimum safety follow-up of 12 months post last dose should be considered. This follow up may need to continue until after the VE endpoint has been achieved.	• *VE: Consider active (e.g. phone calls) and passive (e.g memory aids) follow up. For efficacy endpoint, consider data from 14 days post last dose.* • *Safety: 12 months is important to detect delayed VMED (e.g. in case nAbs levels are waning)* [2] *and other AESIs* • *Immune response: To allow evaluation of persistence of immune response*
	Nasopharyngeal sampling	Pre- (baseline) & post vaccination (during follow-p) virological confirmation of SARS-CoV-2 infection.	• *To evaluate vaccine efficacy against SARS-CoV-2 infection and COVID-19* • *Post vaccination sampling may be triggered by signs & symptoms indicative of SARS-CoV-2 infection.* [3] • *Baseline sampling will allow exclusion of active COVID-19 cases* • *If more frequent periodic sampling (e.g. weekly) is considered, it may allow detection of asymptomatic infections apart from clinical cases*
	Blood sampling	May be considered in all or in a subset to assess immunogenicity e.g. in defined subpopulations. Pre-vaccination samples, at least in a subset of volunteers would allow establishing baseline serostatus and should be strongly considered.	• *To evaluate immune response – both humoral and cell mediated – and attempt to establish a correlate of protection* • *To evaluate seroconversion to antibodies that are different than vaccine antigen. This may supplement the RT PCR in COVID-19 diagnosis* • *The full characterization of the quality of the immune response is important in understanding/ruling out potential VMED*
Endpoints	Efficacy	Trials designed for assessing VE, should consider prevention of WHO defined moderate to critical COVID-19 disease as primary endpoint. In case of low incidence rates, clinically symptomatic COVID-19 of any severity may be considered for primary endpoint. [3,4]	• *To allow earlier demonstration of VE by limiting vaccine-induced disease attenuation cases in the primary efficacy analysis* • *Prevention of mild or asymptomatic infections may be considered as secondary endpoint [3]* • *Other efficacy endpoints may include hospitalization, death, need for mechanical ventilation and MODS due to COVID-19 [3]*
	Safety	Local and systemic reactions should be evaluated in a subset. SAEs and AESI should be evaluated for 6 to 12 months while VMED should be evaluated for 12 months.	• *To confirm the findings of early stage clinical trials* • *To expand the safety database of the vaccine candidate in line with regulatory requirements* • *AESIs may include construct specific and COVID specific outcomes including VMED, if any [2]*
	Immunogenicity	Antibody response (seroconversion, GMTs) to vaccine antigen can be evaluated as a secondary and/or exploratory endpoint (also depending on	• *To confirm the findings from early stage clinical trial results, may suffice in a subgroup of enrolled population*

Section	Element	Consideration	Rationale
		validation status of the respective assay). It may suffice in a subset for a VE trial.	• *To investigate correlate of protection (CoP). If CoP has been established, it may be considered as primary endpoint in future / subsequent trials*. • *To evaluate immune response in special populations if enrolled (pediatric, older adults etc.)*
	Vaccine mediated Enhanced Disease	VMED should be monitored clinically throughout the trial period. [2]	• *Case definition of VMED should be implemented when available*
Independent oversight	DSMB	An independent program DSMB preferably that monitored the safety data during early stage trials.	• *To ensure independent review of safety data and monitor any halting rules* • *To make independent recommendations regarding enrolment continuity based on interim efficacy data*
	Endpoint adjudication committee	Consider implementing an independent committee of experts.	• *To allow objective adjudication of COVID-19 cases that need to be counted towards especially primary efficacy endpoint*
Statistical considerations	Interim Analysis (IA)	In an event-driven VE trial, include IA on accrual of a set number of cases to look for achievement of pre-defined VE criteria or futility. The procedure should be clearly defined in the SAP for the trial.	• *To allow early vaccine efficacy analysis [1]* • *IA may also be useful for other purposes like early immunogenicity data for decision making*

Additional Resources:

1. Vaccine Efficacy Assessment for COVID-19. Version 1.0. 07 May 2020. Available at: https://epi.tghn.org/covid-19/document-forum/
2. Lambert P-H, Ambrosino DM, Andersen SR, Baric RS, Black SB, Chen RT et al. Consensus summary report for CEPI/BC March 12–13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine. 25 May 2020. doi: 10.1016/j.vaccine.2020.05.064.
3. COVID-19 Efficacy Endpoints in Interventional Trials: What Constitutes an Incident Clinical Disease Case and What Triggers Diagnostic Work-Up. Version 2.0. 25 June 2020. Available at: https://epi.tghn.org/covid-19/document-forum/
4. Clinical Management of COVID-19 (WHO interim guidance): https://www.who.int/publications/ i/item/clinical-management-of-covid-19.