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 is not exhaustive. Due to the rapidly evolving situation, this table may not include the latest evidence. Updates will be issued when significant new information becomes available. The purpose of this document 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 document aims to compare guidance and core elements with regards to the design of Early Phase and Advanced Stage clinical trials of COVID-19 vaccine candidates. This comparison is based on the United States Food and Drug Administration (US FDA) Guidance on Development and Licensure of vaccines to Prevent COVID-19, World Health Organization's (WHO) International Randomised Trial of candidate vaccines against COVID-19, a Summary of the June 22, 2020 teleconference on global regulators convened under the auspices of International Coalition of Medicines Regulatory Authorities (ICMRA), and summary documents developed by the Coalition for Epidemic Preparedness Innovations (CEPI).

Early and Advanced Stage Clinical Development Core Elements- Comparison of the Guidance and Considerations

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Key Element		US FDA (1)	WHO (2)	ICMRA (3)	CEPI (4)
Early Stage Clinical Trials					
Study population	Health status	Healthy adult participants at low risk of severe COVID-19. Older adult participants (e.g. over 55 years of age) who do not have underlying comorbidities associated with an increased risk of severe COVID-19 may be enrolled in FIH and other early phase studies. Exclude participants at high risk of SARS-CoV-2 exposure (e.g. healthcare workers).			Adults with no relevant acute or chronic medical disorders and with a healthy medical history, physical examination, laboratory assessment, and clinically judged as such by the investigator. This is to enable safety assessment without interference by underlying medical disorders, allow rapid recruitment, minimize risk of including subjects with conditions that may predispose them to possible VMED, and exclude subjects on con-meds associated with hACE2 receptor upregulation.
	Age	Healthy adults. Subjects over 60 years of age may be included in early stage clinical development provided there are sufficient data to support a low risk of enhanced disease among vaccinees.			Include healthy adults. Older adults are at increased risk of severe COVID-19 and related deaths. To minimize the influence of immunosenescence in FIH trials, risk populations including older adults should be included as early as possible after FIH.
	Gender				Strive for gender equality and adequate representation of both genders. Severe COVID-19 is reported more commonly in males than females. This helps to identify gender-dependent safety risks or immune signals.
Study Design	Control group	Inclusion of placebo control (and blinding) are not required for early phase studies, but may assist in interpretation of preliminary safety data			Include a control group (placebo or active) for comparison of vaccine safety (particularly any cases of VMED) and to generate early efficacy data if COVID-19 cases are detected during the trial.
	Dose levels	Sponsors should at the minimum collect and evaluate clinical safety and immunogenicity data for each dose level and age group (e.g. younger versus older adults) to support progression of clinical development to include larger numbers (e.g., hundreds) of participants and those at higher risk of severe COVID-19			Preferably three dose levels should be evaluated to enable generation of a dose response curve and to inform dose selection.
	Sample size	FIH and other early phase studies (which typically expose 10–100 participants to each vaccine candidate) should first enrol healthy adult participants at low risk of severe COVID-19			Sufficiently sized treatment arms are encouraged to minimize the risk of results being influenced by single extreme values/outliers. The sample size is selected to obtain descriptive estimates of reactogenicity and safety data.

Study conduct	Nasopharyngeal and/or blood sampling				Pre- & post-vaccination assessment of a) SARS-CoV-2 infection to confirm post-vaccination SARS-C0V-2 infection among symptomatic participants which may contribute to early efficacy data, and b) anti-SARS-CoV-2 antibodies (binding or neutralizing) to assess and characterize immune responses in baseline seropositives and seronegatives and any possible impact on VMED (since enrolment of baseline seropositives cannot be completely ruled out).
	Other laboratory analyses				Pre- and post-immunization T cell responses (Th1/Th2) and COVID-19 antigen-specific IgE to enable characterization of the cell-mediated immune response and detection of anti-SARS-CoV-2 IgE which may have a role in possible VMED.
	Follow-up duration				Safety follow-up (SAEs, AESIs only) for preferably 12 months post vaccination to allow reporting of delayed VMED.
Endpoints	Safety	Initiation of late phase trials should be preceded by adequate characterization of safety and immunogenicity (e.g. in a few hundred participants for each vacccine candidate, dose level, and age group) to support general safety, potential for vaccine efficacy, and low risk of vaccine associated ERD. Early phase trials often aim to down-select among multiple vaccine candidates and/or dosing regimens via randomization of participants to different treatment groups. Inclusion of a placebo control group and blinding are not required for early phase studies but may assist in interpretation of preliminary safety data.			Primary - In line with regulatory guidance and conventional clinical development pathway
	Immunogenicity	Preliminary immunogenicity data from early phase development should include assessments of neutralizing versus total antibody responses and Th1 versus Th2 polarization. Immunogenicity studies in animal models, sensitive to the selected COVID-19 vaccine antigen, should be conducted to evaluate the immunological properties of the COVID-19 vaccine candidate and to support FIH clinical trials. COVID-19 vaccine candidates with immunogenicity data demonstrating high neutralizing antibody titers and Th1-type T cell polarization may be allowed to proceed to FIH trials without first completing postvaccination challenge studies in appropriate animal models, provided adequate risk mitigation strategies are put in place in the FIH trials.			Key immunogenicity endpoints (preferably at least 2 weeks following the last vaccination) defined for dose selection should be coprimary or secondary. Additional immunogenicity endpoints may be considered exploratory. Possible humoral and CMI endpoints should consider construct-specific characteristics.
	Efficacy				Confirmed COVID-19 cases during the entire follow-up period (preferably 12 months) should be considered an exploratory endpoint.
Safety oversight	Halting rules	Studies should include pre-specified criteria for halting based on signals of potential vaccine-associated ERD	Each candidate vaccine will be monitored for early evidence of benefit or lack of benefit using prespecified monitoring guidelines and boundaries. This may lead to halting further randomization of participants into a vaccine and/or placebo arm. Further randomization will be halted for vaccine arms that meet lack-of-benefit criteria in an interim analysis. Monitoring for lack of benefit enables halting further randomization to vaccine arms if the incidence of enhanced disease interferes with demonstration of efficacy.	The protocol should include pre-specified criteria for study halt or pause, based on signals of potential vaccine-induced enhanced disease.	Define safety occurrences clearly in the protocol to allow for objective monitoring of study progress and any safety concerns arising during the trial.

	VMED				Possible VMED should be monitored clinically throughout the trial period (e.g. more severe lung disease) to enable early detection in the program. The case definition of VMED should be implemented when available.
	DSMB				An independent program DSMB should be established as early as possible to monitor program safety data. The DSMB will place program-specific data in the context of growing evidence from the current pandemic.

Advanced Stage Clinical Trials

Key Element		US FDA (1)	WHO (2)	ICMRA (3)	CEPI (5)
Study population	Health status	Many thousands of participants, including many with medical comorbidities for trials evaluating protection against severe COVID-19, are needed for late phase clinical trials to demonstrate vaccine efficacy with formal hypothesis testing. It will be important to ensure that elderly subjects represent a meaningful proportion of those enrolled, considering the importance of protecting populations at increased risk for severe disease.	Adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on surveillance data and epidemiologic modelling	Efforts should be made to include diverse populations (e.g. race and ethnicity) in Phase 3 clinical trials. Phase 3 clinical trials to demonstrate vaccine efficacy will need to enrol many thousands of participants, including those with medical comorbidities, to generate relevant data for the key target populations.	Individuals at risk of contracting SARS-CoV-2 infection and COVID-19. Participants with certain underlying medical conditions should be allowed but selected taking into account construct-specific considerations and trial objectives.
	Age	Late phase clinical trials to demonstrate vaccine efficacy with formal hypothesis testing will likely need to enrol thousands of participants, including many with medical comorbidities for trials evaluating protection against severe COVID-19. The iPSP should be submitted as a pre-IND submission if it is expected upon submission of the IND that initial studies will include a phase 3 study. In order to comply with 21 CFR Part 50 Subpart D (Additional safeguards for children in clinical investigations), considerations regarding direct benefit and acceptable risk to support initiation of pediatric studies and appropriate design and endpoints for pediatric studies, should be discussed in the context of specific vaccine development programs.	Recruitment should ensure adequate generalizability of results, including important characteristics such as age (including elderly). Participants must meet inclusion/exclusion criteria for at least one vaccine in the trial.	It is important to include older adults (e.g. over 55 years of age) including those with co-morbidities in Phase 3 clinical trials. Inclusion of this population will need to be guided by safety and immunogenicity data obtained from healthy younger adults and healthy older individuals who participated in Phase 1 and 2 clinical trials with the respective SARS-CoV-2 vaccine. Participants acknowledged the relevance of evaluating safety and efficacy of subjects older than 75 years. Vaccine manufacturers to plan for pediatric assessments of safety and effectiveness for SARS-CoV-2 vaccines, given the epidemiology of COVID-19 in this population, and as safety and effectiveness of SARS-CoV-2 vaccines may be different in children compared with adults. It was acknowledged that initial licensure of SARS-CoV-2 vaccines would likely be in adults.	Enrol adult population, including a pre-defined minimum proportion of older adults. An age-based stratified analysis should be considered. Paediatric enrolment may not be possible in trials conducted for initial licensure; however, children 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	Prior to the enrolment of pregnant women and women of childbearing potential who are not actively avoiding pregnancy into clinical trials, sponsors should conduct developmental and reproductive toxicity (DART) studies of their respective COVID-19 vaccine candidate. Alternatively, sponsors may submit available data from DART studies using a similar product and comparable platform technology if, following consultation, the agency agrees those data are scientifically sufficient. Early in their development programs the FDA encourages vaccine developers to consider data that might support inclusion of pregnant women and women of childbearing potential who are not actively avoiding pregnancy in prelicensure clinical trials. All pregnancies that occur in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination, should be followed up and pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies, assesed.	Outcomes of pregnancies in women who are inadvertently vaccinated will be reported	The decision to include pregnant women in clinical trials is case-by-case and would be based on the totality of data available for the vaccine construct, including available data from developmental and reproductive toxicology studies conducted with the specific vaccine construct or with a different vaccine based on the same platform. Favorable safety and immunogenicity data in women of childbearing potential derived from early Phase clinical trials are also needed.	Pregnant and nursing women may be enrolled as a subset in a pivotal study or as part of a specifically focused study. Requirement for data will depend on the vaccine construct. This will allow for inclusion of pregnant and nursing females in the target population during post-licensure use. Also maintain a pregnancy register for inadvertent pregnancies.
	COVID-19 clinical illness		Some sites will optionally collect blood samples at baseline, following the last vaccination, and at longer time intervals post-vaccination to characterize vaccine-induced immune responses, evaluate immunological markers as correlates of risk of COVID-19, and determine whether there is any risk of COVID-19 in participants seropositive for SARS-CoV-2 at enrolment and whether this is affected by vaccination		Exclude baseline acute COVID-19 cases during screening. Serostatus at baseline needs to be established. Baseline seropositives can be excluded from primary efficacy analysis; however a separate analysis based on serostatus may be considered.
Study design	Vaccine efficacy as primary endpoint	Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial. FDA recommends that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically-confirmed SARS-CoV-2 infection with one or more of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and/or diarrhoea	The primary objective is to evaluate the effect of each vaccine on the rate of virologically-confirmed COVID-19 disease, regardless of severity. COVID-19 disease rates for each vaccine will be compared with COVID-19 rates for the shared concurrently randomized placebo/control group. The key pre-specified analysis of the primary endpoint will include (for each participant) the first COVID-19 case starting at least 14 days after the first dose. Compared to conducting separate trials for each candidate vaccine, evaluating candidate vaccines in parallel with a common placebo group reduces uncertainties in endpoint acquisition rates and increases the likelihood of enrolling enough trial participants to rapidly assess the efficacy of each vaccine. A serological assay (likely based on responses to a non-spike protein) that is able to distinguish viral infection from vaccine immune responses can be used to evaluate vaccine efficacy against infection as a secondary endpoint.	The primary endpoint should be laboratory-confirmed COVID-19 of any severity.	Adaptive event-driven design: continue enrolment until 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 to enable rapid study conduct and early demonstration of vaccine efficacy. In the absence of a predictable incidence rate that can give a reliable sample size estimate, enrolment may continue until a fixed ratio of events across the treatment arms is achieved. Consider interim analyses to detect early VE estimates.
	Vaccine safety as primary endpoint	The safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for vaccines against other infectious diseases. The pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure. Not all participants need to be monitored for solicited adverse events (i.e. reactogenicity) provided that reactogenicity is adequately characterized in all populations intended for licensure.	Evaluation of COVID-19 vaccine safety is one of the primary objectives of this trial. All sites will monitor and report serious adverse events (SAEs) at any time after vaccination. Safety monitoring will be continuous at all sites.		Conventional RCT with fixed sample size calculated to establish vaccine safety and build a safety database as per regulatory requirements.

	Control group	Later phase trials, including efficacy trials, should be randomized, double blinded, and placebo controlled	By using a shared placebo/control group and a common Core protocol to evaluate multiple candidate vaccines in the trial, resources allocated to the evaluation of each candidate vaccine are judiciously saved while a high standard of scientific rigor and efficiency is ensured. Outcomes in recipients of each vaccine candidate will be compared with outcomes in all placebo recipients who were eligible to be randomized to that vaccine. This approach preserves blinding and enables comparison of each vaccine's results directly to results from an equal number of controls who received placebo at the same time and place.		Trial should be controlled by having a placebo or active control arm. Active control may be considered appropriate but corresponding vaccination regimen should be matched.
	Special objectives	The approval pathway (accelerated or traditional) plays no role in the need to demonstrate consistency of manufacture. A formal clinical lot-to-lot consistency study may not be required prior to licensure depending on the product and its manufacturing process. These data could for example be obtained as part of ongoing clinical safety and efficacy studies. Regardless, analytical characterization sufficient to support product consistency should be demonstrated prior to licensure.			Lot to lot (LTL) consistency; feasibility of co-administration with other vaccines (either in separate trials or nested within a pivotal trial). In the absence of LTL consistency trial, include two separate lots if available. A separate bridging trial may be considered in case vaccine efficacy is not established via the use of validated/commercial grade material.
Study conduct	Study sites		Sites with sufficient transmission rates at the time of joining the trial can participate. Participating sites must be able to determine whether trial participants develop COVID-19, perform safety follow-up, and ensure multiple ways exist to contact participants to maintain follow up and retention. To enhance broad international participation, sites may not evaluate all vaccines (due to local regulatory constraints, product availability, or other limiting factors), and may not evaluate all secondary study objectives (due to resource constraints or other limiting factors). New study sites may be added as needed to ensure a high COVID-19 attack rate.		Multiple, geographically diverse sites should be considered for efficacy trials. A large number of sites (catchment areas) increases the probability of exposure to SARS-CoV-2. Recruitment may be started or halted at sites based on the outbreak situation in the region. At the start of the efficacy trial, take into account epidemiological surveillance to identify sites with likely ongoing transmission.
	Followup duration	Follow-up of study participants for COVID-19 outcomes, especially severe COVID-19, should continue as long as is feasible but ideally for at least 1 to 2 years to enable assessment of duration of protection and potential for vaccine-associated ERD as immune responses to the vaccine wane. Ideally, a Biologic License Application submission would include blinded 6-month safety data from at least 3,000 study participants who have received the vaccine at the dose intended for licensure. Further discussion would be needed on the acceptability of alternative proposals for the safety database, including numbers of participants with 6-month safety data to be included in the initial submission and in a safety update submitted during review. Providing multiple safety updates during the course of a BLA review would be counterproductive to the completion of an expedited review.	Follow-up for assessing vaccine efficacy will comprise weekly automated active follow up of participants, where reporting of COVID-19 relevant symptoms (as per WHO case definitions) will trigger testing for SARS-CoV-2 infection. This weekly contact will help reduce loss of trial participants and increase the likelihood of COVID-19 detection. Following a diagnosis of COVID-19, participants will be referred locally for management as required. Blinded study follow up for COVID-19 disease and SAEs is planned to last for at least one year (and preferably longer).	Follow-up of study participants for COVID-19 outcomes should be long enough (i.e. 1 year or longer post-vaccination) to evaluate safety, duration of immune response, and risk of disease enhancement as antibody titres wane	A minimum safety follow-up of 12 months following the 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 primary efficacy endpoint, consider data from 14 days following the last dose; Safety: 12 months is important to detect delayed possible VMED (e.g. in case nAbs levels are waning) and other AESIs; To allow evaluation of persistence of immune response.

	Nasopharyngeal sampling	Acute cases of COVID-19 should be virologically confirmed (e.g. by RT PCR). Virological or serological methods to evaluate antibodies to SARS-CoV-2 antigens not included in the vaccine can be used to monitor and confirm SARS-CoV-2 infection, including asymptomatic infection.			Pre- (baseline) & post-vaccination (during follow-up) 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. 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		Some sites will optionally collect blood samples at baseline, following the last vaccination, and at longer time intervals after vaccination, and explicitly seek consent for sample storage and use of stored material for research purposes. These blood samples can be used for example to assess of the effect of vaccination on antibody levels or on the rate of infection with SARS-CoV-2 (secondary endpoint). This will require the development of a serological assay that can distinguish between responses to infection and vaccination.		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 baseline serostatus to be determined and should be strongly considered.
Endpoint	Efficacy	Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial	The primary objective is to evaluate the effect of each vaccine on the rate of virologically-confirmed COVID-19 disease, regardless of severity. The key pre-specified primary analysis of the primary endpoint will include (for each participant) the first COVID-19 disease episode that occurrs at least 14 days after the first dose. Developers of multidose vaccines may reach an alternative agreement with regulators regarding the primary analysis, which must be prospectively conveyed to the DMC.		Trials designed to assess 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 the primary endpoint.
	Safety	Safety assessments throughout clinical development should include: Solicited local and systemic adverse events for at least 7 days after each study vaccination in an adequate number of study participants to characterize reactogenicity. Unsolicited adverse events in all study participants for at least 21–28 days after each study vaccination. Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations. Longer safety monitoring may be warranted for certain vaccine platforms (e.g. those that include novel adjuvants). All pregnancies in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination should be followed up and pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies, assessed. Data from a CHIM alone would not suffice to support an accelerated, conditional or equivalent or even full license (provided that adequate post-approval efficacy/effectiveness and safety studies are in place)	All sites will monitor and report serious adverse events (SAEs) at any time after vaccination, by baseline SARS-CoV-2 serostatus where available. Safety monitoring will be continuous at all sites. The DMC will also monitor any specific AEs of special interest (AESIs), as required. Safety endpoints that may not be evaluated at all sites will include solicited adverse events (AEs) up to 14 days following each vaccination, other (unsolicited) AEs by body system, MDRA preferred terms up to 28 days post-vaccination, AESIs, and medically-attended events (MAEs). Blinded study follow up for COVID-19 disease and SAEs is planned to last for at least one year (and preferably longer). This will enable further analysis of duration of efficacy and potential for risk of vaccine-induced COVID-19 disease enhancement in the presence of waning immunity.		Local and systemic reactions should be evaluated in a subset of participants. SAEs and AESIs should be evaluated for the full study duration while VMED should be evaluated for 12 months.
	Immunogenicity	Assays used for immunogenicity evaluation should be suitable for their intended purpose (i.e. to assess relevant immune responses to vaccination) and be validated before use in pivotal clinical trials.	Additional secondary and supportive endpoints, for which monitoring is valuable but optional at each study site, include infection with SARS-CoV-2, transmission of SARS-CoV-2, and possible immunological markers as correlates of risk		Antibody response (seroconversion, GMTs) to vaccine antigen can be evaluated as a secondary and/or exploratory endpoint (also depending on validation status of the respective assay). It may suffice in a subset for a VE trial.

	VMED	Follow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue for as long as is feasible but ideally for at least one to two years in order to assess duration of protection and potential for vaccine-associated ERD as immune response to the vaccine wane. Rates of severe disease amongst vaccinees subsequently exposed to SARS-CoV-2 compared to non-vaccinees with similar exposures will be the most important source of information about VMED to support licensure. Continued assessments of COVID-19 disease outcomes and immunogenicity, following submission of the BLA and post-licensure, will be important to further evaluate risk of VMED.	If a vaccine meets a monitoring boundary for enhanced disease, randomization to this vaccine will cease but the result will be reported only if necessary to protect trial subjects or if the finding is confirmed with additional follow-up	Clinical data characterizing the vaccine-induced immune response should include an evaluation of immune markers of potential enhanced respiratory disease outcomes (i.e. assessment of functional immune responses [neutralizing antibody] versus total antibody responses and Th1/Th2 balance). If older subjects (e.g. subjects older than 55 years) are included in Phase 3 clinical studies, preliminary safety and immunogenicity data derived from these populations are also needed.	Possible VMED should be monitored clinically throughout the trial period.
Independent oversight	DSMB	FDA recommends use of an independent data safety monitoring board for monitoring vaccine-associated ERD and other safety signals, especially during later stage development	Trial oversight will be provided by a single Steering Committee (SC) and a single data monitoring committee (DMC). Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the SC, which will not have access to unblinded study data. The role of the DMC will be to apply pre- (and SC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety and data integrity issues.		An independent program DSMB that preferably monitored safety data during early stage trials.
	Endpoint adjudication committee				Consider implementing an independent committee of experts
Statistical consideration	Interim analysis	*Late phase studies should include interim analyses to assess risk of vaccine-associated ERD and futility* . Study sample sizes and timing of interim analyses should be based on the statistical success criteria for primary and secondary (if applicable) efficacy analyses and realistic, data-driven estimates of vaccine efficacy and incidence of COVID-19 (or SARS-CoV-2 infection) for the populations and localities in which the trial will be conducted. To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the *lower bound* of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is *>30%* . The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy. *A lower bound ≤ 30% but > 0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint* , provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.	In the event that one or more vaccines satisfies benefit or lack of benefit criteria in an interim analysis, further randomization of participants to those arms may cease but blinded follow-up of participants will continue for all vaccine arms and the shared placebo/control arm to ensure valid assessment of efficacy for all vaccines under study and to enhance data for evaluating the durability of vaccine efficacy (VE). Subject to adaptation as the trial proceeds, *a successful vaccine will have a sequential-monitoring-adjusted 95% lower bound of the confidence interval on vaccine efficacy that exceeds 30% . The point estimate for VE should be at least 50%* , in agreement with the minimum requirement given in the WHO Target Product Profile. The null hypothesis VE value may be adaptively modified to below 30% during the trial, based on a lower-than-projected COVID-19 attack rate or participant accrual rate, with collaborative decision-making by individuals who only have access to blinded data (e.g. study Steering Committee and blinded study statisticians).	Phase 3 clinical trials should also include interim analyses to assess risk of enhanced disease and futility	In an event-driven VE trial, include interim analyses for a set number of cases to assess achievement of pre-defined VE criteria or futility. The procedure should be clearly defined in the SAP for the trial.

References

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