Guideline on nonclinical and clinical evaluation of covid-19 Vaccine

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1. Introduction

There is an ongoing global health challenge posed by SARS-CoV-2, the virus causing COVID-19, which has evolved since its emergence in 2019. Multiple variants have emerged, including Omicron sublineages such as JN.1, KP.2, and LP.8.1, necessitating periodic updates to vaccine compositions.

As of 2025, several EDA-authorized vaccines are available to prevent COVID-19, including those adapted for variants. Commercial vaccine manufacturers and other entities continue to develop and update COVID-19 vaccine candidates using technologies such as mRNA, protein subunit, viral vectors, and inactivated vaccines.

This guideline describes EDA's current recommendations regarding the data needed to facilitate non-clinical and clinical development, licensure, technology transfer and updates of vaccines to prevent COVID-19. With accumulated real-world data, immune correlates of protection (e.g., neutralizing antibody levels) may serve as surrogates for efficacy in certain contexts, such as variant updates via immune-bridging studies. However, for novel vaccines, the goal remains traditional approval via direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection, severe disease, and hospitalization.

This document provides guideline to developers, companies or sponsors on non-clinical and clinical assessment used by the Egyptian drug authority (EDA) to evaluate COVID-19 vaccines that are submitted for:

- Non-clinical results submission,
- Clinical results submission,
- Clinical trial application submission,
- Registration,
- Emergency use approval.
- Technical support for non-clinical results and clinical data including results and protocol assistance.

Guideline for Good Regulatory Oversight of clinical trials by Egyptian Drug Authority, and its updates shall be applied with this guideline, whenever applicable.

This document should not be read as a standalone document; other relevant documents must also be consulted, including ICH guidelines (e.g., E5 for ethnic factors) and EDA's Guidelines on Emergency Use Approval.

2. Scope

This guideline outlines the following:

- Nonclinical and clinical data that would be required to support approval of "COVID-19" vaccine
- Nonclinical and clinical data that would be required to support approval of a variant vaccine, whether monovalent or multivalent, including annual updates for circulating strains (e.g., JN.1-lineage for 2025-2026)
- Emergency Use Authorization for Vaccines to Prevent COVID-19, including post-authorization surveillance.
- Technology transfer and /or any variation in manufacturing process, with emphasis on comparability for variant adaptations.

3. Legal Provisions:

- Law No. 151 for year 2019 Promulgating law establishing the Egyptian Authority for Unified Procurement, Medical Supply and Technology Management (AUPP) and the Egyptian Drug Authority (EDA) and its executive regulation no.777/2020.
- Law No. 214 for year 2020 Promulgating the law to regulate Clinical Medical Research.
- Prime Minister's Decree No. 927 of 2022 On Promulgating the Executive Regulation of law on regulating Clinical Medical Research Promulgated by Law No. 214 for year 2020.

- Egyptian Drug Authority Chairman's Decree No.111 Of 2022 Concerning Approving the Egyptian Guideline for Regulatory Procedures of Good Oversight on Clinical Research Practice.

- Egyptian Drug Authority Guidelines on Emergency Use Approval.

4. Abbreviations

ACE: Angiotensin converting enzyme
CBRN: Chemical, Biological, Radiological, or Nuclear
CI: Confidence Interval
COVID-19: Coronavirus Disease Of 2019
CTD: Common Technical Document
DART: Developmental And Reproductive Toxicity
DSMB: Data and Safety Monitoring Board reports
DBP: Diastolic Blood Pressure
DNA: Deoxyribonucleic acid
DSMB: Data Safety Monitoring Board
ECMO: Extracorporeal Membrane Oxygenation
EDA: Egyptian Drug Authority
ELISA: Enzyme Linked Immunosorbent Assays
ERD: Enhanced Respiratory Disease
EUA: Emergency Use Authorization
EUL: Emergency use listing
FIH: First in human use
FiO2 : Fraction of Inspired Oxygen
GCP: Good clinical practice
GLP: Good Laboratory Practices
GMT: Geometric Mean Titre
JN.1: SARS-CoV-2 Variant Lineage
LB: Lower Bound
MERS-CoV: Middle East respiratory syndrome coronavirus
NHP: Non-Human Primates
NRA: National regulatory authority
PaO2: Partial Pressure of Oxygen
R&D : Research And Development
RMP: Risk management plans
RNA: Ribonucleic acid
RSV: Respiratory Syncytial Virus
RT-PCR: Reverse Transcription–Polymerase Chain Reaction
SAEs: Serious Adverse Events
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2
SBP: Systolic Blood Pressure
SpO2: Peripheral Oxygen Saturation
SRR: Seroresponse Rate
Th1: T helper Cell type 1
Th2: T helper Cell type 2
VAED: Vaccine Associated Enhanced Disease
VED : Vaccine-enhanced disease
VSV: Vesicular Stomatitis Virus
WHO: World Health Organization

5. Non-clinical Information

5.1. General Considerations

The purpose of nonclinical studies of a COVID-19 vaccine candidate is:
To define its immunogenicity and safety characteristics through in vitro and in vivo testing.
Nonclinical studies in animal models help to identify potential vaccine related safety risks and guide the selection of dose, dosing regimen, and route of administration to be used in clinical studies.

The extent of nonclinical data required to support proceeding to first in human (FIH) clinical trials depends on the vaccine construct, the supportive data available for the construct and data from closely related vaccines.

The Data from studies in animal models administered certain vaccine constructed against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated enhanced respiratory disease (ERD). In these studies, animal models were administered vaccine constructed against other coronaviruses and subsequently challenged with the respective wild-type virus. These studies have shown evidence of immunopathology lung reactions characteristic of a Th-2 type hypersensitivity similar to ERD described in infants and animals that were administered formalin-inactivated respiratory syncytial virus (RSV) vaccine and that were subsequently challenged with RSV virus due to natural exposure or in the laboratory, respectively. Post-approval data from 2021-2025 indicate low ERD risk in licensed vaccines, but monitoring remains essential for novel constructs.

Assays for vaccines with multiple components or adjuvants should be measured with either a multiplex assay or separate single assays. The assays used for immunogenicity evaluation should be validated for their intended purpose and calibrated against WHO international standards when available.

5.2. Immunogenicity:

Immunogenicity studies in animal models responsive to the selected COVID-19 vaccine antigen should be conducted to evaluate the immunologic properties of the COVID-19 vaccine candidate and to support FIH clinical trials.

The aspects of immunogenicity to be measured should be appropriate for the vaccine construct and its intended mechanism of action.

These immunogenicity studies should assess:

- Bio/Immunological markers should include relative levels of neutralizing vs non-neutralizing antibodies, antibody affinity, T-cell response profile (Th1/Th2), characterization of lung histopathology, and other potential complications.

- Studies should include an evaluation of humoral, cellular, and functional immune responses, as appropriate to each of the included COVID-19 antigens, with consideration of the adjuvant effect. Use of isotype-specific enzyme linked immunosorbent assays (ELISA) should be considered to characterize the humoral response. Evaluation of cellular responses should include the examination of CD8+ and CD4+ T cell responses using sensitive and specific assays. The functional activity of immune responses should be evaluated in vitro in neutralization assays using either wild-type virus or pseudo-virus microneutralization.

- For variant updates, compare responses to current strains.

5.3. Toxicity Studies:

When needed to support proceeding to FIH clinical trials, nonclinical safety assessments including toxicity and local tolerance studies must be conducted under conditions consistent with regulations prescribing good laboratory practices (GLP).

Such studies should be completed and analyzed prior to initiation of FIH clinical trials. When toxicology studies do not adequately characterize risk, additional safety testing should be conducted as appropriate.
Nonclinical safety studies will be required prior to FIH clinical trials in case of a COVID-19 vaccine candidate consisting of a novel product type and for which no prior nonclinical and clinical data are available.

Adequate information to characterize product safety may be available from other sources. For example, if the COVID-19 vaccine candidate is made using a platform technology utilized to manufacture a licensed vaccine or other previously studied investigational vaccines and is sufficiently characterized, it may be possible to use toxicology data (e.g., data from repeat

dose toxicity studies, biodistribution studies) and clinical data accrued with other products using the same platform to support FIH clinical trials for that COVID-19 vaccine candidate Thus, performing nonclinical safety studies prior to FIH clinical trials may not be necessary.

For variant updates, bridging nonclinical data may be adequate if comparability is demonstrated.

5.3.1 Design:

The preclinical toxicity study should be adequate to identify and characterize potential toxic effects of a vaccine to allow investigators to conclude that it is reasonably safe to proceed to clinical investigation.

The parameters to be considered in designing animal toxicology studies: the relevant animal species and strain, dosing schedule and method of vaccine administration, as well as timing of evaluation of end-points (e.g., sampling for clinical chemistry, antibody evaluation and necropsy). The route of administration should correspond to that intended for use in the clinical trials.

5.3.2 Animal species, sex, age and size of groups:

Data to be recorded on the animals used for toxicity testing should include information on the source, species and animal husbandry procedures (e.g., housing, feeding, handling and care of animals).

- **The animal species** used should develop an immune response to the vaccine antigen. In general, one relevant animal species is sufficient for use in toxicity studies to support initiation of clinical trials.

"Despite digital modelling predictions based on Angiotensin converting enzyme 2 (ACE2) genetic analysis, some animal species predicted to be susceptible are seemingly resistant, whilst others are susceptible when not expected to be. Pathogenesis studies have, however, been conducted mainly in human ACE2 transgenic mice, hamsters, ferrets and various Non-Human Primates (NHP) models, including Rhesus macaques, cynomolgus macaques and African green monkeys. For variant testing, use models challenged with current strains."

- **The size** of the treatment group depends on the animal model chosen.

➢ **The number of animals** used in studies using non-human primates would be expected to be less than that in studies that used rodents. For mice and rats, it is recommended that at least 10 animals of each sex per group be used for the necropsy at the end of the treatment interval, and at least 5 animals of each sex per group be used for the necropsy at the end of the recovery period.

➢ **The sex of animals** used in studies, both sexes should be used, for small animal models, e.g., rats and mice, it is recommended that approximately 1:1 per group studied.

➢ **The approximate age** at the start of the study for rodents is 6–8 weeks.

5.3.3 Dose, route of administration and control groups:

The toxicity study should be performed using a dose that maximizes exposure of the animal to the candidate vaccine and the immune response induced, for example, peak antibody response. In general, an evaluation of the dose–response is not required as part of the basic toxicity assessment and the lethal dose does not have to be determined. However, pilot dose–response studies may be conducted to determine which dose induces the highest antibody production in the animal model. If feasible, the highest dose (in absolute terms) to be used in the proposed clinical trial should be evaluated in the animal model. The number of doses administered to the test animals should be equal to or more than the number of doses proposed in humans. To better simulate the proposed clinical usage, vaccine doses should be given at defined time intervals rather than as daily doses. For boosters, evaluate additional doses.

5.3.4 Parameters:

Toxicity studies, repeated-dose toxicity studies in particular, should be designed to evaluate a broad spectrum of parameters due to the uncertainty of the in vivo effects and associated outcomes. Toxicity studies should be designed to mimic the intended route of administration in the clinic and to evaluate local reactogenicity (e.g., injection-site inflammation), possible effects on the draining lymph nodes and systemic toxicity (i.e. toxicity that occurs at sites distant from the site of initial administration) including, but not limited to, the systemic effects on the immune system.

➢ **Parameters** to be monitored should include:
- Daily clinical observations
- Weekly body weights

- Weekly food consumption.

During the first week of administration frequent measurements of body weight and food consumption are recommended, if feasible, as these are sensitive parameters indicating "illness".
-Interim analysis of haematology and serum chemistry should be considered approximately 1–3 days following the administration of the first and last dose and at the end of the recovery period (e.g., 2 or more weeks following the last dose).
Haematology and serum chemistry analyses should include, at the minimum, an evaluation of relative and absolute differential white blood cell counts (lymphocytes, monocytes, granulocytes, abnormal cells) and albumin/globulin ratio, enzymes and electrolytes.

-Post-mortem data, including data from gross necropsy (with tissue collection and preservation, including gross lesions and organ weights), should be collected within 3 days following the last dose and following the above-mentioned recovery period. In addition, a description of cellular infiltrates based on routine histological staining, if present, should be reported as part of the post-mortem evaluation, as well as any manifestation of tissue damage at the site of injection and surrounding anatomic structures (e.g. sciatic nerves).

Histopathological examinations of tissues should be performed and special attention should be paid to the immune organs, i.e., lymph nodes (both local and distant from site of administration), thymus, spleen, bone marrow and Peyer's patches or bronchus associated lymphoid tissue, as well as organs that may be expected to be affected as a result of the particular route of administration chosen. Histopathological examinations should always include pivotal organs (e.g. brain, kidneys, liver and reproductive organs) and the site of vaccine administration. The choice of tissues to be examined will depend on the vaccine in question, and the knowledge and experience obtained from previous nonclinical and clinical testing of the vaccine components. For example, full tissue examination will be required in the case of novel vaccines for which no prior nonclinical and clinical data are available.

5.3.5 Repeated – dose toxicity studies

The study design for pivotal toxicity studies that should be conducted with the same vaccine formulation intended to be used in clinical trials. If more than one dose of an antigen or adjuvant is to be evaluated in the clinical study, the formulation containing the highest dose should be included in the pivotal toxicity studies.
Single-dose toxicity study - as a stand-alone study- on the final formulated vaccine product is usually not needed. Acute effects of administering a vaccine can also be monitored in

repeated-dose toxicity studies if they are adequately designed (e.g. an evaluation is conducted after the first administration). Alternatively, acute effects can be assessed in a single-dose design as part of a local tolerance study.

5.3.6 Genotoxicity and carcinogenicity studies:

Genotoxicity studies are normally not needed for the final vaccine formulation. However, they may be required for particular vaccine components such as novel adjuvants and additives. If needed, the in
vitro tests for mutations and chromosomal damage should be done prior to first human exposure. The full battery of tests for genotoxicity may be performed in parallel with clinical trials.
Carcinogenicity studies are not required for vaccine antigens. However, they may be required for particular vaccine components such as novel adjuvants and additives.

5.3.7 Local tolerance

The evaluation of local tolerance should be conducted either as a part of the repeated dose toxicity study or as a stand-alone study. Tolerance should be determined at those sites that come into contact with the vaccine antigen as a result of the method of administration, and also at those sites inadvertently exposed (e.g. eye exposure during administration by aerosol) to the vaccine.

5.3.8 Safety pharmacology studies:

The purpose of a safety pharmacology study is to investigate the effects of the candidate vaccine on vital functions. Although not usually required, safety pharmacology studies may be recommended in some cases. For example, if data from nonclinical and/or human clinical studies suggest that the vaccine may affect physiological functions other than the immune system (e.g. the central nervous system, respiratory or cardiovascular system, renal function or body temperature) then safety pharmacology studies should be incorporated into the safety assessment programme.

* Additional studies for safety assessment have been considered for the specific situation in which the target population for novel vaccine includes very young subjects– such as neonates and elderly patient.

5.4. Studies to Address the Potential for Vaccine-associated Enhanced Respiratory Disease

- Current knowledge and understanding of the potential risk of COVID-19 vaccine-enhanced disease (VED) is limited, as is understanding of the value of available animal models in predicting the likelihood of such occurrence in humans. Nevertheless, studies in animal models (e.g., rodents and non-human primates) are considered important to address the potential for vaccine-associated ERD.
- Post-vaccination animal challenge studies and the characterization of the type of the nonclinical and clinical immune response induced by the particular COVID-19 vaccine candidate can be used to evaluate the likelihood of the vaccine to induce vaccine-associated ERD in humans.
- To support proceeding to FIH clinical trials, sponsors should conduct studies characterizing the vaccine-induced immune response in animal models evaluating immune markers of potential ERD outcomes. These should include assessments of functional immune responses (e.g., neutralizing antibody) versus total antibody responses and Th1/Th2 balance in animals vaccinated with clinically relevant doses of the COVID-19 vaccine candidate.
- COVID-19 vaccine candidates with immunogenicity data demonstrating high neutralizing antibody titres and Th1-type T cell polarization may be allowed to proceed to FIH trials without first completing post vaccination challenge studies in appropriate animal models, provided adequate risk mitigation strategies are put in place in the FIH trials. In these situations, post vaccination challenge studies are expected to be conducted in parallel with FIH trials to ensure the potential for vaccine-associated ERD is addressed prior to enrolling large numbers of human subjects into Phase 2 and 3 clinical trials. For COVID-19 vaccine candidates for which other data raise increased concerns about ERD, post vaccination animal challenge data and/or animal immunopathology studies are critical to assess protection and/or ERD *prior* to advancing to FIH clinical trials
- The totality of data for a specific COVID-19 vaccine candidate, including data from postvaccination challenge studies in small animal models and from FIH clinical trials characterizing the type of immune responses induced by the vaccine will be considered in determining whether Phase 3 studies can proceed in the absence of postvaccination challenge data to address risk of ERD.

5.5. Biodistribution studies

Biodistribution studies in an animal species should be considered if the vaccine construct is novel in nature and there are no existing biodistribution data from the platform technology.

These studies should be conducted if there is a likelihood of altered infectivity and tissue tropism or if a novel route of administration and formulation is to be used.

5.6. Variant-Specific Nonclinical Considerations

For updates to antigen composition, nonclinical immunogenicity studies should demonstrate comparable responses to licensed prototypes. Challenge studies with variant viruses recommended if feasible.

6. Clinical Assessment

6.1. General Considerations

Clinical development programs for COVID-19 vaccines might be expedited by adaptive and/or seamless clinical trial designs that allow for selection between vaccine candidates and dosing regimens and for more rapid progression through the usual phases of clinical development.

The applicant should provide in the CTD a tabulated summary of the clinical development program in one or more tables.

The applicant must provide the English version of the protocols of the clinical trials supporting the application. The protocols should be the final approved versions, incorporating all amendments.

Evidence of approval of the clinical trials by competent Ethics Committees, as well as information about their contact details, are expected to be included in the CTD.

In the absence of a certificate of GCP compliance from the responsible EDA, applicants should provide evidence of GCP compliance for each trial. This might include evidence of the independent monitoring of the trial conduct, audits by the sponsor, available NRA inspection reports or Data and Safety Monitoring Board (DSMB) reports.

In addition, it is important to assess the impact of ethnic factors on the vaccine's safety and effectiveness. These principles are discussed in the guidance document entitled, "E5: Ethnic Factors in the Acceptability of Foreign Clinical Data" dated June 2004.

Post-marketing data, including pharmacovigilance from risk management plans (RMPs), should be integrated to monitor long-term effectiveness against variants and waning immunity, as per EDA's 2023 EUA guidelines and WHO recommendations from May 2025.

6.2. Clinical trials populations

First In human Use (FIH):

- (20–80 participants) to each vaccine candidate being evaluated)
- Healthy adult participants who are at low risk of severe COVID-19

As understanding of COVID-19 pathogenesis continues to evolve, **eligibility criteria** should reflect current knowledge of risk factors for severe disease, such as those described by the Centre for Disease Control and Prevention.

Exclusion criteria:

a) Exclusion participants at higher risk of severe COVID-19 from early phase studies is necessary to mitigate potential risk of vaccine-associated ERD until additional data to inform that potential risk becomes available through ongoing product development.
b) Participants are at high risk of SARS-CoV-2 exposure (e.g., healthcare workers).
c) Older adult participants (e.g., over 55 years of age) may be enrolled in FIH and other early phase studies as long as they do not have medical comorbidities associated with an increased risk of severe COVID-19. preliminary safety data in younger adults (e.g., 7 days after a single vaccination) should be available prior to enrolling older adult participants, especially for vaccine platforms without prior clinical experience.

Data requirements:

Sponsors should collect and evaluate at least preliminary 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 participants at higher risk of severe COVID-19;

- Preliminary immunogenicity data from early phase development should include assessments of neutralizing vs. total antibody responses and Th1 vs. Th2 polarization.
- Additional data to further inform potential risk of vaccine-associated ERD and to support progression of clinical development, if available, may include preliminary evaluation of COVID-19 disease outcomes from earlier clinical development and results of non-clinical studies evaluating protection and/or histopathological markers of vaccine-associated ERD following SARS-CoV-2 challenge.

Late phase clinical trials

Designed to demonstrate vaccine efficacy with formal hypothesis testing will likely need to enroll many thousands of participants (elderly), including many with medical comorbidities for trials seeking to assess protection against severe COVID-19.

- Initiation of late phase trials should be preceded by adequate characterization of safety and immunogenicity (e.g., in a few hundred participants for each vaccine candidate, dose level, and age group to be evaluated) to support general safety, potential for vaccine efficacy, and low risk of vaccine-associated ERD.
- Results of non-clinical studies evaluating protection and/or histopathological markers of vaccine-associated ERD following SARS-CoV-2 challenge and COVID-19 disease outcomes from earlier clinical development are other potentially important sources of information to support clinical trials with thousands of participants.

Special Population Considerations

Although establishing vaccine safety and efficacy in SARS-CoV-2 naïve individuals is critical, vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, which might have been asymptomatic, is also important to examine because pre-vaccination screening for prior infection is unlikely to occur in practice with the deployment of licensed COVID-19 vaccines. Therefore, COVID-19 vaccine trials need not screen for or exclude participants with history or laboratory evidence of prior SARS-CoV-2 infection. However, individuals with acute COVID-19 (or other acute infectious illness) should be excluded from COVID-19 vaccine trials.

Inclusion of **diverse populations** in all phases of vaccine clinical development helps to ensure that vaccines are safe and effective for everyone in the indicated populations.
Evaluation of vaccine safety and efficacy in late phase clinical development in adults should include adequate representation of elderly individuals and individuals with medical comorbidities.

High-risk populations:

- Prioritize high-risk groups such as those aged 65+, immunocompromised, and pregnant individuals in later phases, including diverse Egyptian populations (e.g., urban/rural, ethnic subgroups, and socioeconomic factors per ICH E5 and EDA requirements).

Pediatric populations:

- Plans for paediatric studies, including studies of safety and effectiveness to support use in infants, if applicable, should be included in the clinical development plan, consistent with Egyptian paediatric regulatory requirements. The epidemiology and pathogenesis of COVID-19, and the safety and effectiveness of COVID-19 vaccines, may be different in children compared with adults.

Pregnant women and women of childbearing

- Plans for clinical development in pregnant women and women of childbearing potential should be included, in line with (FDA and EMA, 2025) guidance on safety data in this population.

6.3. Clinical Trial Design

6.3.1. Early phase (phase I/II a):

- Protocols for early-stage trials (phase I/IIa) should be designed to find a suitable candidate formulation, to define the appropriate dose level and immunization schedule, and to make a preliminary assessment of safety and immunogenicity.
- Data on neutralizing antibodies and demonstration of cell mediated immune and binding antibody responses is required.
- The immune responses to be evaluated should include binding antibody titres, functional antibody activity (e.g., virus neutralization assays) and, if feasible, mucosal immune responses and cell-mediated immune responses.
- Frequent technical support assistance from EDA may be needed to guide decision making in adaptive or seamless trials in their early stages.

6.3.2. Later phase trials /Efficacy Trials (phase IIb/III):

- Phase IIb/III efficacy trials should be randomized, blinded, and placebo controlled or active- controlled (when a safe and effective COVID-19 vaccine is available). An individually randomized controlled trial with 1:1 or 2:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy. Other types of randomizations, such as cluster randomization, may be acceptable if there is evidence that potential biases have been avoided.

- Protocols for adaptive trials should include pre-specified criteria for adding or removing vaccine candidates or dosing regimens, and protocols for seamless trials should include pre-specified criteria (e.g., safety and immunogenicity data) for advancing from one phase of the study to the next. For new or modified COVID-19 vaccines, including variant-specific updates, immune-bridging studies are preferred, with non-inferiority criteria: GMT ratio ≥0.67 and SRR difference ≥-10%, as per WHO and FDA 2025 recommendations. Demonstration of vaccine efficacy in preventing COVID-19 may be based on non-inferiority (NI) to a licensed COVID-19 vaccine comparator using an immunological surrogate of protection.
- *The pre-specified NI margin should be justified and should reflect a clinically acceptable difference. For example, if the lower bound of the 95% CI for the geometric mean titre (GMT) ratio is > 0.67 and the lower bound of the 95% CI for the difference in seroresponse rates (SRR) is > -10%, this could be considered to support a conclusion of NI.
- If a trial is designed to demonstrate superiority of one vaccine over another with respect to the selected immunogenicity endpoint(s), the trial should be adequately powered for that purpose.
- If immune correlates of protection are formally established, these could be used as surrogates for COVID-19 disease endpoints to support an approval and/or to extrapolate efficacy to certain populations.
- Cell-mediated immunity assays and binding antibody assays may be important to characterize vaccine immunogenicity as a secondary or exploratory endpoint but are not expected to be used for the purpose of immune-bridging.
- Confirmatory evidence of vaccine efficacy (VE) based on a clinically relevant endpoint is expected to support approval.
- A safety database of at least 3,000 vaccine recipients considered representative of the target population(s) followed for serious adverse events (SAEs) and adverse events of special interest (AESIs) for at least 1 month after completion of the full vaccination regimen is expected to support authorization for emergency use.
- Plans for active safety follow-up after completion of primary analyses should be provided, including for waning of effectiveness and monitoring for potential ERD/VAED.

6.4. Follow-up in clinical trials

Participants in confirmatory clinical trials should be followed for COVID-19 outcomes and safety for as long as feasible, ideally up to 1-2 years after completion of vaccination to assess duration of protection and potential for late-occurring SAEs, including ERD.
For variant updates, follow-up of at least 6 months post-booster is recommended, per FDA 2025 guidance.

6.5. Clinical trial end-point assays - relevance, validation and accreditation

Assays for primary and key secondary endpoints (e.g., virus neutralization, RT-PCR for virologic confirmation) should be validated and conducted in accredited laboratories. • For variants, assays should be updated to detect current strains.

6.6. Vaccine lots used in clinical studies and lot-to-lot consistency studies

Vaccine lots used in confirmatory trials should be manufactured under GMP and representative of the final formulation intended to marketing. Lot-to-lot consistency should be demonstrated in at least 3 consecutive lots, with immunogenicity as the primary measure.
If clinical lot to lot consistency data has not been demonstrated, CMC consistency data must be provided.

6.7. Requirement for a RMP or equivalent document as part of the CTD

Risk management plans (RMP), including pharmacovigilance plans, are part of modern risk management strategies required for vaccines detailing post-authorization safety and effectiveness monitoring, including for rare events and variants. This is particularly relevant in COVID 19 where more knowledge is still being accumulated. For more details regarding RMP requirements; applicant shall follow guideline on Emergency Use Approval (EUA), by Egyptian Drug Authority.

6.8. Efficacy Considerations

Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial.
Acute cases of COVID-19 should be virologically confirmed (e.g., by RT-PCR).
SARS-CoV-2 infection, including asymptomatic infection, can be monitored for and confirmed either by virologic methods or by serologic methods evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine.
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
- Diarrhea

When COVID-19 vaccine might be much more effective in preventing severe versus mild COVID-19, sponsors should consider powering efficacy trials for formal hypothesis testing on a severe COVID-19 endpoint. Regardless, severe COVID-19 should be evaluated as a secondary endpoint (with or without formal hypothesis testing) if not evaluated as a primary endpoint.

Severe COVID-19 should be defined as virologically confirmed SARS-CoV-2 infection with any of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
- Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)

- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

SARS-CoV-2 infection (whether or not symptomatic) should be evaluated as a secondary or exploratory endpoint, if not evaluated as a primary endpoint.

The above diagnostic criteria may need to be modified in certain populations; for example, in pediatric patients and those with respiratory comorbidities. Sponsors should discuss their proposed case definitions with EDA prior to initiating enrollment.

6.9. Statistical Considerations

To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint 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 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.
For non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is >-10%.
For each vaccine candidate, appropriate statistical methods should be used to control type 1 error for hypothesis testing on multiple endpoints and/or interim efficacy analyses.
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 locales in which the trial will be conducted.
Trials should be powered for the primary endpoint with at least 80-90% power, assuming true VE of 60-70%.
Interim analyses for efficacy, futility, or safety should use pre-specified boundaries. For NI in bridging studies, justify margins based on historical data.

6.10. Safety Considerations

6.10.1. Pre-licensure safety evaluation:

The general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases. 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 (including at least a subset of participants in late phase efficacy trials).
- 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).
- For causality assessment of adverse events following immunization during conducting clinical trials and for submission of marketing authorization, please refer to "Causality assessment of an adverse event following immunization (AEFI), WHO, second edition 2019 update"
- All pregnancies in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination should be followed for pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies.

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.

COVID-19 vaccine trials should periodically be monitored for unfavorable imbalances between vaccine and control groups in COVID-19 disease outcomes, in particular for cases of severe COVID-19 that may be a signal for vaccine-associated ERD.

Studies should include pre-specified criteria for halting based on signals of potential vaccine-associated ERD.

Use of an independent data safety monitoring board (DSMB) for vaccine-associated ERD and other safety signal monitoring, especially during later stage development.

6.10.2. Post-licensure safety evaluation

- The number of subjects receiving a COVID-19 vaccine in pre-licensure clinical studies may not be adequate to detect some adverse reactions that may occur infrequently.
- Pre-licensure safety data in some subpopulations likely to receive a COVID-19 vaccine (e.g., pregnant individuals, or individuals with medical comorbidities) may be limited at the time of licensure.
- Safety evaluations should include solicited local/systemic reactions for 7 days post-vaccination, unsolicited AEs for 28 days, SAEs/AESIs (e.g., anaphylaxis, myocarditis, ERD) throughout follow-up.
- Special attention to high-risk groups, with enhanced monitoring per 2025 guidelines.
- Pregnancy outcomes should be followed if exposure occurs.
- The safety follow-up period to monitor the possibility of vaccine-associated ERD and other adverse reactions may not have been completed for all subjects enrolled in pre-licensure clinical studies before the vaccine is licensed.
- Required Post marketing Safety Studies at the time of approval to assess a known serious risk related to the use of the drug, to assess signals of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk. Taking into consideration requirements listed on Guideline on Emergency Use Approval (EUA), by Egyptian Drug Authority.

Note:

- **For interventional studies:** please follow Guideline for good regulatory oversight of clinical trials by Egyptian Drug Authority.
- **For observational, non-interventional PASS/PAES:** Please follow the "PASS module" within the PV regulations by Egyptian Drug Authority.

6.11. Diagnostic and Serological Assays – Key Considerations

Diagnostic assays used to support the pivotal efficacy analysis (e.g., RT-PCR) should be sensitive and accurate for the purpose of confirming infection and should be validated before use.

Assays used for immunogenicity evaluation should be suitable for their intended purpose of assessing relevant immune responses to vaccination and to be validated before use in pivotal clinical trials.

6.12. Specific Considerations in Demonstrating Vaccine Effectiveness

Given the current state of knowledge about COVID-19, the most direct approach to demonstrate effectiveness for a COVID-19 vaccine candidate is based on clinical endpoint efficacy trials showing protection against disease.

For a COVID-19 vaccine, it may be possible to approve a product under these provisions based on adequate and well-controlled clinical trials establishing an effect of the product on a surrogate endpoint (e.g., immune response) that is reasonably likely to predict clinical benefit.

A potential surrogate endpoint likely would depend on the characteristics of the vaccine, such as antigen structure, mode of delivery, and antigen processing and presentation in the individual vaccinated. For example, an immune marker established for an adenovirus-based vaccine cannot be presumed applicable to a Vesicular Stomatitis Virus (VSV)-based vaccine, given that the two vaccines present antigen in different ways and engender different types of protective immune responses.

Since SARS-CoV-2 represents a novel pathogen, a surrogate endpoint reasonably likely to predict protection from COVID-19 should ideally be derived from human efficacy studies examining clinical disease endpoints.

An adequate dataset evaluating the safety of the vaccine in humans would need to be provided for consideration of licensure.

If it is no longer possible to demonstrate vaccine effectiveness by way of conducting clinical disease endpoint efficacy studies, the use of a controlled human infection model to obtain evidence to support vaccine efficacy may be considered. However, many issues, including logistical, human subject protection, ethical, and scientific issues, would need to be satisfactorily addressed. At this time no controlled human infection models for SARS-CoV-2 have been established or characterized.

6.13. Considerations for Booster Doses and Immunocompromised Populations

Recommend additional doses for immunocompromised per FDA/CDC 2025. Boosters annually for variants.

7. Emergency Use Authorization for Vaccines to Prevent COVID-19

The following information must be part of the dossier for EUL application. However, the totality of the available scientific evidence relevant to the product (the preclinical and human clinical study data) will be considered.

Results from both final report and pre specified interim reports are acceptable.

Results for a given vaccine will be reported when the study reaches a monitoring boundary. Interim analyses should be timed considering the potential of such analyses to meet the criteria noted below.

After this report, study subjects will continue to be followed for additional endpoints as additional safety and efficacy data is required. Efficacy against the secondary endpoint of severe disease should be reported at the time that primary endpoint analyses are reported.

Efficacy should be evaluated by accumulating end points at least two weeks after full schedule administered after vaccination for a one dose regimen or at least one week after the last vaccination of a multi-dose regimen. Cases should be accumulated for at least 2 months to exclude that any effect is just only innate immunity or immediate post vaccination neutralization titers of short duration. Annex I is summarizing Specific data that shall be submitted to answer certain questions

Taking into consideration requirements listed on Guideline on Emergency Use Approval (EUA), by Egyptian Drug Authority.

7.1. Efficacy

The primary efficacy endpoint point estimate 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%. In order to evaluate the duration of protection by the vaccine, subjects should continue to be followed for a period to estimate this.

Subgroup analyses of efficacy endpoints stratified by prior infection status at trial enrolment should be done.

Efficacy data including a median follow-up duration of at least two months after completion of administration of all doses in the schedule

7.2. Safety

The general safety evaluation should be no different than for other preventive vaccines.

- **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 (including at least a subset of participants in late phase efficacy trials).
- **Unsolicited** adverse events in all study participants for at least 28 days after each study vaccination.
- **Serious adverse** events in all study participants for at least 6 months after completion of all study vaccinations.

- **Longer safety monitoring** may be needed for certain vaccine platforms (e.g., those that include novel adjuvants). **Specifically,**

▪ **Phase 1 and 2 trials:** data on short and longer term follow up, including data on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study subjects.

▪ **Phase 3 studies:** safety data from a minimum number of vaccinees including a median follow-up duration of at least two months after completion of administration of all doses in the schedule.

7.3. Reports should include:

Adverse events; cases of severe COVID-19 disease among study subjects; and cases of COVID-19 occurring at least 14 days after the last dose is administered.

Subgroup analyses of safety and efficacy endpoints stratified by prior infection status at trial enrolment.

Data on sufficient cases of COVID-19 among trial participants to investigate the low risk for Vaccine Associated Enhanced Disease (VAED).

7.4. Follow up

Blinded study follow-up, for COVID19 disease and for SAEs, should 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. In the event that there is evidence of waning efficacy of a successful vaccine over the period of observation, participants in this trial may be randomized to prospectively designed controlled study of a booster dose. Vaccinated subjects experiencing a respiratory infection in the follow up period should be tested for specific pathogen.

Active safety follow-up must also be implemented in all vaccinees to further document safety: Local and systemic solicited adverse reactions collected for the defined duration of follow-up in an adequate number of subjects to characterize reactogenicity in each protocol-defined age cohort participating in the trial.

7.5. Benefit Risk assessment Report

A detailed review of available data and objective Benefit and Risk assessment of the vaccine [e.g., via the appropriate Brighton Collaboration standardized templates for benefit–risk

assessment of vaccines (by technology platforms) or any other separate document] should be provided at the time of submission.

7.5.1. Risk Management Plan

A detailed RMP including pharmacovigilance and risk minimization plans (or equivalent documents) should be provided

8. Technology transfer and /or any variation in manufacturing process

In case of technology transfer and in case of any variation in manufacturing process, the WHO guideline "Annex 4 Guidelines on procedures and data requirements for changes to approved vaccines" should be followed to evaluate the impact of changes on safety and efficacy and determine need of any additional clinical trial (s).

Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.

9. References:

9.1. WHO. Statement on the antigen composition of COVID-19 vaccines. May 15, 2025 (Clinical Management of Covid-19 “living guideline”-June 2025” .
9.2. COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025
9.3. WHO Technical Report Series, No. 927, 2005 Annex 1 WHO guidelines on nonclinical evaluation of vaccines
9.4. Development and Licensure of Vaccines to Prevent COVID-19, Food and Drug Administration, October 2023
9.5. EMA recommendation to update the antigenic composition of authorized COVID-19 vaccines for 2025-2026. WHO R&D Blueprint COVID-19 Animal Models ad hoc working group, 26MAR-1JUN 2020
9.6. Emergency Use Authorization for Vaccines to Prevent COVID-19, Food and Drug Administration, May 2021
9.7. Guidelines on procedures and data requirements for changes to approved vaccines, Annex 4, WHO Technical Report Series No. 993, 2015
9.8. Guideline For Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority.
9.9. Guideline on Emergency Use Approval (EUA), April 2023.
9.10. Appendix: Considerations for evaluation of modified COVID-19 vaccines (version 31 March 2022)
9.11. Guidelines on clinical evaluation of vaccines: regulatory expectations”, WHO TRS 1004, Annex 9, 2017.
9.12. Considerations for Evaluation of Covid19 Vaccines, 30 March 2022
9.13. Causality assessment of an adverse event following immunization (AEFI), WHO, second edition 2019 update
9.14. Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. WHO TRS 987, Annex2, 2014

History Table

Version No.	Issue date	Summary of Changes
1.0	28 April 2026	Fist version