# Summary Document

## Topic: Vaccine Efficacy Assessment for COVID-19

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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 provides guidance on the assessment of Vaccine Efficacy (VE) for use in COVID-19 interventional trials using an adaptive-designed number-of-events approach. This concept is under development for the WHO's Solidarity trial. It is recommended that all COVID-19 vaccine interventional trials prospectively collect incident COVID-19 cases. The primary outcome measure of interest for establishing VE, is COVID-19 clinical *disease* as opposed to SARS-CoV-2 *infection*. Clinical trials that assess incident COVID-19 cases should use standard criteria to establish the clinical diagnosis of COVID-19 *disease* [defined in a separate summary document] and consider implementing a committee for clinical endpoint adjudication of COVID-19 cases on a continuous basis.

An assumption on background incident rates of clinical COVID-19 endpoints in the placebo arm is impractical and may be counterproductive. During a public-health emergency, incidence rates differ from one day to the next, from location to location, and differ from one risk group to the other. Moreover, COVID-19 spread amongst the population is managed by classic public health interventions such as social distancing, quarantine and isolation, further complicating the assumptions required to estimate the number of persons to be randomized in the interventional trial.

An alternative approach is a design in which power and precision are not dictated by the size of the trial but rather by the overall number of cases identified for the primary endpoint. This means that the size of the trial cannot be accurately predicted ahead of time and that enrolment should continue until the number of required cases has been reached. Sponsors can define a pre-defined minimum sample size based on the size required for the safety database.

Ideally, early stage clinical development trials for COVID-19 vaccine candidates should prospectively collect incident disease cases to aid exploratory assessment of VE. Standardized consistent endpoint definitions for clinical disease across early and advanced stage trials would facilitate pooled analysis.

The demonstration of vaccine efficacy (VE) is fundamental for licensure and the indication for use in target populations. Vaccine efficacy is defined as the ***proportionate*** reduction of the incidence of the target disease in vaccinated participants compared to controls. Vaccine efficacy equals one minus the hazard, odds, or risk ratio.

The spatiotemporal variability in the incidence of disease during a public health emergency (PHE) presents unique challenges. Incident disease cases will shift continuously in time and place with surges in particular areas at different times. In the dynamic phase of the COVID-19 pandemic, even high-quality surveillance and observational data are ill-suited to predict tomorrow's attack rate and best locations for the clinical trial. Public-health interventions such as quarantine and social-distancing aiming to reduce COVID-19 spread until the sporadic occurrence of new infections, further complicate the trial's assumptions. The approach of recruiting persons at highest risk of disease to maximize the trial's power and reduce its sample size, may have limited use when high-risk persons are self-isolating. Exclusive enrolment of high-risk groups also risks poor generalizability if the study population differs from the population for which the vaccine is intended.

The uncertainty of the course of the COVID-19 pandemic makes it very difficult to accurately predict the background incident rate of COVID-19 cases in the clinical trial. However, VE is defined as a ***proportionate*** reduction of incidence and therefore ***independent*** of the background incidence. When it is not possible to reliably estimate the sample size to attain the number of incident COVID-19 cases that are necessary for appropriate precision, an useful alternative might be to conduct an event-driven trial in a large number of sites recruiting persons representative for the vaccine's intended use.

An event-driven trial depends on reaching a sufficient number of incident COVID-19 cases in the control arm and is independent of the number of persons in the trial. The requirement of cases in the control arm explains why a 1:1 randomization between vaccine and control might be most effective. In event-driven trials, enrollment and observation continue until a set number of events have occurred. With this approach, calculations on the number of endpoints needed are based on type I error, power, and assumed (minimum) VE. In an *adaptive-designed* event-driven trial, enrollment continues until there is a pre-defined degree of certainty that the true VE exceeds a pre-defined minimum VE. During a PHE, such an approach could be effective in showing early efficacy. In the adaptive design, the primary objective can be met with a relatively low number of events, for example when at an early analysis point all cases have been found to occur in the control arm and a zero incidence in vaccinated persons for a 100% VE point estimate.

As the point estimate is rarely 100%, it is anticipated that an independent data monitoring committee (IDMC) needs to assess vaccine performance every so many cases. For each distribution for each number of cases, the probability that the true VE exceeds the pre-defined minimum VE can be calculated. When at any analysis point the stopping rule for success has been met, the IDMC would recommend stopping enrollment. Conversely the probability of failing to reach the primary endpoint can be estimated for each distribution for each number of cases. If based on pre-defined criteria the vaccine is performing poorer than expected, and it becomes unlikely that the primary endpoint will be reached, the IDMC would recommend stopping enrolment for futility. If neither is the case, the IDMC would recommend continued enrolment per protocol until the set number of cases has been attained. There are several methods including Bayesian and frequentist to make the calculations that guide the IDMC's decisions. These techniques generally require a stricter significance threshold for individual comparisons to compensate for multiplicity.

The primary goal of COVID-19 efficacy trials will be to obtain data as quickly as possible to support broad use of the vaccine under a defined regulatory framework. The stopping-rules for success, those of attaining the primary endpoint, should be set in agreement with regulatory authorities. An endpoint-driven trial may be the quickest way to licensure and merits consideration. The number of persons randomized in an event-driven trial cannot be predicted ahead of time. This means that enrolment should continue until the stopping rules for success has been met, unless the IDMC recommends termination for futility guided by the stopping rules for failure. A sensible approach is to

plan for a ***minimum*** sample size driven by the required safety database, assuming a 1:1 randomization.

The approach of an event-driven trial with multiple pre-planned analyses requires careful planning, including a clinical endpoint adjudication committee that meets on an ongoing basis, an independent statistician familiar with adaptive designed clinical trials who is not part of the clinical-trial team, and a dedicated statistician in the IDMC. The stopping rules for success and failure must be pre-defined to guide the IDMC in its recommendations.

For best interpretability, a single primary endpoint and a limited number of secondary endpoints should be considered. In COVID-19 efficacy trials, the primary endpoint should measure the disease-related outcome of public-health interest of **virologically-confirmed COVID-19 *illness*** [defined in a separate summary document].

For COVID-19 efficacy trials, the primary analysis should include COVID-19 cases adjudicated by the endpoint committee. Early occurring cases might be censored on a trial-by-trial basis.

**Additional Resources:**

Design of vaccine efficacy trials to be used during public health emergencies; points of consideration and key principles
http://www10.who.int/blueprint/what/norms-standards/AP1_guidelines_Online_Consultation.pdf

WHO draft outline for 'An international randomised trial of candidate vaccines against COVID-19:
https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/

For treatment effect monitoring and stopping rules
https://online.stat.psu.edu/stat509/node/75/

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