Summary Document

Topic: Considerations for Inclusion of Risk Populations into COVID-19 Vaccine Efficacy Trials

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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 discusses the inclusion of individuals from risk groups into COVID-19 vaccine efficacy trials and some challenges posed. Pregnant women and children are not considered within the scope of this paper. Demonstration of vaccine efficacy in a pandemic situation is time critical so that a potentially efficacious vaccine can be deployed for use during the pandemic. While those included in COVID-19 vaccine efficacy trials should be recruited strategically to demonstrate vaccine efficacy at the earliest possible time, such trials should include adequate representation of those at higher risk of severe disease who are likely to be the initial target population for vaccination post approval.

Risk factors for severe COVID-19 include, but are not limited to, older age, diabetes, obesity, and cardiovascular and pulmonary diseases. Older adults should be appropriately represented, and relaxing trial exclusion criteria to allow inclusion of those with co-morbidities will enable critical data to be obtained to better characterize the benefit-risk profile in those most at risk of severe COVID-19. The challenge for vaccine developers is to balance the risk of disease with the risk of infection. If strict non-pharmaceutical interventions (NPI) including shielding at home, are implemented to protect the most vulnerable individuals from SARS-CoV-2 exposure, those at highest risk of severe disease may be at low risk for infection.

Socioeconomic deprivation is an independent risk factor for both infection and disease. Of all risk factors, socioeconomic deprivation appears least affected by NPIs and is unique in that its relative contribution to COVID-19 mortality has been suggested to increase over time. This risk group is anticipated to remain at high risk of infection due to their social and occupational circumstances. Individuals in this group might be less able to comply with social distancing and shielding policies as they are more likely to live in densely populated areas and larger family units, and are less likely to work from home.

Some groups at high risk of severe COVID-19 disease, including those on immunosuppressive therapy, may need to be excluded from specific trials, such as those using live-attenuated viral vaccines. Considering the theoretical possibility of vaccine-mediated enhanced disease, vulnerable individuals at high risk of severe COVID-19 should only be included in trials if preclinical data show an adequate immune response, including Th1/Th2 balance, and there is sufficient safety data from individuals at lower risk of severe disease.

Risk Groups for Severe COVID-19: Predisposing factors for severe COVID-19 include, but are not limited to, older age and presence of underlying health conditions including obesity, diabetes, and chronic cardiovascular, pulmonary, renal, and liver disease. People with active or recent cancer, in addition to those with severe respiratory conditions, are clinically extremely vulnerable. These risk groups would benefit most from a safe and effective COVID-19 vaccine.

Inclusion and Exclusion Criteria in Clinical Trials: Trial exclusion criteria protect individuals by excluding from participation those considered at disproportionate risk of adverse events from the intervention compared to potentially benefitting. Exclusion criteria also aim to minimize the occurrence of adverse events associated with underlying comorbidities or concurrent use of multiple medications that may compromise the safety and efficacy assessment of the intervention. Early (proof of concept) vaccine trials often exclude those less likely to mount an adequate immune response to vaccination (e.g. older adults). Although most early efficacy trials will be powered on the overall trial population, the safety and immunogenicity data from adequately represented risk groups will help to inform health and regulatory authorities of the suitability of the vaccine in risk populations.

The population selected for COVID-19 efficacy trials (trial population) should be representative of the wider population in which the vaccine will most likely be used (target population). The trial population should include an adequate representation of those at higher risk of severe disease, who are most likely to benefit from vaccination. Considering the theoretical possibility of vaccine-mediated enhanced disease, vulnerable individuals at high risk of severe COVID-19 should only be included in trials if preclinical data show an adequate immune response, including Th1/Th2 balance, and there is sufficient safety data from individuals at lower risk of severe disease. The inclusion of risk groups also presents some challenges. Developers should recruit from populations most at risk of *infection* (e.g. healthcare workers, socioeconomically deprived) in order to demonstrate vaccine efficacy against *disease* promptly, as those with symptomatic COVID-19 are a subgroup of those infected. However, those at highest risk of severe disease are less likely to become infected due to implementation of non-pharmaceutical interventions (NPI). Recruitment of individuals at highest risk of severe COVID-19 into a vaccine trial should be considered in the context of public health advice as recommended NPIs may interfere with the recruitment of these individuals, many of whom are shielding. Pre-vaccination screening for SARS CoV-2 infection through polymerase chain reaction is unlikely to occur in practice with the deployment of licensed COVID-19 vaccines. Therefore, individuals with a history or laboratory evidence of prior SARS CoV-2 infection should not be excluded from efficacy trials even though they may not be at risk of further symptomatic disease (1).

Broadening Eligibility Criteria in COVID-19 Efficacy Trials: Broadening the eligibility criteria in clinical trials is key to assessing COVID-19 vaccine safety and efficacy. Adopting more inclusive enrolment of older adults and those with stable chronic conditions (i.e. controlled and on the same medication for at least 3 months prior to enrolment) by relaxing exclusion criteria, will allow critical data to be obtained to better characterize the benefit-risk profile in those most at risk of severe COVID-19.

Older adults: A substantial proportion of older subjects should be recruited in advanced stage clinical trials. Alternatively, an adaptive clinical design could be considered that allows for pre-defined changes, including gradual expansion of the age range, during the trial (2). The adaptive design can incorporate a stepwise age escalation (e.g. 18-60, 61-75, >75) and expand the numbers enrolled in each age stratum on the basis of emerging safety and immunogenicity data generated during the conduct of the trial.

Obesity: COVID-19 efficacy trials should not restrict enrolment based on body mass index (BMI). Obesity is a risk factor for severe COVID-19 (3,4), and the risk increases with increasing BMI. Poor vaccine-induced immune responses in obese persons have been observed for some vaccines (e.g. hepatitis A

and B, influenza, tetanus, and rabies) (5). The use of BMI strata as defined by WHO (i.e. <25, 25-29.9, 30-34.9, 35-39.9, ≥40) could be considered in large efficacy trials for exploratory assessment of immunogenicity by BMI (6).

Diabetes: Diabetes is an independent risk factor for severe COVID-19 (3,4). Thus, persons with controlled diabetes who have been on the same medication for at least 3 months prior to enrolment should be included in the trial population.

Chronic cardiovascular, pulmonary, renal, and hepatic disease: People with these conditions are at increased risk for severe COVID-19 (3). Persons with chronic pulmonary diseases including chronic obstructive pulmonary disease are at a high risk of morbidity and mortality (3). Those with stable disease who have been on the same medication for at least 3 months prior to enrolment, should be included. Certain aspects of recently issued FDA guidance on inclusion of patients with organ dysfunction in oncology trials might be applicable for similar patients in COVID-19 vaccine trials (7).

Cancer: Subjects with a less than 5-year history of haematological malignancy have an increased risk of severe COVID-19. The risk doubles among those with a history of haematological malignancy greater than 5 years (3). However, subjects with a history of prior or concurrent malignancy whose natural history or treatment is unlikely to interfere with the safety or efficacy of the potential vaccine should generally be eligible for enrolment in clinical trials (7).

Socioeconomic deprivation: Socioeconomic deprivation is a risk factor for SARS-CoV-2 infection, COVID-19 mortality, and thus severe COVID-19. The risk of mortality from COVID-19 increases with socioeconomic deprivation (3). Whilst infection rates among the clinically most vulnerable have decreased during lockdown, the risk for those with higher levels of socioeconomic deprivation has been suggested to increase over time (3,8). Socioeconomically deprived people are more likely to live in densely populated areas, have larger family units, and are less likely to work from home and thus may be less able to comply with public health interventions including social distancing and shielding. These populations may also suffer from a higher prevalence of predisposing conditions for COVID-19 morbidity and mortality. It is anticipated that this group will remain at high risk of infection and should be included in clinical efficacy trials. Measures that might facilitate recruitment include, for example, holding recruitment events in non-clinical but trusted locations (e.g. community centers, social commercial venues, places of worship) whilst respecting recommended NPIs (9).

Additional Resources:

1. FDA 2020: Development and Licensure of Vaccines to Prevent COVID-19. Guidance for Industry
2. FDA 2020: Inclusion of Older Adults in Cancer Clinical Trials – Guidance for Industry
3. Williamson E, Walker A, Bhaskaran K, et al. OpenSAFELY: Factors associated with COVID-19 death in 17 million patients. Nature 2020. https://www.nature.com/articles/s41586-020-2521-4
4. WHO 2020 (May 27) Clinical management of COVID-19 – interim guidance https://www.who.int/publications/i/item/clinical-management-of-covid-19
5. Painter SD, Ovsyannikoval IG, Poland GA. Vaccine 2015: The weight of obesity on the human immune response to vaccination. Vaccine. 2015 Aug 26; 33(36): 4422–4429.
6. WHO 2000: Obesity: Preventing and Managing the Global Epidemic: WHO Technical Report Series 894: 8-9. https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/
7. FDA 2019: Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry
8. Pluemper T, Neumayer E. The COVID-19 Pandemic Predominantly Hits Poor Neighbourhoods, or does it? Evidence from Germany. https://www.medrxiv.org/content/10.1101/2020.05.18.20105395v1
9. FDA 2019: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrolment Practices, and Trial Designs Guidance for Industry. https://www.fda.gov/media/127712/download