COVAX

CEPI Gavi The Vaccine Alliance World Health Organization

COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator

Workshop Report

COVAX Clinical Development & Operations SWAT Team Workshop on "*COVID-19 Efficacy Trial Design Considerations & Early Learnings from Ongoing Studies*"

September 24th, 2020

Meeting report prepared by

Dr Julia Granerod

Executive summary

On 24th September 2020, the COVAX Clinical Development & Operations SWAT Team hosted a workshop on "*COVID-19 Efficacy Trial Design Considerations & Early Learnings from Ongoing Studies*." The main aim was to support COVID-19 vaccine developers with the rapid planning and implementation of pivotal Phase 3 vaccine efficacy trials.

The first section of the workshop focussed on scientific considerations for Phase 3 vaccine efficacy trials. Key guidance and best practices from the Food and Drug Administration (FDA), COVID-19 Prevention Network (CoVPN), and World Health Organization's (WHO) Solidarity Trial were summarised as follows:

- An efficacy trial is expected to be randomized, double-blind, placebo controlled.
- The primary endpoint should be laboratory-confirmed COVID-19.
- A secondary endpoint should be severe COVID-19
- Enrolled participants should be followed for a sufficient length of time to establish safety, and in particular to rule out late enhanced disease and to adequately power analyses of vaccine efficacy against severe COVID-19. US FDA guidelines advise following individuals for 1-2 years post-last vaccination.
- Participants diagnosed with COVID-19 should be followed a sufficient period of time to capture the full severity and duration of symptoms
    - Consider collecting a minimal set of specimens among these cases – blood and respiratory specimens at diagnosis and at ~3 weeks post-diagnosis, to evaluate shedding and immune responses to infection that may be modified by the vaccine.
- Success criteria should be that the primary vaccine efficacy estimate is ≥50%, and the lower bound of the appropriately alpha-adjusted confidence interval (CI) >30%.
- Enrolled participants are randomized in a 2:1 or 1:1 ratio to vaccine or placebo.
- Interim analyses may be performed using the same pre-specified analysis methods and criteria for success used for the primary analysis. Even if interim success criteria are met, trials should continue to accumulate more data.

Further discussion points included:

- A burden of disease (BOD) endpoint, which recognizes severe COVID-19 as being a worse clinical outcome than non-severe COVID-19, should be considered as a dual primary or key secondary endpoint.
- Potential vaccines that do not reduce the risk of asymptomatic SARS-CoV-2 infection but reduce symptomatic COVID-19 disease may result in a shift towards more asymptomatic infection with public health implications.
- Infection is a recommended secondary endpoint; however, the frequency of assessing infection should be pragmatic so as not to increase testing substantially.
- Several valid statistical methods for assessment of vaccine efficacy will likely produce similar results (e.g. censored event-time and conditional binomial analyses), but the proposed method of analysis must be pre-specified.

The second section of the workshop focussed on operational considerations for Phase 3 vaccine efficacy trials. Protocols available in the public domain from the major Operation Warp Speed-funded developers were reviewed for lessons learned. Further lessons learned and operational considerations included:

- Early community engagement is important for enrolment.

- A medically attended initial visit should occur early in entry into COVID-19 case evaluation, frequent monitoring should be emphasized, oximetry should be provided routinely for case management, and a paper documentation system should be in place in the event of limited access to technology.
- These trials conducted in the setting of a pandemic are resource intensive (500 participants to 90 staff).
- Inclusion of fatigue and headache, in addition to the more classical symptoms of fever, cough, dyspnoea, tachypnoea, anosmia, and ageusia, as triggering symptoms for PCR would double the number of tests performed but capture the majority of positive cases.
- A balance should be sought between a case definition that will capture the most clinically relevant symptoms but ensure potential cases are not missed.
- Issues related to conducting a trial during the upward trajectory of the epidemic include high seropositivity rates, significant attrition of individuals contributing to endpoint cases as a result of people becoming infected less than two weeks after completion of the vaccination series, and a high force of infection among staff.
- There will be a public expectation and pressure from the community for placebo recipients to be vaccinated as soon as an early efficacy readout is available and contingency plans should be made to ensure that continued follow-up of participants is possible and that the scientific value of the study can be maximized.
- Only cases that occur at least 14 days after completion of the vaccination series should be counted in the per protocol population.
- A coordinated communication plan is encouraged amongst developers to counteract the potential knock on effect of any safety event associated with one vaccine.

The slideset from the meeting can be found here:
https://media.tghn.org/medialibrary/2020/09/200924_VE_Workshop_Complete_Materials.pdf

Agenda

Time (CET)	September 24, 2020	Lead(s)
15:00 –15:05	**Welcome & Meeting Objectives**	Melanie Saville (CEPI)
15:05 – 15:10	**Introduction**	Jakob Cramer (CEPI)
15:10 – 15:20	**Vaccine efficacy: the regulators' perspective** *Obtain an overview of key regulator positions and requirements including vaccine efficacy, duration of protection, immune-bridging*	Svein Rune Andersen, Debra Yeskey (CEPI)
15:20 – 15:45	**Vaccine efficacy: Statistical considerations** *Adaptive / scenario-based strategies to assess vaccine efficacy*	Holly Janes (Fred Hutchinson Cancer Research Center)
15:45 – 15:55	**Vaccine efficacy: Statistical considerations – Novel endpoint approach** *Primary objective, corresponding case definition, novel endpoint approach – burden-of-disease based on scoring*	Devan Mehrotra (Merck)
15:55 – 16:05	**Vaccine efficacy: Solidarity III Trial**	Phil Krause (WHO Vaccines Expert Group)
16:05 – 16:25	**Discussion: How to establish vaccine efficacy** *Panelists: Holly Janes (Fred Hutch), Devan Mehrotra (Merck), Phil Krause (WHO Vaccines Expert Group)*	Moderated by Jakob Cramer (CEPI)
16:25 – 16:30	**BREAK**	
16:30 – 16:40	**Introduction** *Primary endpoints as guided by regulators and selected by developers*	Peter Dull (BMGF)
16:40 – 17:00	**Lessons learned from the field** *General insight into 'Operation Warp Speed' and high-level strategy related to establishing vaccine efficacy, share practical experience related to operational aspects from ongoing Phase III trials*	Mary Marovich (NIH/NIAID), Merlin Robb (HJF)
17:00 – 17:10	**Clinical case workup in efficacy trials: Guidance from community-based surveillance** *Frequency of individual clinical symptoms among COVID-19 patients, positive predictive value, clinical workup*	Amol Chaudhari, (CEPI), Joan Capdevila Pujol (ZOE)
17:10 – 17:50	**Discussion: Operational Considerations** *Panelists: Jacqueline Miller (Moderna), Ricardo Palacios (Instituto Butantan/Sinovac), Shabir Madhi (RMPRU/ChAdOx-Novavax)*	Moderated by Peter Dull (BMGF)
17:50 – 18:00	**Wrap-up and next steps**	**Peter Dull (BMGF)**

Welcome and meeting objectives

Dr Melanie Saville, Director of Vaccine Development at the Coalition for Epidemic Preparedness Innovations (CEPI), welcomed participants to the workshop and began by providing an overview of COVAX. The Access to COVID-19 Tools (ACT) accelerator is a global collaboration to accelerate development, production, and equitable access to new COVID-19 diagnostics, therapeutics, and vaccines. The vaccine pillar of ACT accelerator is also referred to as COVAX. COVAX has three workstreams including the development and manufacturing of vaccines coordinated by CEPI, procurement and delivery at scale of those vaccines coordinated by the Global Alliance on Vaccines and Immunizations (GAVI), and policy and allocation led by WHO. Three COVAX SWAT teams have been set up to address enabling sciences, clinical development and operations, and manufacturing.

Dr Saville emphasized the aim of the workshop was to support COVID-19 vaccine developers with the rapid planning and implementation of pivotal Phase 3 vaccine efficacy trials and specifically to provide developers with:

- Product-agnostic supportive information and considerations on the assessment of vaccine efficacy
- A forum to communicate and address individual challenges.

Introduction

Dr Jakob Cramer, Head of Clinical Development at CEPI, explained that vaccines against COVID-19 will likely become available at large scale within ~six months. Designing Phase 3 efficacy studies with limited knowledge of the pathogen and added time pressure is complex; however, no shortcuts can be taken to establish vaccine efficacy, safety, and trust. This workshop addressed challenges and solutions related to vaccine efficacy and was divided into two sections, scientific and operational considerations for vaccine efficacy in Phase 3 trials.

Vaccine efficacy: scientific considerations for Phase 3 trials

Vaccine efficacy: The regulator's perspective

Dr Svein Rune Andersen, CEPI Head of Regulatory Affairs Europe, summarized current guidance and regulator expectations in terms of vaccine efficacy. The FDA published guidance in June 2020 and high-level recommendations are summarised below:

- An efficacy trial is expected to be randomized, double-blind, placebo controlled.
- The recommended primary endpoint is either laboratory-confirmed COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- The primary or secondary endpoint should be defined as virologically confirmed SARS-CoV-2 infection with one or more of several defined symptoms.
- It is likely that COVID-19 vaccines may be more effective in reducing disease severity than preventing infection.
- SARS-CoV-2 infection should be evaluated as a secondary or exploratory endpoint, if not evaluated as the primary endpoint.
- The primary efficacy endpoint point estimate should be ≥50%, and the lower bound of the appropriately alpha-adjusted CI >30%. This is endorsed by Health Canada, India, China, and WHO and should also be used for any interim analysis designed for early detection of efficacy.

The International Coalition on Medicines Regulatory Authorities expectations on vaccine efficacy and Phase 3 trials include:

- Large efficacy trials including people with medical comorbidities.
- Powered to assess the overall vaccine efficacy across subgroups enrolled.
- Randomized, double-blind, and controlled either using placebo or active comparator.
- Need for stringent success criteria to ensure adequate efficacy; however, a specific numeric value for the lower bound and vaccine efficacy point estimate has not been agreed at this stage.

Vaccine efficacy: Statistical considerations

Prof Holly Janes from Fred Hutch provided an overview of key statistical considerations and best practices with regard to COVID-19 vaccine efficacy trial design drawing from and summarizing the approaches used within the CoVPN, the focal point for US government sponsored COVID-19 vaccine and monoclonal antibody trials.

In brief, a summary of these considerations and best practices include:

- *Randomisation ratio*
    - Enrolled participants are randomized in a 2:1 or 1:1 ratio to vaccine or placebo potentially stratified within risk strata.
    - Major argument in favour of a 2:1 versus 1:1 randomization ratio is increased power for discovering immunological correlates or surrogate endpoints.
- *Endpoints*
    - The common primary endpoint across trials is protocol-specified list of COVID-19 symptoms with virological confirmation of SARS-CoV-2 infection (symptom-triggered).
    - SARS-CoV-2 infection and severe COVID-19 are included as key secondary endpoints.
- *Study duration and timing of primary analysis*
    - All trials are designed to have a follow-up of two years post-last vaccination.
    - The time to primary analysis could be shorter (~7 months) as these are event-driven trials.
- *Primary analysis and success criteria*
    - Vaccine efficacy is classically assessed by Cox proportional hazards model.
    - The primary analysis cohort includes enrolled participants baseline negative for SARS-CoV-2 who received at least one dose of the study product. Only events that occur ≥15 days post last dose of the study vaccine count in the primary analysis.
    - The success criteria adopted is the point estimate for vaccine efficacy must be ≥50% and the lower bound for the 95%CI >30%.
- *Sample size and target endpoint total*
    - 150 primary endpoints needed for 90% power for a vaccine efficacy of 60% with 2:1 randomisation.
    - This would imply a sample size of about 30,000 participants, which is the common sample size across these trials.
- *Interim monitoring*
    - All the trials incorporate multiple types of interim monitoring including potential harm/enhancement, non-efficacy, and efficacy monitoring.
- *Potential outcomes of interim and primary analyses*

- Different potential outcomes can occur at the time of interim or primary analysis.
- If efficacy, non-efficacy, or increased-risk criteria are met, randomisation would cease, and a range of other activities would be triggered. If no criteria were met, randomisation and follow-up would continue as planned.

Vaccine efficacy: Statistical considerations – Novel endpoint approach

Dr Devan Mehrotra, Vice President of Biostatistics at Merck, discussed statistical considerations for COVID-19 vaccine efficacy evaluation and a novel endpoint approach. Key points included:

- A BOD endpoint was proposed. BOD explicitly recognizes severe COVID-19 as being a worse clinical outcome than non-severe COVID-19 and modifies the 2-level disease score endpoint (0=no COVID-19, 1=COVID-19) to a 3-level disease score endpoint (0=no COVID-19, 1=non-severe COVID-19, 2=severe COVID-19). COVID-19 vaccines in development are expected to reduce the incidence of COVID-19, particularly severe COVID-19. This, in addition to simulation results, makes BOD a promising primary, dual primary, or key secondary endpoint.
- If vaccines under development do not materially reduce the risk of asymptomatic SARS-CoV-2 infection, a reduction in the incidence of symptomatic COVID-19 disease may be accompanied by a shift towards more infections that are asymptomatic. This has public health implications and thoughtful consideration of this issue and design implications is warranted.

Vaccine efficacy: Solidarity III Trial

Statistical and endpoint considerations for COVID-19 vaccines in the context of WHO's Solidarity Trial were presented by Dr Phil Krause, Chair of WHO COVID-19 Vaccines Expert Group. Summary points include:

- An endpoint that is not so rare as to render the trial infeasible yet simple to avoid the need for an adjudication committee should be selected. The complexity of having different trial versus surveillance clinical criteria, which has been avoided in the WHO Solidarity Vaccines Trial, was highlighted.
- Some disadvantages of the BOD endpoint include lack of validation or standardisation, difficulty explaining the meaning of this endpoint, and using this approach may only have minimal advantages given the low incidence of severe disease.
- There is general agreement on appropriate success criteria (>50% point estimate with >30% lower bound on alpha-adjusted CI) to ensure weakly effective vaccines will not meet criteria for wide distribution and that studies are of sufficient size to evaluate safety.
- Interim analyses may be performed using the same criteria used for the primary endpoint, and alpha must be appropriately adjusted (e.g. O'Brien-Fleming approach). Even if interim success criteria are met, trials should continue to accumulate more data.
- Any vaccine authorized/listed under emergency use is still investigational, studies that have already begun should continue, and additional safety studies may be initiated.
- Continuation of placebo in areas where a vaccine is licensed and available will not be feasible.

Discussion: How to establish vaccine efficacy

A panel discussion included the following key points:

- There is a consensus that disease should be considered the primary endpoint and infection a secondary endpoint, but *questions remain about the method and frequency for assessing infection.*
    - Seroconversion can be used to assess infection against a protein not contained in the vaccine (e.g. N protein); however, it is unknown how long antibodies against the N protein will prevail.
    - The frequency of assessing infection should be pragmatic so as not to increase testing substantially, and a six-month time point would be acceptable with respect to statistical comparisons.
- *What is known about the duration and usefulness of serial assessments of N protein in natural infection?*
    - A significant drop in the N protein has not been observed over three months but respective antibody tests and long-term follow-up data are required to fully assess this.
- Trials will ultimately be assessed against the primary objective despite secondary objectives achieving statistical significance. *What are strategies to minimise the risk of selecting an inappropriate primary endpoint?*
    - Trials could include BOD or dual or multiple primary endpoints rather than a single primary endpoint.
    - A potential vaccine aims to reduce severe disease. By construction, the BOD endpoint rewards a vaccine that is better at achieving this and can distinguish between two vaccines with equivalent efficacy against disease but where one has a higher efficacy against severe disease.
    - A statistical win must be secured in terms of a single primary endpoint before formally proceeding to secondary endpoints. Thus, rather than have BOD as the only primary endpoint, BOD should be included as a dual primary endpoint (with disease) or at least as a key secondary endpoint. There is a statistical risk, under plausible and clinically relevant scenarios, that the COVID-19 disease endpoint alone may fail to detect vaccine efficacy.
    - Under the idea of an overall 50% vaccine efficacy is the assumption that there will likely be higher efficacy against severe disease. Thus, if the endpoint is adjusted to give more points for impact on severe disease then a higher minimum criterion on that endpoint might be expected.
    - An endpoint that is biased too much toward severe disease might have much less impact on transmission, and a balance is needed.
    - BOD as a secondary endpoint could also be considered in trials currently underway.
- *Should more levels potentially be included in the BOD endpoint?*
    - The BOD scoring system could in concept be extended to include more levels (e.g. death, hospitalisation); however, this might complicate interpretation and coding.
    - A simple 0/1 scoring system going to 0/1/2 maintains a strong correlation between the COVID-19 disease endpoint and BOD and this strong correlation can be leveraged by potentially adopting them as dual primary endpoints.
- *How do the different statistical methods proposed for analysis of primary endpoints refer to the regulator's request of 50-60% efficacy and a lower bound >30?*
    - It is likely that the different statistical methods proposed for assessment of vaccine efficacy (e.g. classic Cox proportional hazards, modified Poisson regression model, beta binomial model, and sequential probability ratio tests) will produce similar results in this context where the incidence of the endpoint is low and there is likely to be good retention of study participants.

    - It is critical that the proposed method is pre-specified.
- *What might be a suitable correlate or proxy for transmission to be assessed in these trials and which should be included as secondary or exploratory endpoints?*
    - The issue of transmission and herd immunity will only be definitively answered after deployment of vaccines and will thus need consideration at that time.
    - The best measure of transmission risk is viral load in participants who have become infected. The period of peak viral load (i.e. before manifestation of symptoms) will not be captured in these trials so any potential vaccine effect on reducing transmission potential as measured by viral load would likely not be captured in these trials. Trials with frequent PCR testing to detect incident infections and which measure viral load early in the course of infection would be required for this.
    - Detection of a virus does not necessarily mean that it has transmission potential, and these important questions will need to be addressed at a later stage.
    - Phase 4 trials may be required to assess efficacy against transmission.

Vaccine efficacy: operational considerations for Phase 3 trials

Introduction: Operational considerations

Dr Peter Dull, Deputy Director of Integrated Clinical Vaccine Development at the Gates Foundation, chaired the second part of the workshop focussed on operational considerations for Phase 3 trials. This unprecedented novel respiratory virus outbreak requires unprecedented vaccine development efforts, the common goal being a global supply of safe and effective vaccines. Distrust of one vaccine will negatively affect all developers. Multiple Phase 3 studies have started with tens of thousands enrolled. Thus, all developers will benefit if all studies are conducted with high quality and answer the right questions. It is critical to continue collaborating and communicating across developers, especially as those already in Phase III trials have already learned critical operational lessons along the way.

Dr Dull reviewed protocols available in the public domain from the major Operation Warp Speed-funded developers. There are slight differences between them in terms of primary efficacy endpoint, age range being enrolled, target vaccine efficacy, number of interim analyses, and triggers for case work up. Developers were encouraged to download these for the learnings.

Lessons learned from the field

Dr Mary Marovich discussed operational considerations and impact on trial design. Summary points include:

- *Enrolment strategies*
    - Early community engagement is important. It is possible that both media focus on expediting vaccine discovery and safety issue coverage may impact enrolment.
- *Case ascertainment and management*
    - There is a consensus that there should be a medically attended initial visit early in entry into COVID-19 case evaluation. Allowing some clinical judgement is probably helpful to exclude expected reactogenicity following vaccination for example or to assess adherence to self-monitoring activities. This would also permit use of a locally resourced but qualified assay for case ascertainment.

    - Frequent monitoring should be emphasized to advance severe cases quickly to higher levels of care and enable identification of enhanced disease.
    - Oximetry should be provided routinely for case management.
    - Technology can challenge participants or participants may have limited access technology; hence a paper documentation system should also be used.
- *Personnel and space management*
    - These are resource intensive trials (500 participants to 90 staff) conducted in the setting of a pandemic.
    - COVID-19 case visits can be incorporated with regular COVID-19 care clinic.
    - Research clinic space can be expanded to accommodate segregated follow-up for possible cases versus screening/enrolment.

Clinical case workup in efficacy trials: Guidance from community-based surveillance

Dr Amol Chaudhari, Clinical Development Lead at CEPI, and Dr Joan Pujol, a data scientist at ZOE, presented a symptom analysis on a prospective, community-based cohort from the COVID-19 Symptom Study.

The COVID-19 Symptom Study App, where users can log up to 20 distinct symptoms daily, was launched in the UK in March. This has resulted in a large prospective community-based cohort to facilitate understanding of how symptoms that may trigger PCR contribute to case finding. Data from the COVID-19 Symptom Study App showed that 14% of positive cases show no classic symptoms (fever, cough, dyspnoea, tachypnoea, anosmia, and ageusia) during the first two weeks of symptoms. Inclusion of fatigue and headache in the triggering symptoms would double the number of tests performed; however, 97.2% of positive cases would be captured. This is particularly evident during the first three days of symptoms, where classic symptoms would capture 68.2% of positive cases while extended symptoms (i.e. classic symptoms plus fatigue and headache) would capture 91.2% of positive cases.

Key discussion points included:

- The number of individuals that need to be tested to detect a single case of COVID-19 is likely to differ at different time points within the outbreak (i.e. force of exposure is variable) and this will be addressed in follow-up analyses.
- The aim is to make these data available as open access.
- The COVAX Clinical SWAT Team is interested in being a vehicle for collating and communicating similar data from developers as it becomes available in the interest of sharing information.

Panel discussion: Operational considerations

Three panel members discussed operational considerations from their own experiences of running COVID-19 vaccine trials. The main points are summarised below.

Dr Ricardo Palacios, Clinical Research Medical Director, Instituto Butantan/Sinovac –

- In some trial protocols, a combination of symptoms is required to trigger a test for SARS-CoV-2. These trials have faced difficulties in how to handle a positive test if there are not enough symptoms.
- An important operational challenge is how to discard a possible case (i.e. when to exclude despite presence of symptoms). Repeat testing can be conducted but sometimes

is not feasible or carried out too late. Serological comparison can be an option but implies that samples have been taken before and after.
- A further issue is if a person tests positive in a lab that is not a study lab (i.e. due to travel).
- With an emergency use authorisation or disclosure from interim analyses that a vaccine is efficacious, the vaccine would need to be offered to the placebo arm. In this case, it is worth considering what meaningful data can still be gained from a study where the control group are being vaccinated and how to optimize getting these data.
- Developers need to consider how to set up follow-up, for example if booster doses are required.

Dr Jacqueline Miller, SVP Therapeutic Area Head, Infectious Diseases (Moderna) -

- Collaboration and advice from other colleagues/experts are important for good decision making in a pandemic situation where information is rapidly evolving.
- Striking a balance between a case definition that will capture the most clinically relevant symptoms versus ensuring potential cases are not missed was highlighted. The Moderna protocol specifies broad symptoms to trigger sampling for SARS-CoV-2 as a request from the regulatory agency to ensure cases were not missed. This has significant cost and resource implications, and there is always a trade-off between ensuring cases are not missed and the frequency of sampling.
- The speed with which recruitment occurs can expedite a vaccine development program but has knock on effects in terms of sites having to manage as well as enrol these subjects, and deal with a substantial volume of data queries.

Dr Shabir Madhi, Professor of Vaccinology, Director of the MRC Respiratory and Meningeal Pathogens Research Unit (AstraZeneca-Novavax) -

- Issues related to conducting a trial during the upward trajectory of the epidemic were discussed. Several protocol amendments have been submitted as a result of high (15-20%) PCR positivity and seropositivity (25%) in asymptomatic volunteers which have sample size implications. The South African study, as other studies, is now designed to consider efficacy in the seronegative group as a primary endpoint.
- Many planned multi-centre studies are assuming a seropositivity rate of 10% which is significantly less than was seen in South Africa. This needs consideration especially if these studies plan to include low- and middle-income (LMIC) settings.
- Significant attrition of individuals contributing to endpoint cases as a result of people becoming infected before two weeks after they've received the second dose of vaccine is another challenge associated with conducting a trial during an epidemic surge.
- Recruiting a high number of staff (90 staff to 500 participants) over a short period of time is a challenge in LMIC settings with restricted budgets.
- A high force of infection among staff (20% of staff developed COVID-19 in first six weeks in South Africa) affects the ability to maintain enrolment as well as staff morale, anxiety, and stress.
- Prompt approval for protocol amendments might not occur in all settings.
- Conducting these studies under the public and media spotlight is a huge challenge, and the principal investigators should make themselves available to counteract the potential for the media to create their own story.
- There will be a public expectation and pressure from the community for placebo recipients to be vaccinated as soon as an early efficacy readout is available. It will be difficult for countries to make a scientific case for placebo recipients to remain unvaccinated through to two years in the event of continuous surge of the epidemic.

A general discussion included the following points:

- *An accurate per protocol population is needed to give the expected point estimate for vaccine efficacy. How can the issue of PCR positive subjects potentially leaking into the per protocol population be addressed?*
    - A swab for PCR is taken at the time of and two weeks after the second vaccination to exclude individuals with asymptomatic infection or individuals pre symptomatic during that window period. Only cases that occur at least 14 days after the second dose of vaccine are counted.
    - Vaccine reactogenicity and nonspecific symptoms (fatigue and headache) can potentially complicate the analysis. A pre-vaccination swab can be used to distinguish true COVID-19 from a reaction to the vaccine. Systemic reactions to the vaccine (Moderna) seem to occur within two to five days of the vaccine dose.
    - The protocol should allow for clinical judgment in terms of decision to swab (i.e. physician decided not to swab a patient who presented with fever and had been vaccinated 24 hours previously).
- *How are cases who test PCR positive outside of the study managed*?
    - In the Moderna study, this would prompt the sick visit with symptomatology capture in the case report form and a repeat nasopharyngeal swab tested using an in-house assay. The possibility for home visits or for subjects to send nasal/salivary swabs has been enabled to limit the spread to others. The case definition also allows for the capture of cases with a positive test outside the study that are unable to comply with this procedure (i.e. those that have gone directly to the emergency department and been admitted). The adjudication committee will review such cases and ultimately define the sample size for efficacy evaluation.
- *Should healthcare workers be targeted for these trials?*
    - It is not thought that this population should be targeted for enrolment as a large proportion were already infected in the first wave (55% in COVID-19 ward and 20% in neonatal units/paediatrics in South Africa) and N95 respirators are now more widely available.
- *What is the impact of a second vaccine dose on safety?*
    - Reactogenicity with the Moderna vaccine occurs mainly after the second dose. Reactions after the first dose are mostly limited to injection site pain and other grade one reactions which has resulted in a high rate (>92%) of compliance in the Phase 3 trial and participants returning for the second dose. The real-world effect of reactogenicity of the second dose remains to be seen.
- *Will a safety event that is associated with a particular vaccine impact on recruitment in other areas?*
    - A safety event associated with one vaccine will no doubt have an impact on recruitment in other trials. This has already been seen following media coverage of the Astra Zeneca vaccine event.
    - A coordinated communication plan and coordinated messaging is encouraged amongst developers not only for Phase 3 trials but also for the post-introduction period.
- *Can we determine a correlate for SARS-CoV-2/COVID-19?*
    - This might require the consolidation of data; however, is complicated by different vaccine efficacies in different populations due to varying forces of exposure in different studies.
    - The COVAX clinical SWAT team is initiating a working group with the aim to move sera to a single laboratory and conduct a combined analysis to determine a correlate.

Wrap-up and next steps

Dr Peter Dull thanked attendees for their participation in the workshop and outlined the next steps as follows:

- The COVAX Clinical Development & Operations SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines.
- Resources will continue to be shared at: https://epi.tghn.org/covaxoverview/clinical/.
- A post-workshop survey will be shared to capture any remaining questions or comments.
- A workshop report will be distributed to summarize today's conversation; for any outstanding questions, we will do our best to direct you to the appropriate resource.

Post-meeting note

A follow-up workshop will be held on October 28th2020 entitled "*Early Efficacy from Covid-19 Phase 3 Vaccine Studies: Ethical, Operational, & Scientific Considerations*."