

COVAX



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

Workshop Report

COVAX Clinical Development & Operations SWAT Team Workshop on “*Early Efficacy from COVID-19 Phase 3 Vaccine Studies: Ethical, Operational, & Scientific Considerations*”

October 28th, 2020

Meeting report prepared by

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Executive summary

On 28th October 2020, the COVAX Clinical Development & Operations SWAT Team hosted a workshop on “*Early Efficacy from COVID-19 Phase 3 Vaccine Studies: Ethical, Operational, and Scientific Considerations.*” The main aim was to discuss country- and vaccine-specific scenarios once early efficacy results will have become available / first emergency approvals will have been issued and to provide relevant guidance to developers.

The first section of the workshop followed up from the previous workshop on vaccine efficacy (September 24th, 2020) and included a discussion on primary efficacy endpoints and symptoms that trigger diagnostic work-up of suspected COVID-19 cases. Key points included:

- The burden of disease (BoD) endpoint could be considered as an additional primary endpoint in a multiple primary endpoint approach to de-risk other primary endpoints.
- Adding moderate COVID-19 disease as defined by the World Health Organization (WHO) is likely to provide added value to the BoD endpoint.
- Data from the COVID Symptom Study show that the most frequently selected symptoms to identify >90% of COVID-19 cases are fatigue, loss of smell, persistent cough, diarrhoea, headache, and sore throat within three days of symptom onset and fatigue, loss of smell, persistent cough, sore throat, fever, and unusual muscle pains within seven days of symptom onset.

The second section of the workshop focused on placebo group vaccination in Phase 3 trials, and included recent experience with novel vaccines in placebo-controlled trials, a discussion of early efficacy scenarios with perspectives from India and Brazil, impact of an efficacious vaccine on ongoing and future COVID-19 vaccine trials, non-inferiority trial design considerations, and evaluating vaccine-associated enhanced disease (VAED) in Phase 3 trials and beyond. Key points included:

- A placebo group should be maintained in Phase 3 trials for as long as is feasible to look at duration of efficacy, risks of enhanced disease, other late adverse effects, and vaccine efficacy in certain subgroups.
- The welfare of research participants should be protected and their right to autonomous choice should be upheld and supported.
- Whether the authorisation/approval relates to the vaccine under study in the placebo-controlled trial or another vaccine in the same country, the key element is whether or not the product has subsequently become locally available and whether there is a recommendation for use in the relevant risk group.
- In the absence of the placebo arm and of non-inferiority studies, other options that might be considered to move later vaccines through licensure includes the possibility of human challenge studies and basing licensure on correlates of protections established in early trials using similar vaccine platforms.
- If placebo crossover to vaccine does occur in a trial, the vaccine arm could also crossover and follow up should be maintained as still have a blinded and randomized trial. In this instance, the sample size for immune correlates analysis is doubled, and differentials in endpoint incidence over time may enable vaccine durability to be assessed, though less reliably than without crossover.
- Defining the non-inferiority margin is central to planning any non-inferiority trial, and discussions between sponsor and regulator should be anticipated for products which are to be studied in the next few months. Additional vaccine characteristics need to be taken into account when discussing non-inferiority margins with regulatory agencies.

- Non-inferiority trials require very large sample sizes (or many years) if the vaccines being compared are truly of similar efficacy.

The slideset from the meeting can be found here:

https://media.tghn.org/medialibrary/2020/11/201028_COVAX_Clinical_Complete_Workshop_Materials.pdf

Agenda

Time (CET)	October 28, 2020	Speaker(s)
14:00 – 14:05	Welcome & Meeting Objectives	Jakob Cramer (CEPI)
Part 1	Follow-Up from Previous Workshop on Vaccine Efficacy (Sep 24, 2020)	
14:05 – 14:20	Primary Efficacy Endpoints <i>COVID-19 Burden of Disease Endpoint & Vaccine-Attenuated Disease</i>	Edde Loeliger (CEPI)
14:20 – 14:30	Set of Symptoms that Triggers Diagnostic Work-Up of Suspected COVID-19 Cases	Joan Capdevila Pujol (ZOE)
Part 2	Placebo Group Vaccination in Phase 3 Trials	
14:30 – 14:35	Introduction - Global Phase 3 Studies and Emergency Use Overviews	Peter Dull (BMGF)
14:35 – 14:50	Recent Experience with Novel Vaccines in Placebo-Controlled Trials <i>Experience with some non-Covid-19 vaccines on issues related to the conduct of placebo-controlled trials and preservation of placebo groups beyond demonstration of efficacy.</i>	Peter Smith (LSHTM)
14:50 – 15:00	Introduce Early Efficacy Scenarios for Discussion	Peter Dull
15:00 – 15:10	Perspectives from an Indian Context	Gagandeep Kang (CMC Vellore)
15:10 – 15:20	Perspectives from a Brazilian Context	Gustavo Santos (ANVISA)
15:20 – 15:55	Panel Discussion: Scenario-based Discussion of Efficacy Results and Implications in Different Trial Settings Panelists: <ul style="list-style-type: none"> • Peter Smith • Gagandeep Kang • Gustavo Santos • Ross Upshur (University of Toronto) 	Moderated by Peter Dull
15:55 – 16:05	Impact of an Efficacious Vaccine on COVID-19 Vaccine Trials <i>Reasons to maintain blinded follow-up to assess correlates, vaccine durability, and vaccine associated enhanced disease</i>	Dean Follmann (NIH/NIAID)
16:05 – 16:15	Non-Inferiority Trial Design Considerations <i>Overview of non-inferiority trial design and sample size calculations</i>	Martha Nason (NIH/NIAID)

16:15 – 16:25	Evaluating VAED in Phase III Beyond: Setting Realistic Expectations <i>Overview of vaccine associated enhanced disease and importance of long-term follow-up</i>	Steven Black (SPEAC)
16:25 – 16:55	Panel Discussion: Operational, Regulatory, & Scientific Considerations Panelists: <ul style="list-style-type: none"> • Dean Follman • Martha Nason • Steve Black • Marco Cavaleri (EMA) • Phil Krause (FDA, Solidarity 3) 	Moderated by Jakob Cramer
16:55 – 17:00	Wrap-up and Next Steps	Jakob Cramer

Welcome and meeting objectives

Dr Jakob Cramer, Head of Clinical Development at the Coalition for Epidemic Preparedness Innovations (CEPI), welcomed participants and set the context for the workshop.

Numerous Phase 3 trials of COVID-19 vaccines are being conducted at present, with more expected to start soon. Following the previous COVAX vaccine efficacy workshop (September 24th, 2020), questions on de-risking the choice of primary endpoints and the criteria for clinical case workup remain to be addressed. The first emergency use authorisation (EUA) for a COVID-19 vaccine could be issued in the United States (US) by the end of 2020. With the release of early efficacy results, developers may experience pressure to offer the trial vaccine to the placebo group in ongoing Phase 3 trials. The approach developers should take for Phase 3 studies that have yet to begin, particularly for countries where there are no national guidelines, remains unclear. These issues are already being discussed in the media, and developers are seeking guidance.

Part 1: Follow-up from previous workshop on vaccine efficacy (September 24th, 2020)

Primary efficacy endpoints

Dr Edde Loeliger, Clinical Consultant at CEPI, addressed the choice of primary efficacy endpoints as a follow-up from the previous COVAX workshop (September 24th, 2020), with a particular focus on COVID-19 BoD endpoint and the possibility of vaccine-attenuated disease (VAD).

A summary of the main points includes:

- Two published Phase 3 protocols have included a BoD endpoint. BoD is included as an exploratory efficacy endpoint in the Moderna protocol whereas the Janssen protocol includes BoD as a secondary efficacy endpoint with several severity categories.
- The BoD endpoint could be considered as a primary endpoint in a multiple primary endpoint approach to de-risk other primary endpoints.
- Multiple endpoint approach differs from a composite endpoint approach and is useful when demonstration of a treatment effect on at least one of several primary endpoints is sufficient, irrespective of which one comes first.
- Simulation suggests that the statistical penalty is relatively modest for closely related COVID-19 clinical endpoints.
- Adding moderate disease, as defined by the WHO, in the BoD endpoint is likely to provide added value to a COVID BOD endpoint because severe COVID-19 is rare and in the WHO severity categorisation, the distinction between mild and moderate COVID is pneumonia.

Set of symptoms that trigger diagnostic work-up of suspected COVID-19 cases

Dr Joan Pujol, Data Scientist from ZOE, presented a symptom analysis on a prospective, community-based cohort from the COVID-19 Symptom Study.

Users of the COVID-19 Symptom Study App can log up to 20 distinct symptoms daily and record results of any polymerase chain reaction (PCR) testing. This has resulted in a large prospective community-based cohort to facilitate understanding of how symptoms that may

trigger PCR contribute to case finding. US and United Kingdom (UK) data from the COVID-19 Symptom Study App showed that:

- Symptoms of pneumonia alone (e.g. cough, dyspnoea, fever) are not very predictive of a positive PCR result but this increases when pneumonia symptoms are combined with anosmia/ageusia (i.e. 'classic' symptoms).
- 33% and 19% of positive cases do not show any of the classic symptoms during the first three or seven days of symptoms, respectively.
- An extended list of symptoms, which includes the classic symptoms plus fatigue and headache, increases the number of PCR+ cases detected above 90% but doubles the number of tests required.
- These findings were shown to be consistent across age groups (18-54, 55+) and for the UK and US cohorts.
- Results of an optimisation method to identify sets of triggering symptoms which take into account the trade-off between recall and number of required tests showed that sets identifying a high proportion of cases tend to include most of the extended symptoms, but headache is more likely to be present during the first three days and fever tends to be present during the seven-day scenario. Shortness of breath is less useful, as it tends to occur later in the disease (i.e. after 7 days) or co-occur with other selected symptoms.
- The most frequently selected symptoms to identify >90% of cases are fatigue, loss of smell, persistent cough, diarrhoea, headache, and sore throat for the 3-day scenario and fatigue, loss of smell, persistent cough, sore throat, fever, and unusual muscle pains for the 7-day scenario.

Part 2: Placebo group vaccination in Phase 3 trials

Introduction - Global Phase 3 studies and emergency use overviews

Dr Peter Dull, Deputy Director of Integrated Clinical Vaccine Development at the Gates Foundation, chaired the second part of the workshop. Multiple Phase 3 efficacy placebo-controlled studies for "Wave 1" COVID-19 vaccines have initiated, many of which are multi-country studies. Further vaccines are in development and these "Wave 2" vaccines may have product characteristics which are critical for global impact (e.g. higher efficacy, better tolerability profiles, scalability, impact on shedding, suitable for specific population subgroups). Evaluation of these vaccines is important and a path to licensure is required. Immune correlates are recognised as critical, but information is limited at present. Identification of a correlate will likely only occur after initial efficacy studies are completed and may be platform specific. On October 22 at the Vaccines and Related Biological Products Advisory Committee meeting, the US Food and Drug Administration (FDA) stated that "availability of a licensed vaccine does not automatically preclude continuation of blinded, placebo-controlled trials" and that "continuation of placebo-controlled follow-up after EUA will be critical to ensure that additional safety and effectiveness data are accrued to support submission of a licensure application as soon as possible following an EUA."

Thus, the second part of the workshop aimed to:

- Review key historical examples of placebo-controlled vaccine studies and relevance for COVID-19
- Discuss country- and vaccine-specific scenarios with early efficacy results.

Recent experience with novel vaccines in placebo-controlled trials

Prof Peter Smith, from the London School of Hygiene and Tropical Medicine, discussed experience with some non-Covid-19 vaccines on issues related to the conduct of placebo-controlled trials and preservation of placebo groups beyond demonstration of efficacy.

Key points are summarised as follows:

- Participation in a vaccine trial should be driven by altruism. Participants in trials should not be unduly advantaged relative to those in the same communities not in trials, but nor should they be unduly disadvantaged.
- Early examples of different approaches to unvaccinated group include:
 - The unvaccinated group was never vaccinated in a Medical Research Council (MRC) trial of BCG vaccine (started in 1950-2) and this enabled efficacy to be evaluated over 20+ years.
 - All unvaccinated individuals were offered the vaccine at nine months in a MRC trial of live measles vaccine (started in 1964). Twenty percent declined vaccination and were followed for two years, enabling demonstration (but not in a randomised situation) that high efficacy remained for the next two years.
- Recent examples of placebo group preserved beyond demonstration of efficacy:
 - The placebo group was maintained in rotavirus vaccine trials to measure protection in the second year after vaccination.
 - In a dengue vaccine trial (Dengvaxia), follow-up with the placebo group continued for five years. Evidence of vaccine enhanced disease in a subgroup was found only from the second year after the last dose, after efficacy with the primary endpoint had been achieved in the first year after the last dose.
 - In malaria vaccine trial (RTS,S/ASO1), placebo groups were maintained to assess decline of protection over time and the impact of a booster dose.
- Situations in which use of a placebo in vaccine trials may be justifiable when there is already an efficacious vaccine were considered by a WHO working group several years ago and include:
 - Developing a locally affordable vaccine (e.g. Rotavac in India)
 - Evaluating the local safety and efficacy of an existing vaccine (e.g. Rotarix/Rotateq in Africa)
 - Testing a new vaccine when an existing vaccine is not yet in local use (e.g. Rotasil in Niger) – this consideration is likely relevant for COVID-19 vaccines
 - Determining the local burden of disease (e.g. vaccine-probe studies – Hib)
- Head-to-head vaccine comparisons with clinical outcome are rarely done mainly due to the large sample size required but might be viable where a new vaccine is much more efficacious than an existing vaccine.

Introduce early efficacy scenarios for discussion

Dr Peter Dull introduced specific early efficacy scenarios for discussion including:

- Vaccine A demonstrates efficacy at interim analysis and sponsor initiates application for emergency use, all within the same country
- Vaccine A has been approved for emergency use or full licensure by the National Regulatory Authority (NRA), but product is not yet available in country
- Vaccine A has been approved by the NRA for emergency use or full licensure but supply only sufficient for high-risk populations
- Vaccine B has ongoing Phase 3 trial in the same country as approved Vaccine A
- Vaccine B has planned Phase 3 trial in the same country as approved Vaccine A

Perspectives from an Indian context

Prof Gagandeep Kang, Professor of Microbiology at Christian Medical College Vellore, explained that three COVID-19 vaccines are being evaluated in clinical trials in India at present. A Phase 2/3 study is being conducted by the Serum Institute of India in collaboration with AstraZeneca (AZ) and the University of Oxford. A total of 1,600 participants aged between 18 and 99 years are being recruited and randomized 3:1 to receive the vaccine versus placebo. Four hundred participants are included in an immunogenicity cohort where regular blood samples are taken; the other participants are monitored for safety. This vaccine is simultaneously being evaluated in other parts of the world, and data from this vaccine may become available to the regulator in the next few months. The Bharat Biotech vaccine (BBV152) has been evaluated in 1,125 individuals in a Phase 1/2 study and will involve 28,500 individuals in a Phase 3 study. The third vaccine, Cadila, is in Phase 1/2 trial with ~1,000 participants.

An Indian perspective with regards to the specific aforementioned scenarios are as follows:

- *Vaccine A demonstrates efficacy at interim analysis and sponsor initiates application for emergency use, all within the same country*
 - This scenario will not happen in India for a while, as the only currently approved trial with a clinical efficacy endpoint is just beginning recruitment; however, a manufacturer producing a vaccine that is being evaluated outside India for clinical efficacy can still apply for licensure if some safety and immunogenicity data have been generated in India. This has been done previously with Phase 3 efficacy data from another country for a vaccine that is being manufactured in India (e.g. pneumococcal vaccine). This could however, result in emergency use or licensure for i) other parts of the world (not India) with an export license for the manufacturing, or ii) India, but the vaccine may not immediately be approved for national programmatic implementation, or iii) India, with plans for programmatic introduction. For scenarios i) and ii), ongoing trials will not be affected, but ii) will affect planned trials and for iii), any ongoing trials will be affected.
- *Vaccine A has been approved for emergency use or full licensure by the NRA, but product is not yet available in country*
 - Ongoing trials are unlikely to be affected.
- *Vaccine A has been approved by the NRA for emergency use or full licensure but supply only sufficient for high-risk populations*
 - This situation has been seen before with the rotavirus vaccines. It was decided that if people were enrolled in a trial it was an ethical responsibility to inform them about the licensure of another vaccine, but also to continue the study until the full readout was available, given that the licensed vaccine was being introduced in a phased manner
- *Vaccine B has ongoing/planned Phase 3 trial in the same country as approved Vaccine A*
 - So long as a vaccine is not part of the national program in India, it has been possible to consider going ahead with a trial of a second vaccine still including a placebo arm (e.g. Rotavac licensed/Rotasil studies conducted).
 - The COVID-19 pandemic presents a different situation where rollout of the vaccine may start for high risk populations and to subsequent populations over time. This presents the challenge of how to prove that Vaccine B is potentially better than Vaccine A.
 - In India, developers may have vaccines where study designs may differ from one another and still be on a path to licensure.

Perspectives from a Brazilian context

Dr Gustavo Santos, General Manager of Medicines and Biological Products at ANVISA, explained that different institutions in Brazil are responsible for different aspects with regards to vaccines. ANVISA is the regulatory agency in charge of evaluation of clinical trial applications, evaluation of registration of the products, and checking if vaccines comply with the technical requirements for use in the population. CONEP is responsible for ethical discussions on human studies conducted in Brazil, while the Ministry of Health is responsible for supply of vaccines to the population, including deciding priority groups for vaccination and distribution of vaccines throughout the country. ANVISA has established an expert committee for decisions on clinical trials conducted in Brazil, how these will be evaluated, and technical requirements, especially with regards to COVID-19. EUA is not available in Brazil. Thus, the expectation is to have the full documentation for registration of a vaccine. Four vaccines are currently in clinical trial in Brazil. The idea of a tech transfer to a Brazilian institution is a possibility for two of these vaccines (Ox/AZ and Instituto Butantan); thus, a rolling submission procedure has been established and non-clinical data are available for review. Experts from ANVISA and the Ministry of Health agree that although it is important to foresee scenarios, the main answer will come from actually seeing the data.

Comments on the specific scenarios were as follows:

- *Vaccine A demonstrates efficacy at interim analysis and sponsor initiates application for emergency use, all within the same country*
 - If the vaccine demonstrates efficacy at interim analysis, documents will/can be submitted for full licensure. No vaccination of the placebo arm would be expected.
- *Vaccine A has been approved for emergency use or full licensure by the NRA, but product is not yet available in country*
 - The trial continues (as it is interim analysis), and full data are submitted at the end of the study. No vaccination of the placebo arm would be expected.
- *Vaccine A has been approved by the NRA for emergency use or full licensure but supply only sufficient for high-risk populations*
 - This relates to the Ministry of Health and how vaccine is going to be supplied. It would be reasonable to continue to maintain the placebo group for the low-risk population that is not targeted by the National Immunization Technical Advisory Groups (NITAG) for vaccination.
- *Vaccine B has ongoing/planned Phase 3 trial in the same country as approved Vaccine A*
 - Continuation of the placebo arm will not be enforced in Brazil. This is an ethical decision and the sponsor and participants should be made fully aware of the availability of a Vaccine A (with efficacy and risk/adverse events clearly transparent on the label) and given the option to continue in the placebo arm of the Vaccine B trial or to be vaccinated with Vaccine A.
 - If participants decide to be vaccinated, the regulatory agency will have to review the data and consider the effect on the approved protocol or planned studies.

Panel discussion: Scenario-based discussion of efficacy results and implications in different trial settings

Professor Ross Upshur, from the University of Toronto and Co-Chair of the WHO COVID-19 Ethics Working Group, highlighted some fundamental principles of research ethics to help frame thinking about what happens when we enrol human subjects into research. Key points included:

- The importance of protection for human subjects in extant research ethics guidance documents has been reaffirmed as well as the importance of upholding them. Of particular importance for COVID-19 vaccine trials are social and scientific value, that subjects have been fairly selected, that there is a favourable risk benefit ratio to participating in the trials, independent review by an ethics and scientific committee has been conducted, informed consent has been obtained, and respect maintained for potential and enrolled subjects.
- It is unclear whether the possibility of interim analysis unblinding and the potential offering of a vaccine has been mentioned in ongoing COVID-19 vaccine trials (i.e. through enrolment and gaining informed consent) as this would be an important consideration.
- Respect for enrolled subjects should be maintained and they have the right to withdraw from the study at any time without consequence and their data will be protected and not shared without permission.
- Subjects should be informed of newly discovered risks/benefits and of the research results.
- The obligation to offer a treatment is not based solely on considerations of efficacy; safety needs to be very clearly demonstrated.
- Maintaining the public trust in the vaccination research is critically related to our assurance of the safety of vaccines.
- Community engagement is important, and it is unclear to what extent the community has been engaged in these vaccine trials to ascertain their perspectives on what kind of assurance of safety and efficacy they would require to find the vaccine acceptable.

A panel discussion included the following key points:

- What happens with the placebo group is dependent on what is included in the informed consent. Provided too strong a commitment has not been made at the start of the trial as to what will happen when vaccines become available, there are circumstances where continuation of placebo can occur in population subgroups who are not eligible to receive the vaccine as part of the National Program (e.g. continue trial in non-elderly until vaccine becomes available for non-elderly in wider population). It should be noted however that there is a practical possibility of losing a substantial proportion of the recruited study population if the target population for enrolment was these same high-risk populations (e.g., health-care workers and/or elderly).
- Whether the authorisation/approval relates to another vaccine or the vaccine under trial, actions, including sharing information with participants and potential unblinding, could/should be restricted to those participants in the study matching the recommended use at a particular point in time and only in the localities where vaccine is available outside of the context of the study.
- When vaccines become available for subsets of the population in large countries like Brazil and India, it is likely that those vaccines will be rolled out by geographic area over time and there may be a delay before vaccines become available in areas in which trials are ongoing.

- If a EUA/licensed product becomes available in the community, an elderly high-risk person may decide individually to leave the study to be vaccinated. Unblinding of the group for an individual should only be made after they decide to leave the trial. This will keep the analytics clean so that there is still a pathway to a credible analysis for those who remain in the study.
- *What is the effect of an approval by an NRA outside the country where the trial is being conducted of a multi-regional study? Of a separate study using the same vaccine?*
 - Approval in another country is not immediately recognized by Brazil and may not affect ongoing studies.
 - If an NRA outside the country approves the vaccine, it is not automatically approved in country. The company that wants to license it in country must devise a package for approval within that country. If a global clinical trial has been approved, the regulator will be informed that this interim analysis or licensure has happened and asked for their opinion. In India, the regulators would likely request data generated in India and ask for the study to continue as a placebo-controlled study, particularly if it is an interim analysis that leads to a conditional approval. If it is a full licensure, the regulator will review and consider whether this is sufficient data to constitute a bridging study so that the company can apply for licensure in the country.
- *What happens in a situation where the first vaccine to license has limited efficacy and the next has presumed increased efficacy but will be delayed by one to two months relatively?*
 - This is of concern as wave 2 vaccines have features that may be more attractive for widespread use (e.g. perhaps higher neutralizing titres), and the first vaccines appear to have modest efficacy.
 - This may affect population acceptance of a product. There may initially be lower uptake of partially effective vaccines if people think better vaccines are in the pipeline.
 - A communication strategy is required to explain to populations some of these nuances (e.g. trade-off between a higher and lower vaccine efficacy). It is important that these issues are understood by the public, both trial participants and the wider public as it will affect uptake when emergency use or any other of these mechanisms take effect. The International Federation of Pharmaceutical Manufacturers and Associations and/or Developing Countries Vaccine Manufacturers Network might get involved in developing this to make available to developers and enable them to get ahead of the misinformation likely to be generated.
 - The NITAGs have a critical role to play as they will make recommendations to governments regarding use of vaccines, prioritization framework, and delivery of vaccines. They should be brought in early to discuss why there needs to be consideration of multiple aspects that relate to both the development of vaccines and future use. The NITAGs are a good platform to start this engagement as most countries have them, most of them are reasonably functional, and they don't have a stake in this as developers do.
- Once a product is EUA'd or licensed and there is an announcement that it will be available to high risk populations, it is important to ensure vaccine is indeed available so as not to undermine the studies and lose the placebo group.
- The consensus is to try to maintain the placebo arm of these trials for as long as possible.

Impact of an efficacious vaccine on COVID-19 vaccine trials

Prof Dean Follmann, member of Operation Warp Speed Statistics Group and Chief of Biostatistics Research Branch (NIH/NIAID), discussed the impact of an efficacious vaccine on COVID-19 vaccine trials and reasons to maintain blinded follow-up to assess correlates, vaccine durability, and VAED.

Summary points included:

- If a vaccine trial shows efficacy, blinded follow-up should be continued for as long as possible to assess durability and VAED.
- If placebo crossover to vaccine does occur, follow up should be maintained, ideally blinded, to maintain a randomized trial of immediate versus delayed vaccination. Continued follow-up allows vaccine durability to be assessed, though less reliably than without crossover. In addition, the sample size for immune correlates analysis is doubled.

Non-inferiority trial design considerations

Dr Martha Nason, member of Operation Warp Speed Statistics Group and Mathematical Statistician at Biostatistics Research Branch (NIH/NIAID), presented an overview of non-inferiority trial design and sample size calculations.

Key points included:

- Defining the non-inferiority margin is central to planning any non-inferiority trial.
- Discussions should be happening now between regulators, developers, ethicists, and other stakeholders regarding defining the margin and how this might vary depending on the situation and on the vaccine efficacy of the first vaccine.
- Non-inferiority trials are an option of last resort if two vaccines are thought to have similar efficacy because of the very large study sizes required; however, they may be plausible if superiority is suspected. If a new candidate vaccine is approximately equal to an established comparator vaccine in terms of efficacy, non-inferiority will take a long time or require a very large sample size.
- If a new vaccine is 10% higher on the vaccine efficacy scale than an established comparator vaccine (70% versus 60%), demonstration of non-inferiority may take 2-3 years if comparable sample size is used as in current Phase 3 conventional vaccine efficacy trials, assuming plausible incidence rates for endpoints (alternatively, sample size will have to be increased significantly).

Evaluating VAED in Phase 3 beyond: setting realistic expectations

Dr Steve Black presented an overview of VAED and the importance of long-term follow-up.

Summary points included:

- There is a possibility that VAED may occur after some COVID-19 vaccines.
- Risk might be higher for unadjuvanted inactivated vaccines that develop a Th2 oriented response.
- As there is no biomarker for VAED, it is not currently possible to differentiate a vaccine failure from a vaccine failure with enhanced disease on an individual level.
- Assessment of all vaccine failures using a standardized protocol and disease severity score is critical.

Panel discussion: Operational, regulatory, and scientific considerations

A panel discussion included the following key points:

- Key regulatory considerations included:
 - The results of efficacy studies with first-generation vaccines must be considered before an in-depth discussion on non-inferiority margins can take place.
 - Immune bridging represents an option to help define benefits and risks for next-generation vaccines. However, it will take time to identify correlates of protection and determine their robustness across vaccine platforms. Regulators are keen to speed up the collection of data, particularly immunogenicity data, from these trials to facilitate this process.
 - It is important to ensure that good efforts are in place to collect information on immune markers from ongoing trials. Importantly, any correlate of protection or immune marker identified that could be linked to protection may differ across vaccine platforms.
 - It is important to continue comparison between vaccines from the same platform. This may facilitate bridging in the future.
 - If the recommendation for vaccination does not cover the entire population immediately, it may be worth considering the feasibility of conducting a placebo-controlled trial in the population (i.e. excluding those eligible for vaccination).
 - The use of human challenge models is not a priority but might be a useful possible option if this model is developed.
- *How do we help additional vaccines move through licensure if we've lost the placebo arm and non-inferiority studies are not feasible?*
 - In the hypothetical absence of the placebo arm and non-inferiority studies, other options to help additional vaccines move through licensure includes the possibility of human challenge studies and correlates of protection.
 - Data for a correlate of protection does not have to come from a controlled trial although it does need to come in a situation where people are still getting infected despite vaccination. Thus, if we want to identify a correlate of protection at a time when a non-inferiority trial is believed impossible due to not enough people getting infected, then it will also be a challenge to come up with a correlate of protection. This needs to be considered now.
- It should be highlighted that it is essential to maintain placebo in these studies for as long as possible to look at duration of efficacy, risks of late enhanced disease, and to accumulate sufficient endpoints to assess vaccine efficacy in certain subgroups. Maintaining the placebo arm will also enable refinement of the vaccine efficacy point estimate, which may then allow advisory groups to decide which vaccines to use in different settings, and refinement of the point estimate against severe disease. The BoD endpoint can be used to assess vaccine efficacy; however, the current strategy employed in clinical trials is to use any symptomatic disease as the endpoint but follow participants for a longer period of time to enable conclusions about the impact of a vaccine on severe disease to be made. In this case, if the placebo arm disappears, so does the ability to acquire this information.
- It is important to look not only at what has been considered for vaccines but how these ethical questions have been considered for drugs where one could argue the stakes are much larger and still the conclusion has been made that situations where some might have concerns about the ethics actually do allow for ethical completion of placebo controlled trials (e.g. cancer drug trials).

- It should be noted that a vaccine made available under an “Emergency Use” provision is still investigational and important questions remain unanswered.
- *What kind of arguments are required to define the non-inferiority margin for vaccine efficacy studies?*
 - The amount of time it would take to obtain a result will depend on the background infection rate in the place of conduct of the non-inferiority trial. It may be possible to come up with shorter timelines depending on where these trials are conducted.
 - The 10% non-inferiority margin proposed in the FDA guidance will not work for all situations or for many plausible situations, and the question of the right non-inferiority margin remains. This will need to be reconsidered by the FDA and wider community. The real question for the non-inferiority margin becomes 1) what do we want to show, and 2) what are the important outcomes that we want to either demonstrate or rule out. There may be room for some relaxation of non-inferiority margins under some circumstances that may make non-inferiority trials smaller. Non-inferiority trials should not be ruled out as part of our armamentarium.
 - With regards to differences between vaccines (e.g. one is live replicating vaccine and difficult to use in immunocompromised or pregnant women), scientifically there is good reason to relax the traditional non-inferiority margin. Regulators would consider the characteristics of a new vaccine and possible added value, and this would feed into the discussion of how to set the non-inferiority margin.
- *Do the same considerations that make non-inferiority trials difficult also not apply to a crossover where the delayed vaccine is compared to more recent vaccination?*
 - Power calculations have been conducted and the situation with crossover appears better than for non-inferiority trials.
- *Might potential bias be an issue in individuals who crossover as they represent a subgroup for which the vaccine is recommended and how will this be handled?*
 - Blinding could be maintained in the trial, and a placebo could be used to vaccinate those in the vaccine groups.
- *The first data from ongoing Phase 3 trials will come from interim analysis based on just a few dozens of confirmed cases potentially resulting in a higher point estimate than the actual vaccine efficacy established based on the full follow-up. Will this affect non-inferiority trials that are potentially started early on, or will this be another reason to insist on continuing with placebo-controlled trials and starting other controlled trials in the meantime?*
 - Statistical variability at these early time points increases the likelihood that if efficacy is declared the point estimate is biased high. Uncertainty around what the actual initial efficacy of the vaccine might be also complicates thinking about what the non-inferiority margin should be. This is another strong reason why it is that these trials should be completed with the placebo group and should be followed to their normal completion to obtain reliable estimates of efficacy.
 - In the meantime; however, consideration needs to be given from a regulatory standpoint as to what could be acceptable (in terms of clinical development and study design) for achieving a potential approval for developers coming in the second wave.
- Animal studies have been encouraging regarding the efficacy of some vaccines although the follow up time between vaccination and challenge has been quite short in those studies.

Wrap-up and next steps

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

- The COVAX Clinical SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines
- We will be holding a next workshop on advances toward identifying Immune Correlates of Protection (CoP) on November 19th, 2020.
- We will continue to share resources at the website here: <https://epi.tghn.org/covax-overview/clinical/>
- We will distribute a workshop report to summarize today's conversation and a post-workshop survey to collect feedback.