COVID-19 Vaccine Efficacy Trial Design
Key Statistical Considerations

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VIDD/Fred Hutch
# OWS/CoVPN phase 3 COVID vaccine trials

<table>
<thead>
<tr>
<th>Dose (1 vs 2)</th>
<th>2020</th>
<th>2021</th>
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<tr>
<td></td>
<td>Jul</td>
<td>Aug</td>
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<tr>
<td>Moderna</td>
<td><img src="#" alt="bar" /></td>
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<td>AstraZeneca</td>
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<td>Janssen</td>
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<td>Novavax</td>
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<tr>
<td>Sanofi</td>
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- **Enrollment (est.)**: Green bar
- **Case accrual period**: Purple bar
- **Correlates report**: Red triangle

*Correlates report includes ~3 months for BLA filing, VRBPAC, and last assays.*
‘Prototypical’ CoVPN Vaccine Efficacy Trial

**Population:** ~30,000 adults age 18 and over, at risk of SARS-CoV-2 infection and COVID-19 disease (no screening for prior infection)

- Enriched for high risk based on age, co-morbidities, race/ethnicity
- For U.S., underrepresented minorities enrolled at or above U.S. demographic frequencies

**Randomized** to 2:1 (or 1:1) to Vaccine or Placebo, potentially within risk strata

**Follow-up** for 2 years post-last vaccination

**Primary endpoint:** virologically-confirmed symptomatic disease
Follow-up and Sampling Schedule

- Enrollment
  - Dose 1
  - Dose 2*

- Collection of nasopharyngeal swab, anterior nasal swab, or saliva cup
- Centralized testing via NAAT or antigen test for COV-DIS
- Pos Result
  - Collection of:
    - Sera
    - Nasopharyngeal swabs, anterior nasal swabs, or saliva cups
    - All COV-DIS endpoints

- Specified symptoms triggering specimen testing
- Weekly participant contacts for symptom-triggered nasopharyngeal swabs, anterior nasal swabs, or saliva cups

- Blood storage* for retrospective virus detection and antibody detection (seroconversion)

*Also for immunogenicity & immune correlates analyses
Post-COVID-Diagnosis Follow-Up

To assess vaccine effect on severity and duration of symptoms and viral shedding (2⁰ endpoints)

All Cases

Day 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Self-assessed symptoms/signs

Nasal swab

Blood draw

If SARS-CoV-2 positive on Day 21

If SARS-CoV-2 negative on Day 21

Collection of data on disease severity (signs, symptoms) via diary card/mobile app

Obtain sample (self-collected from nasal swabs) for SARS-CoV-2 detection by PCR (Central lab)

Blood draw

All Cases:
Continue clinical monitoring and safety f/u through study completion

Day 22 23 24 25 26 27 28* 29 30 31 32 33 34 35

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Endpoints

Common primary endpoint
Protocol-specified list of COVID-19 symptoms with virological confirmation of SARS-CoV-2 infection (symptom-triggered)

Mehrotra et al. Ann Int Med 2020
Endpoints

Key Secondary Endpoints
Positive SARS-CoV-2 PCR or seroconversion

COVID endpoint plus one protocol-specified severe disease event

Mehrotra et al. *Ann Int Med* 2020
**Study Duration and Timing of Primary Analysis**

**Event-driven primary analysis***
When target number of primary endpoints have accrued:
- 150 events if 2:1
- 170 events if 1:1

**Continued blinded f/u if positive result at primary analysis**

- Trials sized so that under conservative assumptions around COVID-19 incidence, primary analysis likely to occur within ~7 months of trial start
- Continued blinded f/u necessary to evaluate durability of VE (2° objective) and to adequately power VE against severe COVID

* Rationale for target event totals next slides
Primary Analysis and Success Criteria

Vaccine efficacy, $VE = [1 - \text{Endpoint hazard ratio (vaccine/placebo)}] \times 100\%$

• Assess by proportional hazards model with separate placebo arm baseline hazard function for each study site x randomization stratum (anticipate heterogeneity in epidemics across sites)

Primary analysis cohort: participants baseline negative for SARS-CoV-2 (PCR/serology) in ‘full analysis set’ (FAS) [enrolled ppts receiving 1+ dose], counting events 15+ days after last dose*

Success criteria: estimated $VE \geq 50\%$, and lower bound on 95% confidence interval $\geq 30\%$

• Per FDA guidance and satisfies WHO Target Product Profile

* Some trials perform primary analysis among ‘per-protocol’ participants
Math models predict substantial population impact of vaccines with 50% VE against COVID disease

All vaccines reduce COVID-19 disease by 50% and reduce SARS-CoV-2 infection by 10-17%

Deterministic compartmental model calibrated to King County, WA stratified by age, SARS-CoV-2 infection status, COVID-19 treatment status and vaccination. 45% of population vaccinated starting Dec 1, 2020, proportionally across age groups, over ~6 mo. Absent vaccination, 20% of infections are asymptomatic; asymptomatic infections are 30% less infectious than symptomatic infections, but more transmissible due to lower rates of diagnosis and quarantine. (Swan, Dimitrov et al. in preparation)
Sample Size and Target Endpoint Total

Success Criteria:
Estimated VE ≥ 50% and LB of 95% CI ≥ 30%

150 primary endpoints needed for 90% power for VE=60%
(2:1 Vaccine:Placebo Allocation)

• Work backwards to identify sample size
  o Specify proportion enrolled baseline SARS-CoV-2 negative
  o Specify 6-month placebo-arm incidence in baseline SARS-CoV-2 negative group

• E.g., 90% baseline SARS-CoV-2 negative and 1% 6-month placebo incidence implies total N = 30,000
<table>
<thead>
<tr>
<th>Type</th>
<th>Purpose</th>
<th>Methodology and Frequency</th>
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| Potential harm/enhancement  | Stop vaccinations as early as possible if evidence of increased risk associated with the vaccine | Nominal 1-sided 0.05-level exact binomial tests of fraction of endpoints in vaccine arm, *continuously* from 8th primary endpoint to time of primary analysis  
  • COVID and severe COVID |
| Non-efficacy                | Early detection of absent or weak vaccine efficacy, to deliver result to field in a timely manner | Two interim analyses at 35% and 70% of primary endpoint total. Nominal 95% CI monitoring  
  (Friedlin et al.)         |
| Efficacy                    | Early detection of vaccine efficacy, to permit rapid licensure            | Two interim analyses at 35% and 70% of primary endpoint total. O’Brien- Fleming monitoring  |

Freidlin, Gray, and Korn (2010, *Clin Trials*)
Potential Outcomes of Interim and Primary Analysis

Interim or Primary Efficacy Analysis

- Efficacy Criteria Met
  - Randomization Ceases
  - Blinded Follow-Up Continues, to Evaluate VE Durability
  - Result is Reported Publicly
  - Select Group of Investigators Provided Unblinded Data to Produce Reports

- No Criteria Met
  - Randomization and Follow-Up Continue as Planned

- Non-Efficacy or Increased-Risk Criteria Met
  - Randomization Ceases
  - Oversight Group Determines Whether and How Long to Continue Blinded Follow-Up
  - If Demonstrated Vaccine-Harm or Major Concern, Participants Unblinded/Notified to Enable Follow-Up, Treatment, as Required
  - Result is Reported Publicly
Importance of Continued Follow-up, Following Efficacy Signal (Interim or Primary Analysis)

- To establish longer-term safety of vaccine
- To define durability of vaccine efficacy
- To evaluate vaccine efficacy against severe COVID-19 and death (rare endpoints)
- To establish safety and efficacy across subpopulations defined by baseline SARS-CoV-2 status, age, race/ethnicity and other risk factors
A major research focus of OWS/CoVPN is identifying immunological biomarkers that are surrogates of vaccine-induced protection

• For accelerating development and licensure of COVID vaccines
  • Future vaccines could be approved based on several-hundred person trials establishing adequate immune response induced (traditional or provisional approval pathway)

• For bridging vaccine efficacy to new settings/populations not included in efficacy trials, e.g. adolescents and pregnant women

• For evaluating durability of vaccine efficacy
Key Attributes of Correlates Program

Harmonized trial designs

- Similar protocols, e.g. primary and secondary endpoint definitions
- Common laboratories for characterizing immunogenicity
- Data sharing agreements/mechanisms and common statistical group
Case-Cohort Sampling Design*

Measure antibody markers in random subcohort and all SARS-CoV-2 infection endpoints (both symptomatic and asymptomatic) in each phase 3 trial

*Prentice RL (1986, Biometrika)
Statistical Frameworks for Evaluating Immunological Correlates

To assess Day 57 antibody biomarkers as various types of correlates

1. **Correlates of risk** in vaccine recipients (risk prediction)
   - Relative risks of outcome across levels of the biomarker
   - Absolute risk of outcome across levels of the biomarker
   - Machine learning models for predicting outcome from multiple biomarkers

2. **Correlates of VE** in vaccine recipients (effect modification / principal stratification)
   - VE across subgroups of vaccine recipients defined by biomarker level in vaccine recipients

3. **Mediators of VE** (mechanisms of protection / natural direct and indirect effects) (e.g., Cowling et al. for influenza)
   - Proportion of VE mediated by a biomarker (or biomarkers)

4. **Surrogate endpoint** evaluation techniques (e.g., Buyse, Molenberghs et al.)
   - E.g., strength of association of individual-level causal effects on the biomarker and on the endpoint

5. **Intervened effects on risk** (Hejazi et al., 2020, Biometrics)
   - How much would risk be lowered by shifting the biomarker distribution upwards?
Immune Correlates Analysis of Phase 3 Data Sets

Data Analysis & Automated Reporting Software
(Development Infrastructure on Previous Slide; Real Analysis Code behind SCHARP Firewall)

Trial-specific Data Sets
(behind SCHARP Firewall)

Reproducible Trial-specific Data Analysis Reports
(behind SCHARP Firewall)

Reports Posted on SCHARP Atlas (or other preferred portals) with Restricted Sponsor/OWS Access
OWS/CoVPN phase 3 COVID vaccine trials

- AstraZeneca: Enrollments (est.) in Sep, Case accrual period in Oct.
- Janssen: Enrollments (est.) in Nov, Case accrual period in Dec.
- Novavax: Enrollments (est.) in Nov and Dec, Case accrual period in Jan and Feb.
- Sanofi: Enrollments (est.) in Jan and Feb, Case accrual period in Mar and Apr.

Correlates report:
(allow ~3 months for BLA filing, VRBPAC, last assays)
THANK YOU
Random Subcohort for Measuring Immunological Biomarkers
(N=1620 Participants)

**Random Subcohort Sample Sizes for Biomarker Measurement**

<table>
<thead>
<tr>
<th>Baseline Covariate Strata¹</th>
<th>Baseline SARS-CoV-2 Negative²</th>
<th>Baseline SARS-CoV-2 Positive³</th>
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<tbody>
<tr>
<td>Vaccine</td>
<td>150 150 150 150 150 150</td>
<td>50 50 50 50 50 50</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 20 20 20 20 20</td>
<td>50 50 50 50 50 50</td>
</tr>
</tbody>
</table>

¹Randomization strata (based on age and high-risk conditions) cross-classified by underrepresented minority status.
²CoR analysis focuses on baseline negative vaccine recipients. The placebo group baseline negative strata are assigned small sample sizes given expectation that almost all Day 57 bAb and nAb readouts will be negative/zero given the absence of prior exposure to SARS-CoV-2 antigens.
³Study differences in natural+vaccine-elicited responses vs. natural-elicited responses.

Randomly sample participants into the subcohort once baseline SARS-CoV-2 serostatus data are available.

Generate sufficient sample size within baseline subgroups defined by key factors
- Randomization arm, baseline SARS-CoV-2 serostatus, randomization x underrepresented minority (in U.S.) strata

Subcohort sampling is uniform across the enrollment period, to represent the entire cohort.