COVID-19 Vaccine Efficacy Trial Design

Key Statistical Considerations

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VIDD/Fred Hutch

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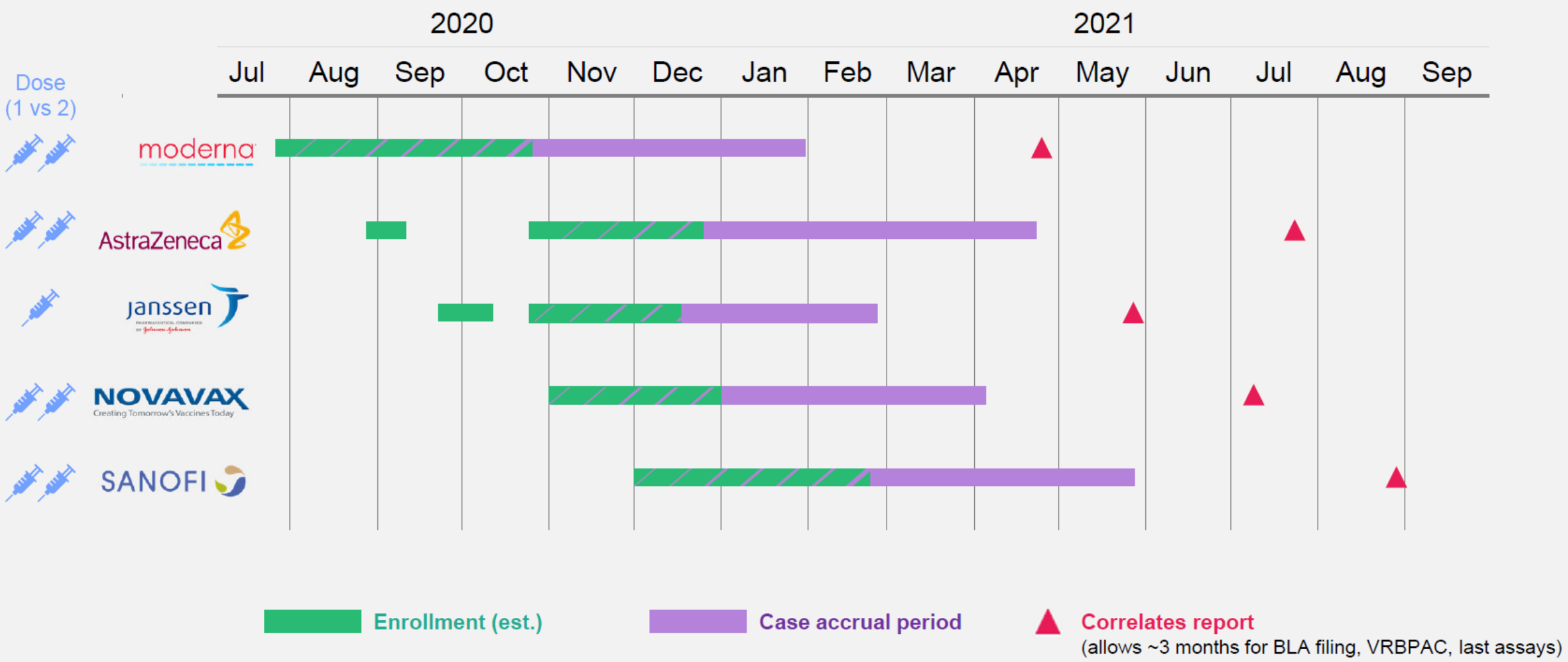
OWS/CoVPN phase 3 COVID vaccine trials



‘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)

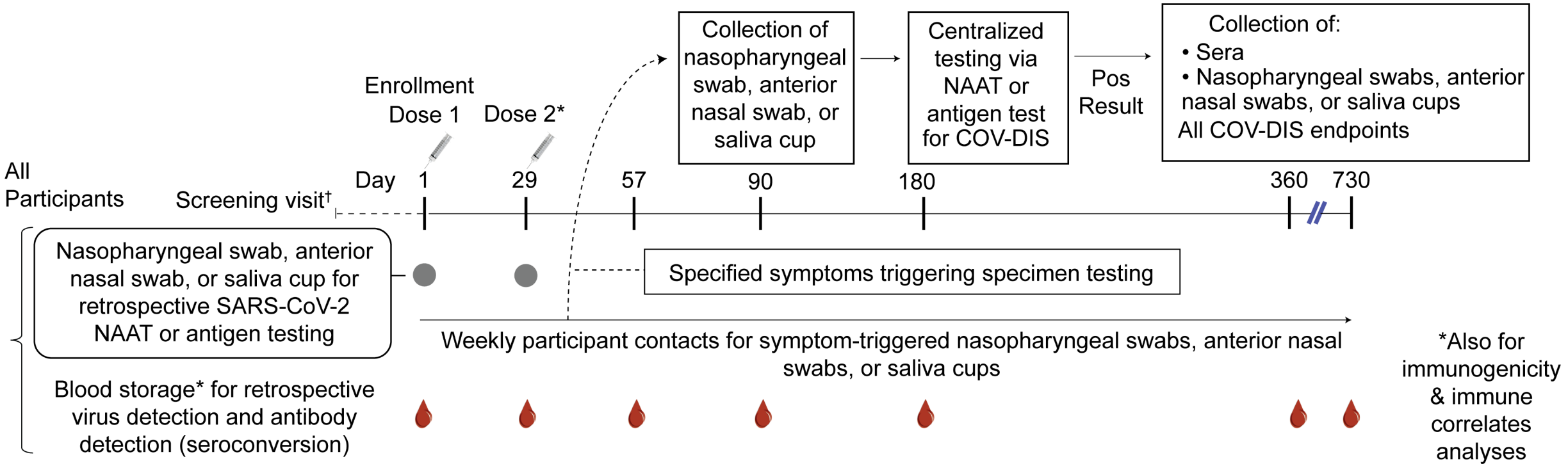
- Enriched for high risk based on age, co-morbidities, race/ethnicity
- For U.S., underrepresented minorities enrolled at or above U.S. demographic frequencies

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

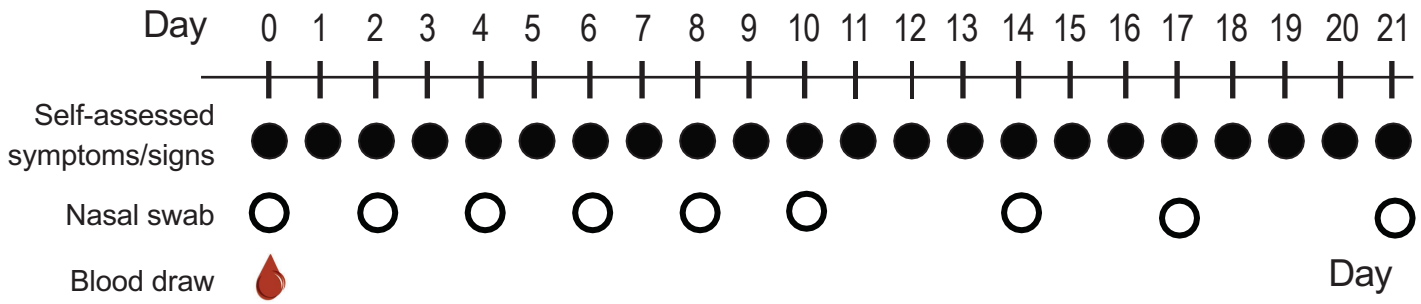
Follow-up and Sampling Schedule

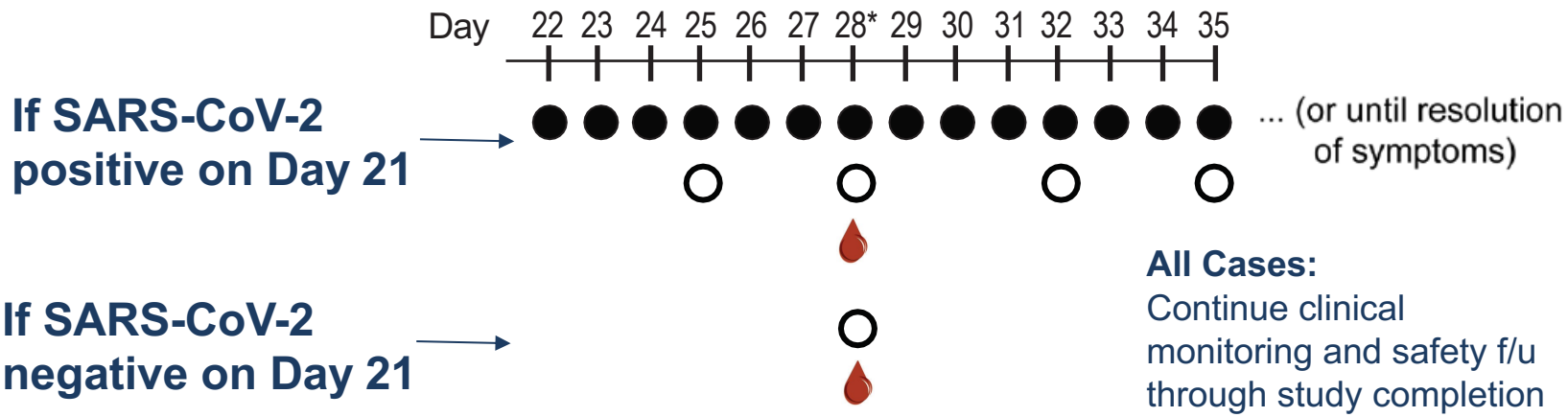


Post-COVID-Diagnosis Follow-Up

To assess vaccine effect on severity and duration of symptoms and viral shedding (2^0 endpoints)

All Cases





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

- 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

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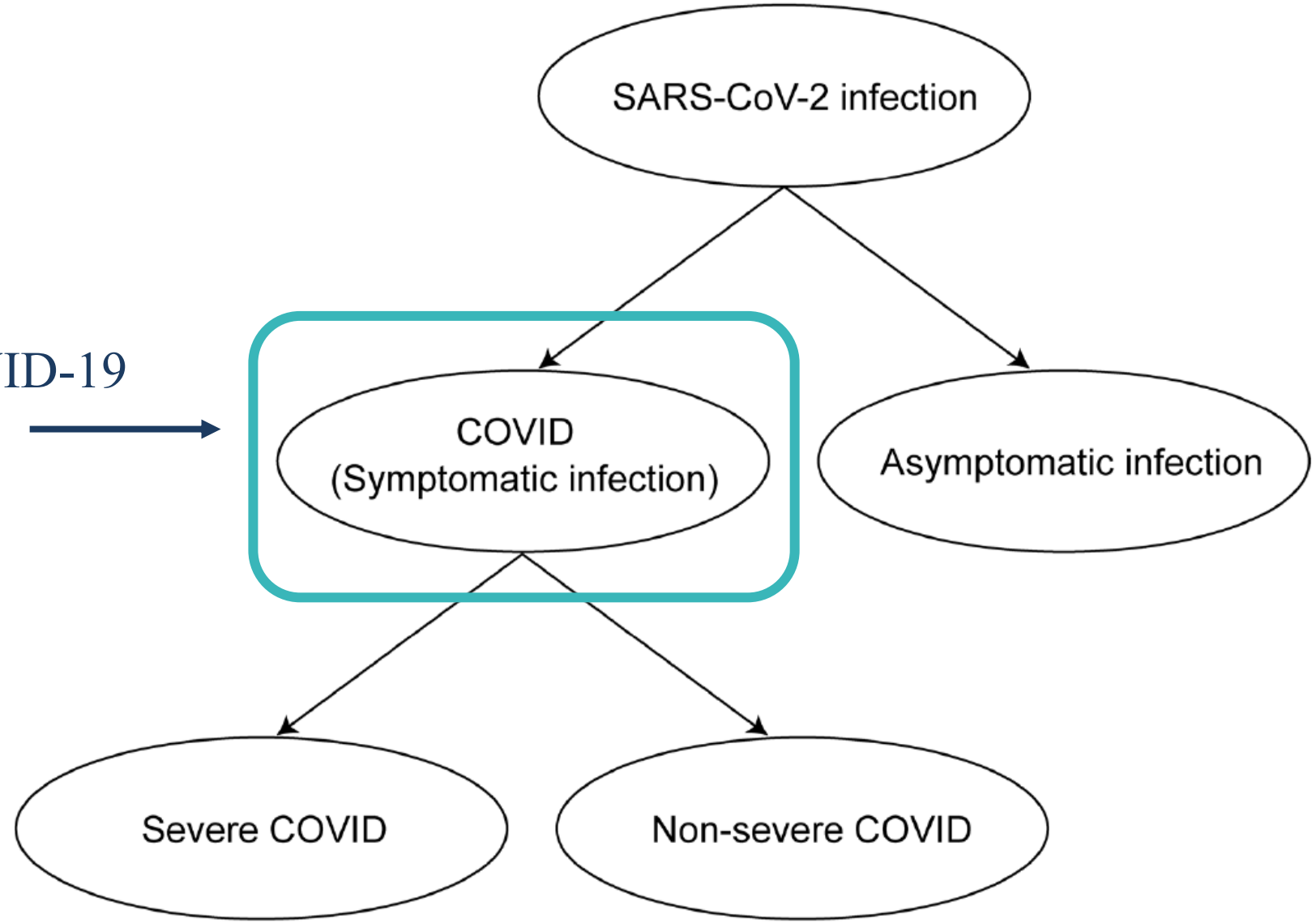
Endpoints

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



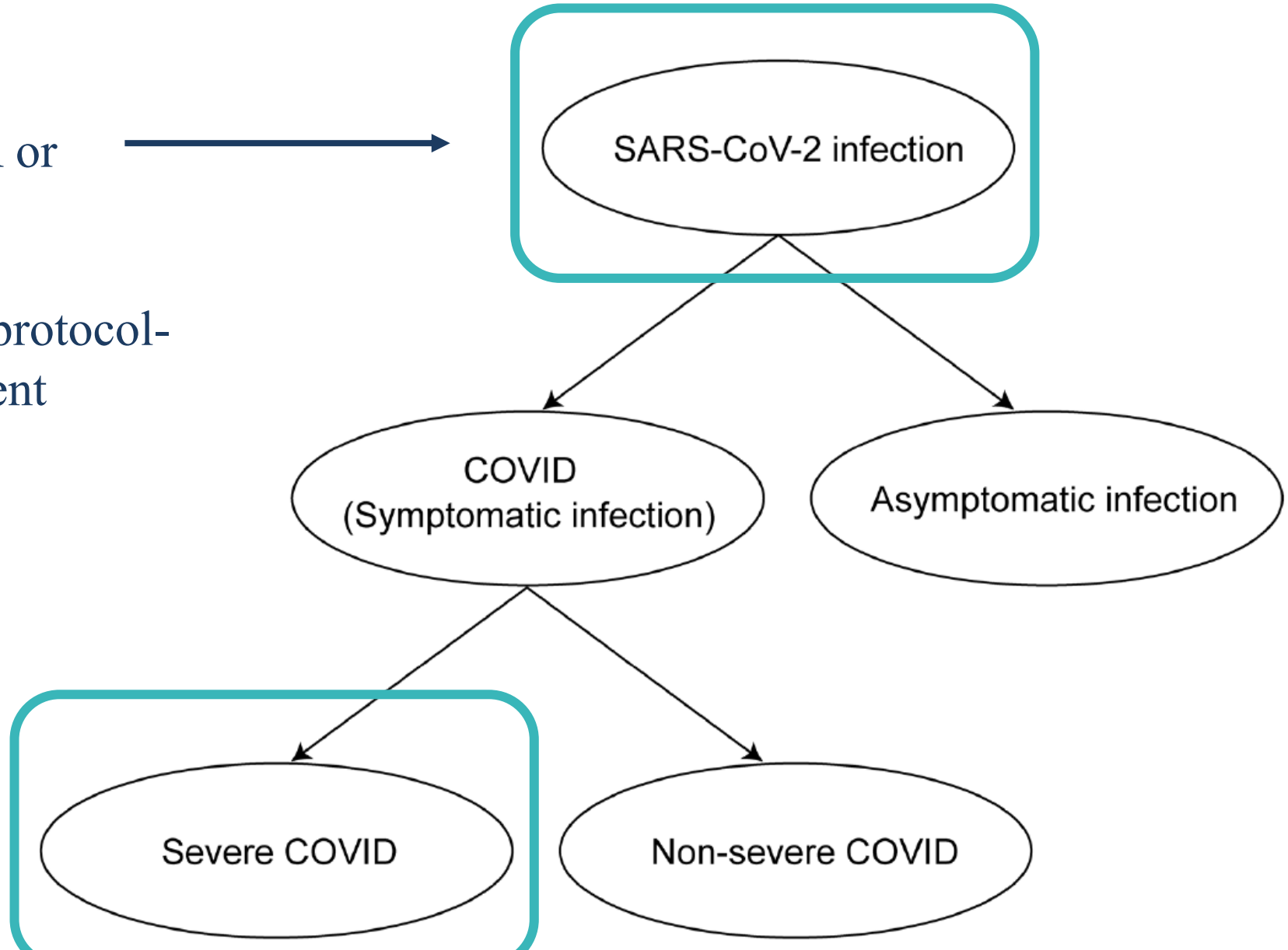
Mehrotra et al. *Ann Int Med* 2020

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

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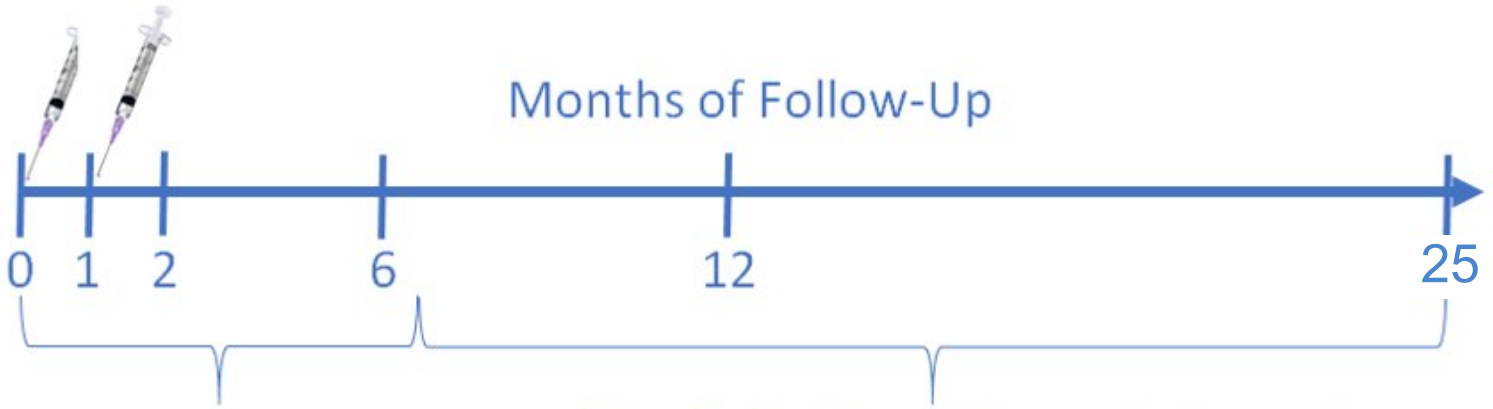
Study Duration and Timing of Primary Analysis



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 (2º 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 – Endpoint hazard ratio (vaccine/placebo)] x 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 ≥ 50%, and lower bound on 95% confidence interval ≥ 30%

- Per FDA guidance and satisfies WHO Target Product Profile

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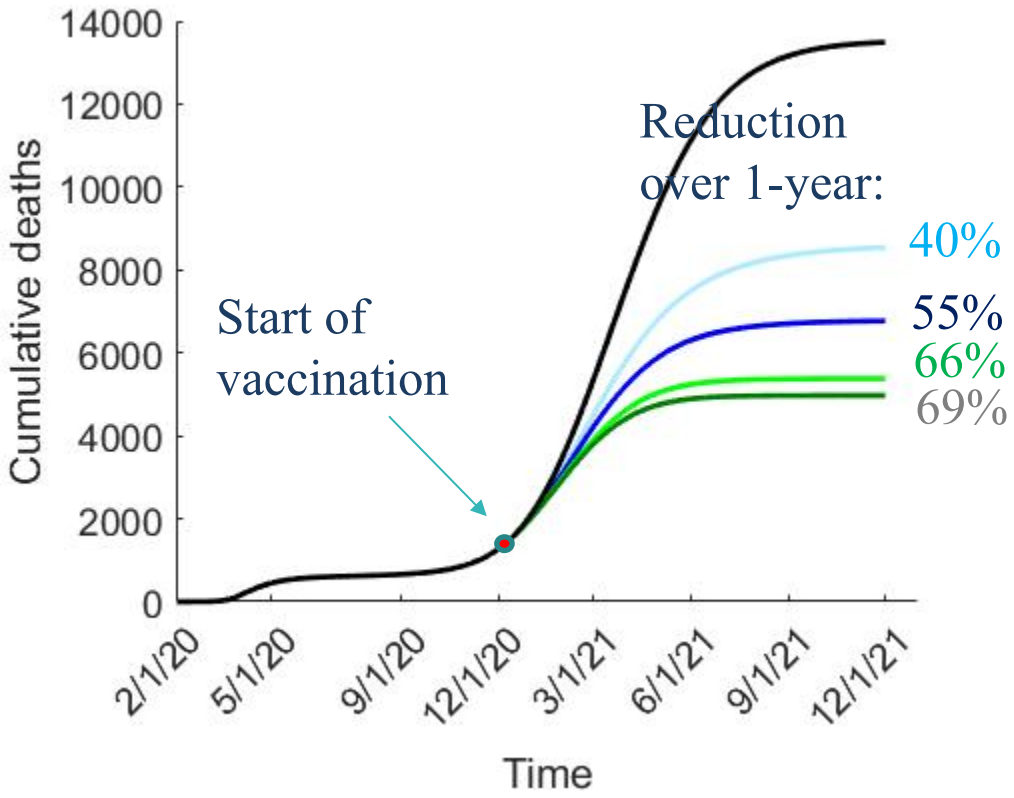
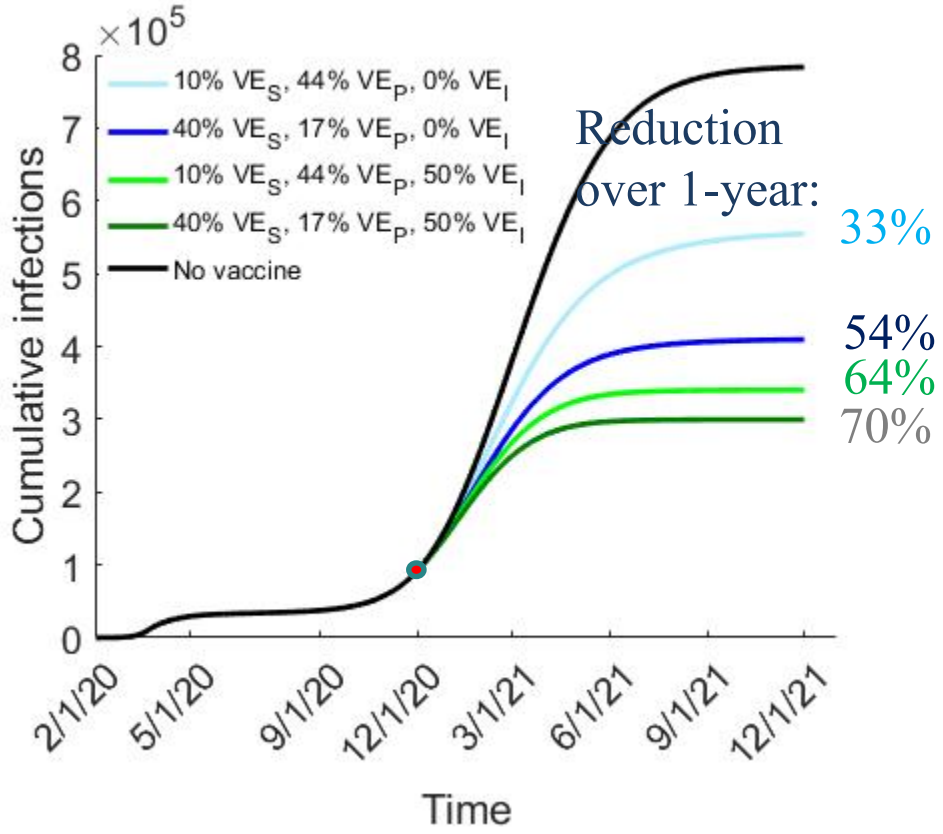
* Some trials perform primary analysis among 'per-protocol' participants

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
  - Specify proportion enrolled baseline SARS-CoV-2 negative
  - 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

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Interim Monitoring

Type	Purpose	Methodology and Frequency
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*)

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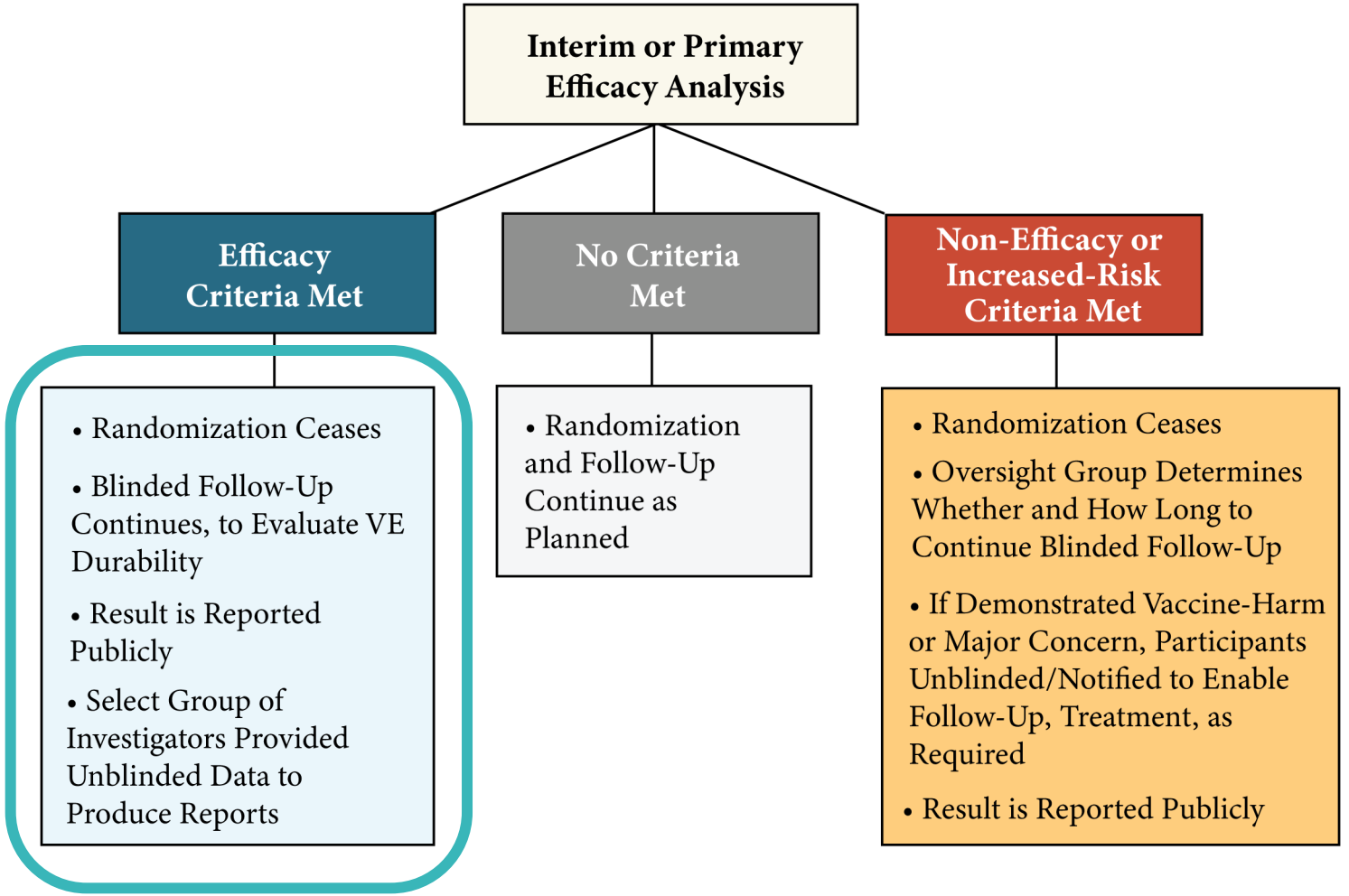
Potential Outcomes of Interim and Primary Analysis



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

OWS/CoVPN Immune Correlates Program

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

- Phase 3 trial
- Phase 3 trial
- Phase 3 trial
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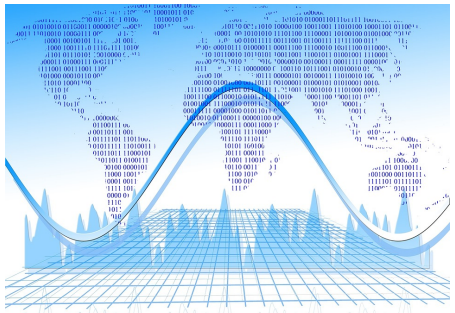
- Phase 3 trial

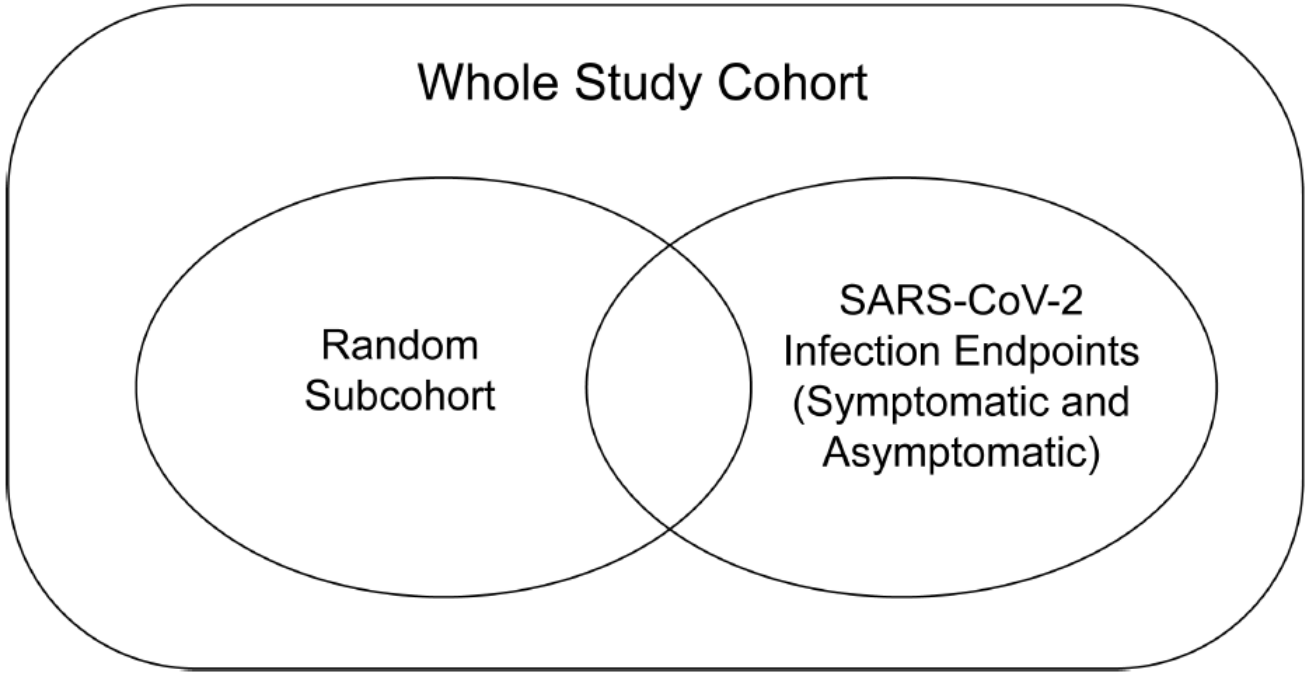
Common laboratories for characterizing immunogenicity



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*



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*Prentice RL (1986, *Biometrika*)

Statistical Frameworks for Evaluating Immunological Correlates

To assess Day 57 antibody biomarkers as various types of correlates

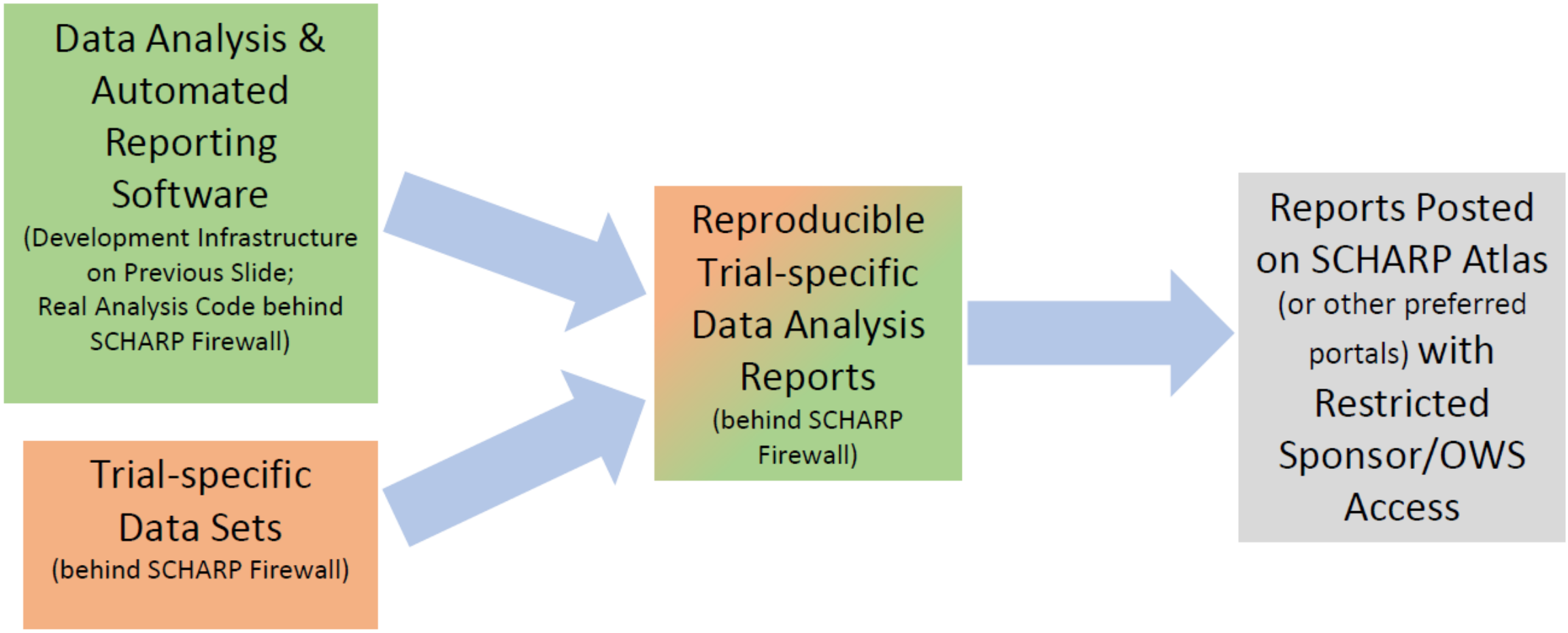
CoR

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

CoP

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



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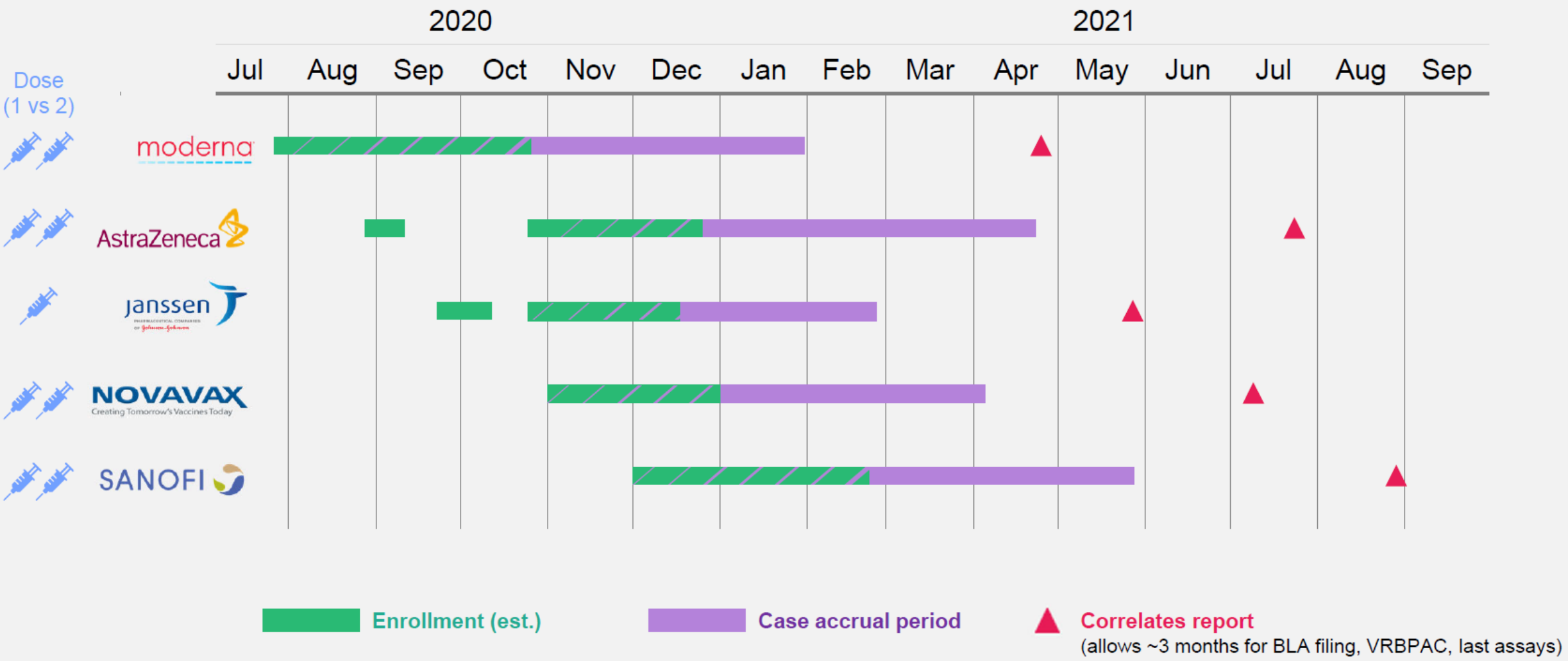

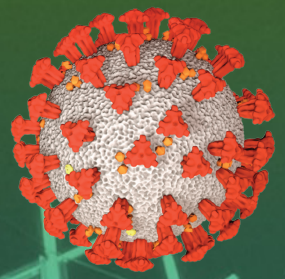

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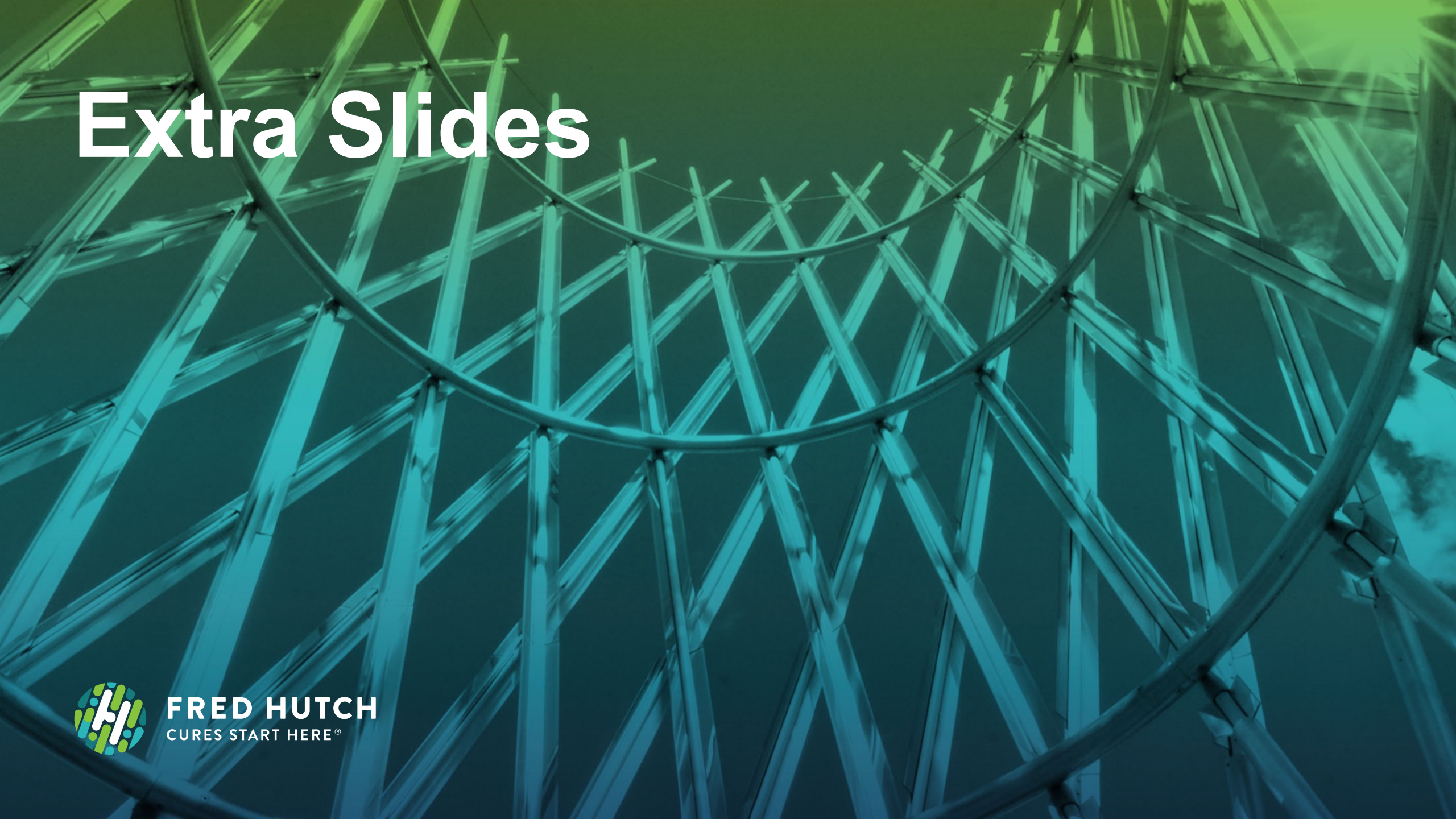
Extra Slides



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Random Subcohort for Measuring Immunological Biomarkers (N=1620 Participants)

Random Subcohort Sample Sizes for Biomarker Measurement												
	Baseline SARS-CoV-2 Negative[2]						Baseline SARS-CoV-2 Positive[3]					
Baseline Covariate Strata[1]	1	2	3	4	5	6	1	2	3	4	5	6
Vaccine	150	150	150	150	150	150	50	50	50	50	50	50
Placebo	20	20	20	20	20	20	50	50	50	50	50	50

[1]Randomization strata (based on age and high-risk conditions) cross-classified by underrepresented minority status.

[2]CoR 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.

[3]Study 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

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