SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN

A randomized controlled study to assess SARS CoV-2 infection, viral shedding, and subsequent potential transmission in individuals immunized with Moderna COVID-19 Vaccine, Version 4

CoVPN 3006

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STATISTICAL ANALYSIS PLAN

Protocol Name:	A randomized controlled study to assess SARS CoV-2 infection, viral shedding, and subsequent potential transmission in individuals immunized with Moderna COVID-19 Vaccine
Protocol Number:	CoVPN 3006
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1. LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
Ab	Antibody
AUC	Area under the curve
CACC	Case-Ascertained Close Contact
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CoVPN	COVID-19 Prevention Network
CRF	Case report form
CT	Cycle threshold
FAS	Full analysis set
FAS-P	Full analysis set with PCR data
GEE	Generalized estimating equations
IPCW	Inverse-probability-of-censoring weighting
ITT	Intention-to-treat
mRNA	Messenger ribonucleic acid
PCC	Prospective Close Contact
PCR	Polymerase chain reaction
RCT	Randomized clinical trial portion of the study
RNA	Ribonucleic acid
RT-PCR	Real time polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
VED	Vaccine efficacy against COVID-19 disease
VEI	Vaccine efficacy against infectiousness
VES	Vaccine efficacy against susceptibility
VL	Viral load

2. INTRODUCTION

This SAP describes the statistical analysis of CoVPN 3006, a partly randomized and controlled study to evaluate the effects of the mRNA-1273 COVID-19 vaccine on SARS-CoV_2 infection and viral load.

The SAP was modified after the study was stopped early in January 2022, to reflect that some study objectives cannot be addressed, and other study objectives require modification of analysis methods.

2.1 General Design Considerations

This is a Multicenter, randomized, controlled, open-label trial augmented by anobservational cohort. Participants were enrolled into one of three cohorts with two distinct groups comprising the Main Cohort.

Main Cohort (main study participants)
Up to approximately 18,000 healthy volunteers, aged 18 through 29 years, who will be followed for up to 5 months after enrollment; up to 6,000 randomized to Immediate Vaccination Group, up to 6,000 randomized to Standard of Care Group, and up to 6,000 non-randomized to Vaccine Declined Group.

Prospective Close Contact (PCC) Cohort
Up to approximately 36,000 volunteers who are in frequent close physical proximity with main study participants

Case-Ascertained Close Contact (CACC) Cohort
Expected average approximately 3 contacts per incident case. Actual total number dependent on incidence rate. Up to approximately 2250 volunteers aged 18 years and older whohave been in close contact with a SARS-CoV-2 positive case from the Main Cohort

Table 2-1 Schema for the Main Cohort

		Injection schedule in months			
Group	N	0	1	4	5
Randomized Groups					
Immediate Vaccination [1]	Up to 6000	Moderna COVID-19 Vaccine	Moderna COVID-19 Vaccine	-	-

Standard of Care[2]	Up to 6000	-	-	Moderna COVID-19 Vaccine[3]	Moderna COVID-19 Vaccine[3]
Observational Group					
Vaccine Declined[4]	Up to 6000	-	-	_4	_4
Total	Up to 18,000				

1 Immediate Vaccination Group: participants receive Moderna COVID-19 vaccine on enrollment and are given recommendations to follow federal, state, and local guidelines on COVID-19 precautions following vaccination, such as masking, physical distancing, isolation and quarantine.
2 Standard of Care Group: participants are given recommendations to follow federal, state, and local guidelines on COVID-19 vaccination and COVID-19 precautions, such as masking, physical distancing, isolation and quarantine.
3 Vaccine will be offered if participant has not received vaccine outside of the study.
4 Vaccine Declined Group includes participants who prefer not to be vaccinated. If requested, participant will be offered vaccine if they have not received vaccine outside of the study

2.2 Study Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
1. To evaluate the efficacy of Moderna COVID-19 Vaccine against SARS-CoV-2 infection (i.e., to evaluate vaccine efficacy against infection or VES).	SARS-CoV-2 infection diagnosed by PCR among participants who were SARS-CoV-2 seronegative at enrollment
2. To evaluate the effect of Moderna COVID-19 Vaccine on peak nasal viral load as a measure of infection and a proxy of infectiousness	Peak viral load in nasal samples from participants diagnosed with SARS-CoV-2 infection among participants who were SARS-CoV-2 seronegative at enrollment
Secondary Objectives	**Secondary Endpoints**

1. To evaluate the impact of Moderna COVID-19 vaccine on secondary transmission of SARS-CoV-2 infection, using data for the Prospective Close Contact (PCC) cohort and Case-Ascertained Close Contact (CACC) cohort (ie, to evaluate vaccine efficacy against infectiousness or VEI)	Number of adjudicated* secondary transmission events in PCC and CACC cohorts from main study participants who were SARS-CoV-2 seronegative at enrollment. *based on questionnaire-based epidemiologic data, antibody and viral dynamics, and viral sequence data
2. To evaluate the efficacy of Moderna COVID-19 Vaccine to prevent serologically confirmed SARS-CoV-2 infection	SARS-CoV-2 antibodies to the nucleocapsid protein post visit 3 (month 1), among participants who were SARS-CoV-2 seronegative at enrollment
3. To evaluate vaccine efficacy against COVID-19 disease, (ie, to evaluate VED) using weekly e-diaries and confirmatory PCR testing	SARS-CoV-2 infection confirmed by PCR among participants who were SARS-CoV-2 seronegative at enrollment, coincident with the following symptoms: • at least TWO of the following systemic symptoms: Fever (≥ 38ºC),chills, myalgia, headache, sore throat, OR at least ONE of the following signs/symptoms: cough, shortness of breath or difficulty breathing, new olfactory or taste disorder, clinical or radiographical evidence of pneumonia, thromboembolic event, myocardial infarction, myocarditis, chilblains, or multi-inflammatory syndrome

4. To evaluate vaccine effect on additional measures of magnitude of viral load over time, e.g. area under the viral load curve, duration of shedding, and time to log10 viral load above 105 copies/mL	Summary measures of the viral load curve, all evaluated among participants diagnosed with SARS-CoV-2 infection who were SARS-CoV-2 seronegative at enrollment: • Transmission potential endpoint, defined as 0 for an individual without SARS-CoV-2 infection, and peak log10 viral load, for an individual with SARS-CoV-2 infection • Area under log10 viral load curve (AUC) • Duration of viral shedding (viral load above assay limit of detection) • Area under log10 viral load curve above 10^5 copies/mL • Duration of viral shedding above 10^5 copies/mL • Time from enrollment to viral load above 10^5 copies/mL
5. To evaluate vaccine efficacy against SARS-CoV-2 infection, the vaccine effect on viral load, and the vaccine effect on secondary transmission in all enrolled participants without regard to baseline SARS-CoV-2 serostatus	• SARS-CoV-2 infection diagnosed by PCR [Primary endpoint 1] • Peak log10 viral load in nasal samples from participants who are diagnosed with SARS-CoV-2 infection [Primary endpoint 2] • Number of secondary transmission events in the PCC and CACC [Secondary endpoint 1]
6. To evaluate the immunogenicity of the vaccine	Magnitude and response rate of immune responses to vaccination measured at Months 0, and 2 stratified by baseline SARS-CoV-2 serostatus as measured by binding antibody and neutralization assays in the case-cohort immunogenicity set
7. To evaluate immune responses 1 month post-second vaccination as correlates of risk of SARS-CoV-2 acquisition, viral load, secondary infection, and COVID-19 disease among vaccine recipients in the Immediate Vaccination Group	Magnitude and response rate of immune responses to vaccination in the Immediate Vaccination Group and measured at Months 0 and 2, stratified by baseline SARS-CoV-2 serostatus, as measured by binding antibody and neutralization assays in the case-cohort immunogenicity set

8. To evaluate vaccine efficacy against asymptomatic SARS-CoV-2 infection	SARS-CoV-2 infection by PCR or periodic serology among participants seronegative for SARS-CoV-2 at baseline and without any prior reporting of symptoms that led to confirmation of a COVID-19 disease endpoint

9. To evaluate vaccine efficacy against SARS-CoV-2 infection and COVID-19 disease and the vaccine effect on viral load and secondary transmission among participants who received all planned immunizations at the designated immunization visits within specific visit windows	Endpoints evaluated among participants who were SARS-CoV-2 seronegative at enrollment • SARS-CoV-2 infection diagnosed by PCR [Primary endpoint 1] • Peak log10 viral load in nasal samples from participants who are diagnosed with SARS-CoV-2 infection [Primary endpoint 2] • Number of secondary transmission events in the PCC and CACC [Secondary endpoint 1] • SARS-CoV-2 infection coincident with signs and symptoms of COVID-19 listed under Secondary endpoint 3
10. To evaluate the association between measures of the magnitude of viral load over time and secondary transmission of SARS-CoV-2 infection, among individuals with incident SARS-CoV-2 infection in each treatment group, i.e. to conduct analyses aimed at evaluating viral load measures as surrogates of secondary transmission	• Peak log10 viral load [Primary endpoint 2] and other viral load summaries [Secondary endpoints 4] • Number of secondary transmission events in the PCC cohort and CACC cohort [Secondary endpoint 1]
11. To evaluate vaccine effects on peak viral load and on secondary transmission of SARS-CoV-2 infection separately among individuals with asymptomatic vs. symptomatic SARS-CoV-2 infection	• Peak log10 viral load [Primary endpoint 2] and other viral load summaries [Secondary endpoints 4] • Number of secondary transmission events in the PCC cohort and CACC cohort [Secondary endpoint 1] • SARS-CoV-2 infection diagnosed using PCR, with and without signs and symptoms of COVID-19 listed under Secondary endpoint 3
Exploratory Objectives	

1. To evaluate the associations between demographic and clinical factors and secondary transmission of SARS-CoV-2 infection and COVID-19 disease, among individuals with incident SARS-CoV-2 infection in the main study cohort and their contacts in the PCC and CACC
2. To assess if and how vaccine efficacy against SARS-CoV-2 infection, transmission and COVID-19 disease depends on baseline demographic, clinical, socio-economic indicators, and/or behavioral characteristics of study participants
3. To assess if and how vaccine efficacy against SARS-CoV-2 infection and COVID-19 disease depends on genotypic or neutralization phenotypic characteristics of SARS-CoV-2 (sieve analysis)

2.3 Randomization

14,400 participant slots (20% more than the planned 12,000 participants) were randomized into the Immediate and SoC groups with the 1:1 allocation ratio, stratification by site and place of residence (Dormitory or campus housing, Fraternity or sorority house, Apartment building or condo, Stand-alone house (non-fraternity or sorority, Shelter ,RV / Trailer, Staying with friends / Couch surfing, No residence and Other) and 1:1:1 mix of block sizes 8, 10 and 12 created in a random order. Released randomized participants could not be re-randomized into the study (but were allowed to enroll in the Vaccine Declined group). The released randomization slots were not re-used by other (replacement) participants.

2.4 Blinding

This analysis plan has been drafted after early stopping of the randomization portion of the study for operational futility and the subsequent unblinding of the blinded statisticians (Drs. Brown and Janes). Due to operational futility, we did not expect the analyses of the randomized participants to be fully powered and planned to consider them as post-hoc.

2.5 Sample Size and Power

At the design stage, sample size calculations assumed 48,000 person-months of follow-up (even between vaccinated and unvaccinated, with the latter potentially including the Vaccine Declined group), 5% loss-to-follow-up rate, 10% baseline sero-positivity, 98% per-protocol rate, SARS-CoV-2 infection endpoint post Day 29 among baseline seronegative participants in the D29- set with 4% event incidence over 16 weeks (constant over time) among unvaccinated. Under these assumptions, the study had 90% power to detect VE > 57% using one-sided 0.025-level log-rank test. Additionally, assuming 50% VE we expected (50% probability) at least 225 post-Day 29 events to be available to estimate the vaccine effect on mean peak log10 viral load. The assumed 225 events, SD in peak log10 viral load = 1.8 (equal in both arms), 1-sided 0025-level two-sample t-test yielded 96.9% power.

Due to early termination of the trial, the study is underpowered to address primary study objectives.

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

Full Analysis Set (FAS): Limited analyses (e.g. participant characteristics at the baseline) will be carried out among all main study participants that satisfy inclusion criteria and enroll in the study.

Full Analysis Set with PCR data (FAS-P): Only FAS participants with study PCR data will contribute acquisition and viral load (ΔVL) endpoint data and will be used as a main study secondary data set to estimate endpoint parameters. FAS-P participants will be further limited to participants enrolled as randomized to estimate vaccine efficacy against infection (VES). This set will be considered a main study secondary data set.

Baseline SARS-CoV-2 negative set (Main study primary data set): To account for ramping vaccine efficacy (VE), the protocol stipulated that primary analyses would be conducted among all baseline SARS-CoV-2 negative participants, and again among participants in the "Day 29 Negative Set"--the set of participants without seroconversion or PCR-confirmed infection on or prior to second vaccination on Day 29. The intent of this plan was to evaluate effects of the full two-dose vaccine regimen. Given that time of second vaccination is not easily defined in the SoC and Vaccine Declined groups and given that some participants in the Immediate Vaccination group began swabbing and accruing person-time and infection events before first vaccination, primary analyses will instead be conducted among all eligible enrolled baseline SARS-CoV-2 negative participants (Baseline SARS-CoV-2 negative set). All person-time and events will be included, and ramping VE will be accommodated using analyses that estimate vaccine effects according to number of doses received. Baseline SARS-CoV-2 negativity will be defined as PCR negative based on the first resulted (see section 3.2.9 for exclusions) nasal swab and seronegative based on the first qualifying (see section 3.2.8 for exclusions) blood sample closest to the first resulted swab. Note that blood collection for determining baseline serostatus was intended to occur coincident with initiation of swabbing; however, some participants had blood collected well before they began swabbing, and others had blood collected well after the initiation of swabbing. The analysis will summarize the distribution of time between first resulted swab and first blood. Qualifying blood sample closest to the first resulted swab date will be defined as either the closest qualifying blood sample on or before the first resulted swab date (if it exists) or the closest qualifying blood sample after the first resulted swab date (if no qualifying blood sample exists on or before the first resulted swab date). Primary analyses of vaccine efficacy against infection (VES) and of the vaccine effect on viral load (ΔVL) will be conducted among Baseline SARS-CoV-2 negative set participants that were enrolled as randomized.

All primary and secondary analyses will be done according to enrollment group, ie, Immediate Vaccination Group, Standard of Care Group, or Vaccine Declined Group.

3.2 Statistical Analysis Issues

3.2.1 Time scales

The analysis will utilize two different time scales. "Calendar time" will be defined as time since enrollment of the first study participant. "Study time" will be defined as time from either the first

nasal swab (if the first swab result was negative) or 90 days after the first swab (if first swab positive). Note that while randomization would be the ideal origin for study time, some participants did not begin swabbing until days or even weeks into the study, and infection status and timing of infection cannot be determined prior to the initiation of swabbing.

3.2.2 Incident infection

An incident SARS-CoV-2 infection will be defined as the first instance of a positive PCR result that follows at least one negative PCR result. Therefore, for participants who are baseline SARS-CoV-2 positive (i.e. seropositive at first blood collection or PCR positive on first swab), an incident infection occurs only 90 days after the first swab and once there is at least one negative PCR followed by a positive PCR.

3.2.3 Seroconversion

A seroconversion event will be defined as the first instance of a positive serology result that follows at least one negative serology result.

3.2.4 Censoring approaches

The following analyses will use the following censoring approaches (as specified in analytical approach). For the primary endpoint, “test” refers to a PCR test of a nasal swab. For the secondary endpoint of seroconversion, “test” refers to serology of a blood sample.

- ITT censoring: In the SoC arm, follow-up time is censored at the last negative test prior to end of study vaccination or the last negative test if the participant is not vaccinated on study (both are ignored if the first positive test occurs after the last negative test). In the Immediate Vaccination arm and the Vaccine Declined group, follow-up will be censored at the last negative test (ignored if the first positive test occurs after the last negative test). The timing of any test is considered to be the day on which the assay was collected, where day is defined from 3AM to 3AM of local time of the site.
- Outside vaccination censoring: Follow-up time is censored at the first ITT censoring or the last negative RT-PCR test prior to outside vaccination (first vaccine dose) unless the first positive RT-PCR test occurs after the last negative test. For participants with a second outside vaccine dose date but with no study vaccine and no recorded first outside vaccine dose date the first outside vaccine dose date will imputed as the second outside vaccine date minus 28 days. The imputed date will be also used in enumerating their vaccines (participant dispositions), in the outside study vaccination endpoint (see section 3.2.5) but not in the exclusion criteria.

3.2.5 Outside study vaccination

For participants in the RCT, immediate vaccination is assigned randomly, but participants are not blinded to vaccine assignment and may seek vaccination outside the study. If outside vaccine uptake occurs completely at random, no adjustments or additional analyses need to be complete. If, however, uptake is related to risk, analyses that don’t properly account for that relationship will produce biased results. A series of analyses will investigate this based both on baseline variables and potential time-varying predictors as follows.

First, we define calendar time to early outside vaccination as time any vaccination that happens outside the study before study vaccine was offered to the SoC group starting from September

21, 2021. Time to outside vaccination will be an interval-censored calendar time (days from the first participant's enrollment) starting from first nasal swab (if the first swab result was negative) or 90 days after the first swab (if first swab positive) and ending at outside vaccination or ITT censoring. Baseline predictors of outside vaccination and calendar time will be included in univariate Cox proportional hazards models fit using all baseline SARS-CoV-2 negative participants from the SoC group, stratified by site. Any predictors with a p-value above 0.10 will be used as adjustment variables in primary efficacy analyses of Section 7.

Time-varying covariates will then be assessed as predictors of outside vaccination in univariate Cox models. If any are found to be associated with outside vaccination (after adjustment for potential baseline predictors), those will be accounted for in efficacy analyses described in Section 7 through covariate adjustment or IPCW.

Baseline variables to be assessed: Age, sex, race/ethnicity, place of residence, attributes from the Baseline SARS-CoV-2 Infection Risk Assessment CRF

Due to small numbers in some groups, race/ethnicity will be dichotomized as under-represented minority, defined as Black or African American, American Indian or Alaska Native or Native Hawaiian or Other Pacific Islander race or Hispanic or Latino ethnicity. Place of residence will be categorized into four groups: 1. "Apartment building or condo", 2. Dorm/campus housing/frat/sorority (combines "Dormitory or campus housing" and "Fraternity or sorority house"), 3. "Stand-alone house (non-fraternity or sorority)" and 4. "Other" (combines all other categories).

Selection of variables to study will be informed by an assessment of data completeness. Variables missing for more than 10% of records to be included in the analysis will be excluded from consideration. Single imputation will be used to fill in missing records for the variables that are selected for study.

3.2.6 SARS-CoV-2 exposure

Given the open-label nature of the study, it is possible that individuals in the Immediate Vaccination, SoC, and Vaccine Declined groups have different exposure to SARS-CoV-2. While the randomized groups are ensured to balance with respect to baseline factors, individuals in the Vaccine Declined Group are likely to differ from those in the randomized groups based on both baseline and time-varying factors related to exposure. Imbalanced exposure between groups may lead to bias in analyses that compare endpoint distributions between groups. A series of analyses will explore predictors of SARS-CoV-2 exposure based on baseline SARS-CoV-2 negative participants in the SoC group. Separate but identical analyses will explore predictors of exposure in the Vaccine Declined group.

The outcome of interest will be time to incident infection. Calendar time will be the time scale and participants will be censored using 'outside testing censoring'. Baseline and time-varying variables listed above in Section 3.2.5 will be screened univariately for their associations with SARS-CoV-2 infection based on Cox proportional hazards models that stratify on study site . Variables with p-values less than 0.10 will be retained. Retained baseline variables will be screened further to remove highly correlated variables; for pairs with absolute value of Spearman correlation > 0.90, a randomly chosen member of the pair will be retained. Cox regression with lasso penalty, stratified on study site and implemented with glmnet and with the retained variables from the previous step, will be used to derive a 'risk score' that is used for

adjustment in multiple analyses described below. The linear predictor of the penalized Cox model will be used as the risk score. This risk score will be included as a covariate in efficacy analyses described in Section 7.

3.2.7 Noncompliance with swabbing

Noncompliance with daily nasal swabbing may result in missed endpoints and incompletely observed viral load trajectories.

Alluvial plots will be used to explore noncompliance over study and calendar time, by enrollment group and study site and other baseline covariates. Descriptive tables will summarize noncompliance over study time by enrollment group. Compliance will be defined in two ways, with swabs expected starting from either 1. enrollment date or 2. first swab date (or enrollment date if participant had no swabs). Days with a swab will be expected until minimum of the day before the date CRF-confirmed study completion, 111 days after enrollment and the last expected swabbing date (Dec. 31, 2021). Additionally, swabs will not be expected after outside vaccination
or termination. Time (weeks) after these two events (outside vaccination and termination) will be displayed separately in the plots. Compliance metric for participant weeks with at least one expected swab day will be the % (of expected) days with a swab, categorized as 0%,1-29%, 30-58% and 59-100% (these categories will be labelled as 0, 1-2, 3-4 and 5-7, respectively, corresponding to a week with 7 expected swab days).

A GEE model will be used to explore predictors of time-varying non-compliance. Baseline and time-varying covariates listed in 3.2.5 will be considered for inclusion in the model. Participants will be censored at the earliest of outside vaccination or study termination.

If predictors of non-compliance, other than enrollment group, study time, calendar time, and covariates associated with outside vaccination (Section 3.2.5) or exposure risk (Section 3.2.6) are identified, these will be accounted for in efficacy analyses described in Section 7 through covariate adjustment or IPCW.

3.2.8 Blood sample exclusions

Prior to deriving the baseline serostatus and the seroconversion event, the following blood sample data will be excluded to account for replacements or problematic samples:

- Original insufficient in-clinic samples when replacement samples were collected for the same visit (see Section 8 of the Phlebotomy Specimen Collection Study Specific Procedures)
- Self-collected (TASSO) samples resulted as “Test Not Performed” by the lab (due to various reasons, e.g. insufficient/incorrect/damaged/expired/unused sample, processing error)
- In-clinic samples with more than 90 days between blood draw and lab processing
- TASSO samples with more than 7 days between blood draw and lab receipt

3.2.9 Nasal swab record exclusions

If duplicate records exist for the same nasal swab, only one record will be retained, and the other records will be excluded from the analysis. The nasal swab data are recorded on two occasions. First, the participants are instructed to scan the swab bar code before application, recording the bar code as an “order number” with the date and time of the scan. Second, the

swab results are recorded when the swab is resulted by the lab (attaching the qualitative result to the order number, date and time). If a given swab order is recorded multiple times (i.e., records with different date-times), the participant likely scanned the same swab multiple times. If that occurs, only the resulted record will be retained (if a result exists; note: multiple results cannot occur) or only the earliest un-resulted record (if no result) will be retained.

Nasal swab results other than “Detected” and “Not Detected” (i.e., “Inconclusive”, “Indeterminate”, “Cancelled. Specimen Issue”, “Invalid Specimen”) will be excluded. Notably, they will be excluded from the first swab result determination which will be allowed to be only positive (“Detected”) or negative (“Not Detected”).

4. GENERAL ANALYSIS METHODS

By-enrollment-group baseline characteristics will be summarized as counts and percentages for categorical variables and median (IQR) for continuous variables. No p-values will be produced for the comparison of the baseline characteristics.

5. TRIAL PARTICIPANT DISPOSITION

5.1 Disposition of Participants

The disposition of trial participants by group will be presented in a CONSORT diagram and table. The disposition, data source and group used to define each variable are described in the table below. The statistic to describe each measure will be the number and the percentage of participants. The table will display also dispositions and the diagram will show selected dispositions.

Disposition(s)	Definition/Data Source	Group(s)	CONSORT diagram
Screened	Any record in the source Sources: Screening Outcome CRF, Participant Type CRF	1. All screened, 2. RCT[1] screened, 3. Vaccine Declined screened	No (1), Yes (2&3)
Not randomized	Not in Rave randomization or without a randomization arm Source: Rave randomization	RCT screened	Yes
Not randomized, reason	With a given screening status (reason) Sources: Screening Outcome CRF	RCT not randomized	Yes
Not randomized, Ineligible, reason	With a given reason for Ineligibility Sources: Screening Outcome CRF	RCT not randomized and Ineligible	No
Not randomized, Eligible/Not enrolled,	With a given reason for Not Enrolled Sources: Screening Outcome CRF	RCT not randomized	No

Disposition(s)	Definition/Data Source	Group(s)	CONSORT diagram
reason		and Eligible/Not enrolled,	
Randomized	With a randomization arm Source: Rave randomization	RCT[1] screened	Yes
Randomized, by assignment (Immediate and SoC)	With a given randomization assignment Source: Rave randomization	RCT[1] screened	Yes
Randomized, Enrolled in the observational arm	Vaccine Declined participant type and enrolled Sources: Participant Type CRF, Screening Outcome CRF	1. Immediate randomized[1], 2. SoC randomized[1]	Yes
Not enrolled	Not enrolled screening status Sources: Screening Outcome CRF	1. Immediate randomized, 2. SoC randomized, 3. Vaccine Declined	Yes
Not enrolled, reason	With a given not enrolled screening status (reason) Sources: Screening Outcome CRF	1. Immediate randomized, 2. SoC randomized, 3. Vaccine Declined	Yes
Not enrolled, Ineligible reason	With a given not ineligibility reason Sources: Screening Outcome CRF	1. Immediate randomized, 2. SoC randomized, 3. Vaccine Declined	No
Not enrolled, Eligible/Not enrolled reason	With a given not eligible/not enrolled reason Sources: Screening Outcome CRF	1. Immediate randomized, 2. SoC randomized, 3. Vaccine Declined	No
RCT Enrolled, by arm	Not Vaccine Declined participant type and enrolled Sources: Participant Type CRF, Screening Outcome CRF	1. Immediate randomized, 2. SoC randomized	Yes
Vaccine Declined Enrolled	Enrolled Sources: Screening Outcome CRF	Vaccine Declined	Yes

Disposition(s)	Definition/Data Source	Group(s)	CONSORT diagram
Retrospectively determined ineligible, Not between 18-29 years old	Calculated age at enrollment (enr. date-DOB) is not 18-26 (v1-3) or 18-29 (v4) Sources: Screening Outcome CRF, Demographics e-Diary	1. Immediate enrolled, 2. SoC enrolled, 3. Vaccine Declined enrolled	Yes
Retrospectively determined ineligible, Prior COVID vaccine	Outside vaccination date[2] <= enrollment date Sources: Screening Outcome CRF, Outside vaccination CRF	1. Immediate enrolled, 2. SoC enrolled, 3. Vaccine Declined enrolled	Yes
Retrospectively determined ineligible	Not between 18-26/18-29 years old OR prior COVID vaccine See the previous two rows	1. Immediate enrolled, 2. SoC enrolled, 3. Vaccine Declined enrolled	Yes
FAS	Between 18-26/19-29 years old AND no prior COVID vaccine See the previous row (this is a complement)	1. Immediate enrolled, 2. SoC enrolled, 3. Vaccine Declined enrolled	Yes
Without PCR, With study PCR	Participant without vs. with study PCR Source: Study PCR lab data	1. Immediate FAS, 2. SoC FAS, 3. Vaccine Declined FAS	Yes
Baseline SARS-CoV-2 seropositive	Baseline seropositive Source: Serostatus lab data	1. Immediate FAS with study PCR, 2. SoC FAS with study PCR, 3. Vaccine Declined FAS with study PCR	Yes
No qualifying serostatus at baseline	Baseline serostatus unknown among qualifying[3] samples Source: Serostatus lab data	1. Immediate FAS with study PCR, 2. SoC FAS with study PCR,	Yes

Disposition(s)	Definition/Data Source	Group(s)	CONSORT diagram
		3. Vaccine Declined FAS with study PCR	
Baseline SARS-CoV-2 seronegative and PCR positive	Baseline seronegative AND baseline PCR positive Sources: Study PCR and serostatus lab data	1. Immediate FAS with study PCR, 2. SoC FAS with study PCR, 3. Vaccine Declined FAS with study PCR	Yes
Baseline PCR and seronegative	Baseline PCR negative AND baseline seronegative Sources: Study PCR and serostatus lab data	1. Immediate FAS with study PCR, 2. SoC FAS with study PCR, 3. Vaccine Declined FAS with study PCR	Yes
Vaccination status at last study PCR result: “No vaccine” “1 outside vaccine” “2 outside vaccines” “1 study vaccine” “2 study vaccines” “1 study vaccine + 1-2 outside vaccines”	Corresponding number of outside[2]&study vaccines on or before the last study PCR result date Sources: Study vaccination CRF, Outside vaccination CRF, Study PCR	1. Immediate FAS with study PCR, 2. SoC FAS with study PCR, 3. Vaccine Declined FAS with study PCR 4. Immediate FAS baseline PCR and seronegative, 5. SoC FAS baseline PCR and seronegative, 6. Vaccine Declined FAS baseline PCR and seronegative	No
End-of-study Vaccination status at last study PCR result: “No vaccine”	Corresponding number of outside[2]&study vaccines on or before the termination date Sources: Study vaccination CRF, Outside vaccination CRF, Study Termination CRF	1. Immediate FAS with study PCR, 2. SoC FAS with study PCR,	No (1-3, 6), Yes (4-5)

Disposition(s)	Definition/Data Source	Group(s)	CONSORT diagram
"1 outside vaccine" "2 outside vaccines" "1 study vaccine" "2 study vaccines" "1 study vaccine + 1-2 outside vaccines"		3. Vaccine Declined FAS with study PCR 4. Immediate FAS baseline PCR and seronegative, 5. SoC FAS baseline PCR and seronegative, 6. Vaccine Declined FAS baseline PCR and seronegative	
Vaccine receipt and offer at end of study: "No vaccine before early termination" "1-2 outside vaccines before early termination" "Completed study, not offered vaccine, not vaccinated at end of study" "Completed study, offered vaccine, not vaccinated at end of study" "Completed study with 1-2 outside vaccines by end of study"	Corresponding: - completion (Study Termination CRF = "Scheduled exit visit/end of study") - number of outside^2&study vaccines on or before the termination date - Indication site contacted the participant personally to offer vaccination on site or at an affiliated Walgreens = "Yes" Sources: Outside vaccination CRF, Study Termination CRF, COVID-19 Final Vaccination Status CRF	1. Vaccine Declined FAS with no study PCR, 2. Vaccine Declined FAS with study PCR, 3. Vaccine Declined FAS baseline PCR and seronegative	No (1, 2), Yes (3)
Termination status	Given study termination status Source: Study Termination CRF	1. Immediate FAS with no study PCR, 2. SoC FAS with no study PCR,	No

Disposition(s)	Definition/Data Source	Group(s)	CONSORT diagram
		3. Vaccine Declined FAS with no study PCR, 4. Immediate FAS with study PCR, 5. SoC FAS with study PCR, 6. Vaccine Declined FAS with study PCR	

[1] includes participants screened for RCT, then randomized but enrolled in the Vaccine Declined group. These participants are also counted in the Vaccine Declined group.
[2] if the date of the first outside vaccine dose was missing and the date for the second one was present, the first date was imputed as the second date minus 28 days.
[3] see section 3.2.8
v1-3 = protocol versions 1-3, v4 = protocol version 4

6. BASELINE DATA

The following baseline characteristics will be summarized by enrollment group for FAS participants: sex, gender (participants with multiple choices reported multiple times), race (participants reporting multiple races reported as 'Multiple'), ethnicity, age (calculated from the date of birth to enrollment, where enrollment is defined as randomized for the RCT arms and the enrollment date on the Screening CRF for the observational arm), residence, number of roommates (0, 1 and >1), number of people in shared communal space (0, 1, 2 and >2), in-person on-campus class attendance (CRF categories), in-person work, volunteer, or on-campus study time (CRF categories), fraternity/sorority membership, current participation in any in-person team sport, sitting inside a bar, restaurant, café or cafeteria (last 2 wks), usual frequency of alcohol consumption (last 2 wks) (CRF categories), usual number of alcohol drinks when consuming (last 2 wks) (CRF categories), potential exposure to a contact with SARS (CRF flags for 1. someone with a recent positive test, 2. someone with possible symptoms, but no diagnosis or test, 3. third party notification system and 4. no contact according to the participant's knowledge), frequency of wearing mask when around other people inside (last 2 wks) (CRF categories), frequency of physical distancing from others when leaving home (last 2 wks) (CRF categories), frequency of meeting in a group 10+ when leaving home (last 2 wks) (CRF categories), frequency of encountering other people not wearing masks when leaving home (last 2 wks) (CRF categories). The Immediate Vaccination arm will be labelled as "Immediate", the Standard of Care arm as "Standard of Care" and the observational (Vaccine Declined) arm as "Observational". Separate summary tables will be created for FAS and SARS-CoV-2 negative participants.

7. PRIMARY EFFICACY/EFFECTIVENESS ANALYSES

Time to event definitions
Except where specified, time is defined as calendar time as opposed to study time. The event occurs at the time of specimen collection for the first study swab positive for SARS-CoV-2.

7.1 Descriptive analysis

Tables

The following table will be used to describe SARS-CoV-2 incidence by group and vaccine receipt. It will be produced first including only baseline SARS-CoV-2 negative participants, and then again including all FAS-P participants. Each participant's incident exposure period will start. from either the first nasal swab (if the first swab result was negative) or 90 days after the first swab (if first swab positive). The participant's exposure will be broken down to unvaccinated, one-dose and two-dose exposure periods. The unvaccinated exposure period will include days and events up to (and including) the date of the first study vaccination or censoring, whichever occurs first. The one-dose exposure period will include days and events starting the day after the first vaccine and ending on the date of the second vaccine or censoring, whichever occurs first. The two-dose exposure period will include days starting the day after the second vaccine. The 95% confidence interval for the incidence rate will be calculated using the exact method.

Group	Exposure: number of study vaccine doses	Censoring	Number of incident infections	Person-years	Incidence rate (95% CI)
Immediate arm	Unvaccinated	Outside vaccination		See note 1	
	Unvaccinated	ITT		See note 1	
	Single dose	Outside vaccination		See note 2	
	Single dose	ITT		See note 2	
	Two doses	Outside vaccination		See note 3	
	Two doses	ITT		See note 3	
SoC arm	Unvaccinated	Outside vaccination		See note 4	
	Unvaccinated	ITT		See note 4	
Vaccine Declined arm	Unvaccinated	Outside vaccination		See note 4	
	Unvaccinated	ITT		See note 4	

Note 1: Total number of person-years from the incident follow-up start to the first of study vaccination, infection or censoring.
Note 2: Total number of person-years from the last of incident follow-up start and first dose to the first of second dose, infection or censoring.
Note 3: Total number of person-years from the last of incident follow-up start and second dose to the first of infection or censoring.
Note 4: Total number of person-years from the incident follow-up start to the first of infection or censoring.
Incident follow-up start = either the first nasal swab (if the first swab result was negative) or 90 days after the first swab (if first swab positive)

We will also tabulate counts of SARS-CoV-2 infection events by calendar month (of the first positive nasal swab), arm and presence of symptoms (present vs. absent vs. unknown - see section 9.4).

Plots

Plots of monthly incidence of infection by calendar time (calendar month) by study group will be displayed. Versions with and without the Vaccine Declined group will be created. Months at the beginning and/or end of study may be combined if the total follow-up in them is small. The 95% confidence interval for the incidence rate will be calculated using the exact method.

Kaplan-Meier curves will be used to display cumulative incidence of infection across study groups by study time (time since first PCR). Multiple sets of plots will be produced, corresponding to different 'treatment' of the SoC and Vaccine Declined groups:

1. One set of curves (a curve for each enrollment group) with outside vaccination censoring. Endpoints are otherwise defined as they are for each primary or secondary outcome.
2. One curve for Immediate arm and another curve for SoC arm, censoring at outside vaccination

7.2 Primary efficacy analysis

Objective: To evaluate the effect of mRNA-1273 vaccination on acquisition of SARS-CoV-2 infection
Endpoint: Incident infection by study PCR subject to Outside Vaccination Censoring.
Data sets: Baseline SARS-CoV-2 negative participants enrolled as randomized
Exposure: Randomization, and number of study vaccine doses received within the Immediate Vaccination group
Adjustment covariates: Baseline factors: Age, sex, race/ethnicity, place of residence, attributes from the Baseline SARS-CoV-2 Infection Risk Assessment CRF
Analysis: Vaccine efficacy will be estimated using a time-varying Cox model that stipulates the following hazard function

$$h(t) = h_{0S}(t)\exp\{\alpha_1 I(T_1 < t) + \alpha_2 I(T_2 < t) + \beta X\}$$

where *t* is time since study initiation (calendar time), T_1 is the calendar time of the first dose of study vaccine and T_2 is the calendar time of the second dose of study vaccine, $h_{0S}(t)$ is an unspecified baseline hazard that depends on study site, and *X* is a vector of baseline covariates identified in Section 3.2.5 and 3.2.6 as associated with exposure and/or censoring. The efficacy of one dose of study vaccine will be measured by $1 - e^{\alpha_1}$ and the efficacy of two doses measured by $1 - e^{\alpha_2}$. The model will be fit using the R survival package. Two-sided 95% confidence intervals for the VE estimates will be calculated using the Wald method.

If the set of covariates that is associated with SARS-CoV-2 exposure and/or censoring is too large to permit covariate adjustment, an IPCW analysis will be performed. Specifically, the above Cox model will be fit using a time-dependent weight that corresponds to a (standardized) probability of censoring. The analysis will be implemented using the R ipcwswitch package.

7.2.1 Supportive analyses

- ITT analysis: We will repeat the primary analysis using ITT censoring.
- All FAS analysis: includes those baseline SARS-CoV-2 negative and baseline SARS-CoV-2 positive in the analysis.

7.2.2 Exploratory analyses

The time-varying Cox model of 7.1.1 will be used for estimation, but ITT censoring will be employed.

7.3 To evaluate the vaccine effect on SARS-CoV-2 viral load

Given the early termination, the study is underpowered to look at the vaccine effect on viral load. Therefore a limited, descriptive analysis will be performed. Descriptive statistics for peak viral loads on the cycle threshold (CT) scale among FAS-P acquisitions (censored at outside vaccination) will be tabulated by lab (Corteva vs. UW/Northwell), target (N1 and N2) and arm. Peak viral load will be defined as the minimum observed CT per participant, lab and target. Participants with CT data from both labs will be excluded. Descriptive statistics will include N, mean, minimum, median, quartiles and median. Results are stratified by lab to address potential differences between labs. We will also present the descriptive statistics for the number of days with a positive study PCR (qualitative) per participant among FAS-P acquisitions, broken down by arm.

8. IMMUNOGENICITY ANALYSES

Immunogenicity analyses will be described in a separate 'Immune Correlates SAP'.

9. SECONDARY ENDPOINTS

9.1 To evaluate the impact of Moderna COVID-19 Vaccine on secondary transmission of SARS-CoV-2 infection, using data for the Prospective Close Contact (PCC) cohort and Case- Ascertained Close Contact (CACC) cohort (i.e., to evaluate vaccine efficacy against infectiousness or VEI)

Because there were inadequate number of contacts enrolled into this study, the analyses needed to complete this objective cannot be performed.

9.2 To evaluate the efficacy of Moderna COVID-19 Vaccine to against COVID-19 disease

Objective: To evaluate vaccine efficacy against COVID-19 disease, (i.e., to evaluate VE_D).
Outcome: PCR-confirmed COVID-19 diagnosis where symptomology on a given day as reported by e-diary (weekly or daily) occurs no more than 3 days prior to and no more than 14 days after the administration of the first nasal swab that is PCR positive. This represents a slight departure from the protocol that only relies on weekly testing to expand to also include daily symptom questionnaires that start after a positive test to increase precision of the disease definition.
Data sets:
Definition of Endpoint: COVID-19 is defined as symptomatic disease based on the following criteria as assessed in daily and weekly self-reported symptom logs, coincident with virologic confirmation (RNA PCR Ct < 40):

- at least one of the following signs/symptoms: hospitalization, fever, chills, cough, shortness of breath, difficulty breathing, tiredness/fatigue, muscle aches, joint aches, body aches, headache, change in sense of taste, change in sense of smell, sore throat, nasal congestion, runny nose, nausea, vomiting, diarrhea, oral ulcers (mouth sores) and clinical or radiographical evidence of pneumonia

This definition defers from the primary endpoint definitions in the phase 3 COVID vaccine trials (e.g. COVPN 3001) and the protocol because some symptoms were not collected (thromboembolic event, myocardialinfarction, myocarditis, chilblains, or multi-inflammatory syndrome) and symptom diaries for some participants were incomplete and/or not collected during the specified time interval.

Symptom onset date will be defined as the first symptomatic day according to the daily or the weekly symptom log that is in the interval starting no more than 3 days prior to and no more than 14 days after the first positive nasal swab. We will assume symptomatic logs represent symptom presence on the day of the log for the daily logs and in the period between a given log and the preceding log (or enrollment if no preceding log) for weekly logs. The latter assumption may be violated if participants experienced the symptom only for part of the period (cannot be determined from the log).

A participant will be defined as having reached the endpoint if they have the diagnosis above. The time of the endpoint will be the onset of symptoms. Participants who do not have the endpoint will be censored at the earlier of first positive PCR without symptoms (or with missing symptom logs) and outside vaccination censoring. As a supportive analysis, we will also consider censoring at the earlier of first positive PCR without symptoms and ITT censoring . Death and hospitalization with positive PCR will be counted in the endpoint.

Analysis Details:
A participant will be defined as having reached the endpoint if they have the diagnosis above. The time of the endpoint will be the onset of symptoms. Participants who do not have the endpoint will be censored at the last time they were known to be symptom- and infection-free. Death and hospitalization will be counted in the endpoint. Rate tables and VE estimation analogous to analyses of the acquisition endpoint will be produced. The same set of covariates will be adjusted for in VE estimation as for the acquisition endpoint.

9.3 To evaluate SARS-CoV-2 variants

For all participants in the FAS infected prior to outside vaccination censoring, Spike sequencing will be performed on the specimen with the highest SARS-CoV-2 viral load. SARS-CoV-2 variants will be determined, where possible, and the distribution of variants will be tabulated overall and by enrollment group and vaccine receipt. This will be done first including ‘successful and borderline’ variant calls, where ‘borderline’ includes both ‘non-suspicious’ and ‘suspicious’ calls; and then again including only ‘successful’ and ‘non-suspicious’ calls. Successful will be defined as successful sequencing (indicated by the lab), borderline as borderline sequencing data available (missing genome data; also indicated by the lab), suspicious as indication of potential contamination according to phylogenetic analysis, and non-suspicious defined as lack of the latter indication.

10. CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
2.0	Date of last signature	7.3	Added analysis plan for peak viral load endpoint