Protocol Component
Eligibility Criteria
Treatment strategies
Assignment procedures
Follow-up period
Outcome
Causal constraints of interest
Analysis Plan

Target Trial
Individuals aged 18–65 with no prior history of COVID-19 infection, not currently pregnant, and no history of severe allergic reactions to vaccines. Vaccination with a two-dose mRNA COVID-19 vaccine schedule versus no vaccination. Random assignment of eligible individuals to receive either the vaccine or placebo, with participants blinded to their treatment assignment. Follow participants from the date of randomization until the earlier of (1) confirmed symptomatic COVID-19, (2) withdrawal from the study, or (3) 6 months. Incidence of symptomatic COVID-19 (confirmed by PCR test). Intention-to-treat. Kaplan-Meier survival analysis to estimate the cumulative incidence of symptomatic COVID-19 in each group. Cox proportional hazards model to estimate hazard ratios (HR) for COVID-19 in the vaccinated versus unvaccinated group.

Emulated Target Trial
Individuals from an observational database aged 18–65 with no record of prior COVID-19 diagnosis, no pregnancy recorded at baseline, and no known contraindications to vaccination.
Observational: Comparison between individuals receiving the mRNA COVID-19 vaccine (first and second doses) and those who remain unvaccinated throughout the follow-up period.
Individuals self-select into vaccinated or unvaccinated groups based on personal or provider decision. Propensity scores are used to adjust for baseline differences between groups.
Follow individuals from the first vaccination date (or an analogous index date for unvaccinated individuals) until the earlier of (1) symptomatic COVID-19 diagnosis, (2) loss to follow-up, or (3) 6 months.
Incidence of symptomatic COVID-19 (based on confirmed diagnostic codes or PCR test results in the observational dataset).
Observational equivalent to intention-to-treat effect.
Use sequential inverse probability weighting (IPW) to adjust for time-varying confounders, fit a Cox proportional hazards model stratified by age group, and estimate hazard ratios. Baseline covariates: age, sex, comorbidities, occupation (e.g., healthcare worker), and geographic location.