Estimating Vaccine Efficacy Over Time After a Randomized Study is Unblinded

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Abstract

The COVID-19 pandemic due to the novel coronavirus SARS CoV-2 has inspired remarkable breakthroughs in development of vaccines against the virus and the launch of several phase 3 vaccine trials in Summer 2020 to evaluate vaccine efficacy (VE). Trials of vaccine candidates using mRNA delivery systems developed by Pfizer-BioNTech and Moderna have shown substantial VEs of 94-95%, leading the US Food and Drug Administration to issue Emergency Use Authorizations and subsequent widespread administration of the vaccines. As the trials continue, a key issue is the possibility that VE may wane over time. Ethical considerations dictate that all trial participants be unblinded and those randomized to placebo be offered vaccine, leading to trial protocol amendments specifying unblinding strategies. Crossover of placebo subjects to vaccine complicates inference on waning of VE. We focus on the particular features of the Moderna trial and propose a statistical framework based on a potential outcomes formulation within which we develop methods for inference on whether or not VE wanes over time and estimation of VE at any post-vaccination time. The framework clarifies assumptions made regarding individual- and population-level phenomena and acknowledges the possibility that subjects who are more or less likely to become infected may be crossed over to vaccine differentially over time. The principles of the framework can be adapted straightforwardly to other trials.

Key words: Crossover; Inverse probability weighting; Potential outcomes; Randomized phase 3 vaccine trial; Waning vaccine efficacy

1 Introduction

The primary objective of a vaccine trial is to estimate vaccine efficacy (VE). Typically, these trials are double-blind, placebo-controlled studies in which participants are randomized to either vaccine or placebo and followed for the primary endpoint, which is often time to viral infection, on which inference on VE is based, where VE is defined as a measure of reduction in infection risk for vaccine relative to placebo, expressed as a percentage.

Vaccine trials have become the focus of immense global interest as a result of the COVID-19 disease pandemic due to the novel coronavirus SARS-CoV-2. The pandemic inspired unprecedented scientific breakthroughs in the rapid development of vaccines against SARS-CoV-2, culminating in the launch of several large phase 3 vaccine trials in Summer 2020. Trials in the US studying the vaccine candidates using messenger RNA (mRNA) delivery systems developed by Pfizer-BioNTech and Moderna began in July 2020 and demonstrated substantial evidence of VEs of 94-95% at interim analyses, leading the US Food and Drug Administration (FDA) to issue Emergency Use Authorizations (EUAs) for both vaccines in December 2020 and to the rollout of vaccination programs shortly thereafter.

Implicit in the primary analysis in these trials is the assumption that VE is constant over the study period and, with primary endpoint time to infection, VE is represented by the $1 -$ the ratio of the hazard rate for vaccine to that for placebo, estimated based on a Cox proportional hazards model. As the trials continue following the EUAs, among the many issues to be addressed is the possibility that VE may wane over time. Principled evaluation of the nature and extent of waning of VE is of critical public health importance, as waning has implications for measures to control the pandemic. Were all participants in the trials to continue on their randomized assignments (vaccine or placebo), evaluation of potential waning of VE would be straightforward. However, once efficacy is established, ethical considerations dictate the possibility of unblinding all participants and offering the vaccine to those randomized to placebo. After consultation with stakeholders, Pfizer and Moderna issued amendments to their trial protocols specifying unblinding strategies and modifications to planned analyses.

Crossover of placebo subjects to vaccine of necessity complicates inference on waning of VE and has inspired recent research (Follmann et al., 2020; Fintzi and Follmann, 2021; Lin, Zeng and Gilbert, 2021). We propose a statistical framework within which we develop methods for inference on whether or not VE wanes over time based on data where subjects are unblinded and those on placebo may cross over to vaccine and in which assumptions made regarding individual and population phenomena are made transparent. It is possible that subjects who are more or less likely to become infected could be unblinded and cross over to vaccine differentially over time, which could lead to biased inferences due to

confounding; accordingly, this possibility is addressed explicitly in the framework. The first author (AAT) has the privilege of serving on the Data and Safety Monitoring Board for all US government-sponsored COVID-19 vaccine trials and is thus well-acquainted with the unblinding approach for the Moderna trial. Accordingly, the development is based on the specifics of this trial, but the principles can be adapted to the features of other trials.

In Section 2, we review the Moderna trial and the resulting data. We present a conceptual framework in which we precisely define VE as a function of time post-vaccination in Section 3. In Section 4, we develop a formal statistical framework within which we propose methodology for estimation of VE and describe its practical implementation in Section 5. Simulations demonstrating performance are presented in Section 6.

2 Clinical Trial Structure and Data

We first describe the timeline of the Moderna Coronavirus Efficacy (COVE) trial (Baden et al., 2020) on the scale of calendar time. The trial opened on July 27, 2020 (time 0), and reached full accrual at time $\mathcal{T}_A$ (October 23, 2020). On December 11, 2020, denoted $\mathcal{T}_P$, the FDA issued an EUA for the Pfizer vaccine, followed by an EUA for the Moderna mRNA-1273 vaccine on $\mathcal{T}_M =$ December 18, 2020. Amendment 6 of the study protocol was issued on December 23, 2020 and specified the unblinding strategy (see Figure 2 of the protocol) under which, starting on $\mathcal{T}_U =$ December 24, 2020, study participants are scheduled on a rolling basis over several months for Participant Decision clinic visits (PDCVs) at which they will be unblinded. If originally randomized to vaccine, participants continue to be followed; if randomized to placebo, participants can receive the Moderna vaccine or refuse. Let $\mathcal{T}_C$ denote the time at which all PDCVs have taken place. The study will continue until time $\mathcal{T}_F$ at which all participants will have completed full follow-up at 24 months after initial treatment assignment. Assume that the analysis of vaccine efficacy using the methods in Sections 4.4 and 5 takes place at time $\mathcal{T}_C \leq L \leq \mathcal{T}_F$, where all participants have achieved the primary endpoint, requested to be unblinded, or attended the PDCV by L.

Under this scheme, we characterize the data on a given participant as follows. Let $0 \leq E \leq \mathcal{T}_A$ denote the calendar time at which the subject entered the trial, X denote baseline covariates, and $A = 0$ (1) if assigned to placebo (vaccine). Denote observed time to infection on the scale of calendar time as U, and $\Delta = \mathrm{I}(U \leq L)$, where $\mathrm{I}(B) = 1$ if B is true and 0 otherwise. At $\mathcal{T}_P$, availability of the Pfizer vaccine commenced, at which point some subjects not yet infected requested to be unblinded. Denote by R (calendar time) the minimum of (i) time to such an unblinding, in which case $\mathcal{T}_P \leq R < \mathcal{T}_U$, and

3

Table 1: Summary of notation. *All times are on the scale of calendar time, where time 0 is the start of the trial.*

Trial Milestones

$\mathcal{T}_A$	Full accrual reached, October 23, 2020
$\mathcal{T}_P$	Pfizer granted EUA, December 11, 2020
$\mathcal{T}_M$	Moderna granted EUA, December 18, 2020
$\mathcal{T}_U$	Participant Decision clinic visits (PDCVs) commence, December 24, 2020
$\mathcal{T}_C$	PDCVs conclude
$\mathcal{T}_F$	Follow-up concludes, trial ends
ℓ	Lag between initial vaccine dose and full efficacy, 6 weeks, $\mathcal{T}_P - \mathcal{T}_A > \ell$
L	Time of analysis of vaccine efficacy using the proposed methods; $L >$ time at which all subjects have achieved the endpoint, requested unblinding, or attended the PDCV, $L \leq \mathcal{T}_F$

Observed Data on a Trial Participant

E	Study entry time, $0 \leq E \leq \mathcal{T}_A$
X	Baseline information
A	Treatment assignment, placebo, $A = 0$, or vaccine, $A = 1$
U, Δ	Time to infection, indicator of infection by time L, $\Delta = \mathrm{I}(U \leq L)$
R, Γ	Time to requested unblinding, PDCV/requested unblinding, or infection, whichever comes first

    $\Gamma = 0$: $R = U$, infection occurs before requested/offered unblinding
    $\Gamma = 1$: $R =$ time to requested unblinding, $\mathcal{T}_P \leq R < \mathcal{T}_U$
    $\Gamma = 2$: $R =$ time to PDCV or requested unblinding, $\mathcal{T}_U \leq R < \mathcal{T}_C$

Ψ	If $A = 0$, $\Gamma \geq 1$, indicator or whether subject receives Moderna vaccine, $\Psi = 1$, or refuses, $\Psi = 0$

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define $\Gamma = 1$; (ii) time of PDCV, so $\mathcal{T}_U \leq R < \mathcal{T}_C$, and let $\Gamma = 2$; or (iii) time to infection, in which case $R = U$ and $\Gamma = 0$. If $\Gamma \geq 1$ and $A = 1$, so that the subject was randomized to vaccine, s/he continues to be followed; if $A = 0$, s/he can choose to receive the Moderna vaccine, $\Psi = 1$ or refuse, $\Psi = 0$. We distinguish the cases $\Gamma = 1$ and 2 to acknowledge different unblinding dynamics before and after $\mathcal{T}_U$. Because a very small number of participants requested unblinding before $\mathcal{T}_P$, and, although the protocol allows participants to refuse unblinding at PDCV, all subjects are strongly encouraged to unblind, we do not include these possibilities in the formulation.

Table 1 summarizes the timeline and observed data. The trial data are thus

$$O_i = \{E_i, X_i, A_i, U_i, \Delta_i, R_i, \Gamma_i, \mathrm{I}(\Gamma_i \geq 1, A_i = 0)\Psi_i\}, \quad i = 1, \ldots, n, \tag{1}$$

independent and identically distributed (iid) across i.

3   Conceptualization of Vaccine Efficacy

Similar to Halloran, Longini, and Struchiner (1996) and Longini and Halloran (1996), we consider the following framework in which to conceptualize vaccine efficacy. The study population, comprising individuals for which inference on vaccine efficacy is of interest, is that of individuals susceptible to infection, represented by the trial participants. There is a population of individuals outside the trial with which trial participants interact, assumed to be much larger than the number of participants, so that interactions among participants are much less likely than interactions with the outside population. The probability that a trial participant will become infected at calendar time t depends on three factors: $c(t)$, the contact rate, the number of contacts with the outside population per unit time; $p(t)$, the prevalence of infections in the outside population at t; and $\pi(t)$, the transmission probability at t, the probability a susceptible individual in the study population will become infected per contact with an infected individual from the outside population. Dependence of $\pi(t)$ on time acknowledges the emergence of new variants of the virus, which may be be more or less virulent, as in the COVID-19 pandemic. Assuming random mixing, $p(t)c(t)$ is the contact rate at time t with infected individuals, and the infection rate at time t is $p(t)c(t)\pi(t)$.

We adapt this framework to the COVID-19 pandemic. The prevalence rate in the pandemic can vary substantially in time and space, so denote by S the trial site at which a participant is enrolled, and let $p(t, s)$ be the prevalence at time t at site $S = s$. Although $p(t, s)$ varies by t and s, assume it is unaffected by the individuals in the trial and thus represents an external force. We view the contact rate as individual specific; accordingly, for an arbitrary individual in the study population, let the random variables $\{c_0^b(t), c_1^b(t), c_0^u(t), c_{1\ell}^u(t), c_1^u(t)\}$ denote potential contact rates. These potential outcomes can be regarded as individual-specific behavioral characteristics of trial participants, where some may be more careful and make fewer contacts while others take more risks, and behavior can vary over time and by vaccination and blinding status. Here, $c_a^b(t)$ is the contact rate at time t if the individual were to receive vaccine, $a = 1$, or placebo, $a = 0$, and be blinded to this assignment; by virtue of blinding, it is reasonable to take $c_1^b(t) = c_0^b(t) = c^b(t)$. The Moderna vaccine is administered in two doses, ideally 4 weeks apart, and is not thought to achieve full efficacy until 2 weeks following the second dose. Thus, letting ℓ denote the lag between initial dose and full efficacy, $c_{1\ell}^u(t)$ and $c_1^u(t)$ reflect behavior of an individual who is unblinded and vaccinated in the periods prior to ℓ and after ℓ, respectively, allowing for unblinded vaccinees to, e.g., behave more cautiously before full efficacy is achieved. The rate $c_0^u(t)$ reflects behavior of an unblinded individual on placebo and does not play a role in the development. Similar to the stable unit treatment value assumption (Rubin, 1980), assume that $c_{1\ell}^u(t)$ and $c_1^u(t)$ are the same whether the individual was randomized to vaccine and unblinded before t or was randomized to placebo and subsequently unblinded

and crossed over to vaccine before t.

Finally, for an arbitrary participant, let the random variable $\pi_0(t)$ be the potential individual-specific transmission probability per contact at t if s/he were to receive placebo, and let $\pi_1(t, \tau)$ be the same if s/he were to receive vaccine and have been vaccinated for $\tau \geq 0$ units of time. As we now demonstrate, this formulation allows us to represent VE as a function of τ and thus consider whether or not VE wanes over time since vaccination.

With the set of potential outcomes for an arbitrary individual in the study population who enrolls at site S thus given by $\{c^b(t), c_0^u(t), c_{1\ell}^u(t), c_1^u(t) \; t > 0, \pi_0(t), \pi_1(t, \tau), \; \tau \geq 0\}$, the infection rate in the study population at calendar time t if all individuals were to receive placebo and be blinded to that assignment is $\mathcal{I}_0^b(t) = E\{p(t, S)c^b(t)\pi_0(t)\}$; likewise, the infection rate at t if all individuals were to receive vaccine at time $t - \tau$ and be blinded to that assignment is $\mathcal{I}_1^b(t, \tau) = E\{p(t, S)c^b(t)\pi_1(t, \tau)\}$. The relative infection rate at t is then

$$\mathcal{R}^b(t, \tau) = \frac{\mathcal{I}_1^b(t, \tau)}{\mathcal{I}_0^b(t)} = \frac{E\{p(t, S)c^b(t)\pi_1(t, \tau)\}}{E\{p(t, S)c^b(t)\pi_0(t)\}}. \tag{2}$$

Accordingly, vaccine efficacy at time t after vaccination at $t - \tau$ is $VE(t, \tau) = 1 - \mathcal{R}^b(t, \tau)$, reflecting the proportion of infections at t that would be prevented if the study population were vaccinated and on vaccine for τ units of time during the blinded phase of the study.

In the sequel, we assume that $\mathcal{R}^b(t, \tau)$ and thus $VE(t, \tau)$ depend only on τ and write $\mathcal{R}^b(\tau)$ and $VE(\tau) = 1 - \mathcal{R}^b(\tau)$. This assumption embodies the belief that, although infection rates may change over time, the relative effect of vaccine to placebo remains approximately constant and holds if (i) $\{\pi_1(t, \tau), \pi_0(t)\} \perp\!\!\!\perp \{S, c^b(t)\}|X$, where $\perp\!\!\!\perp$ means "independent of" and this independence is conditional on X; and (ii) $E\{\pi_1(t, \tau)|X\}/E\{\pi_0(t)|X\} = q(\tau)$, so does not depend on t and X. Condition (i) reflects the interpretation of $\pi_1(t, \tau)$ and $\pi_0(t)$ as inherent biological characteristics of an individual, whereas S and $c^b(t)$ are external and behavioral characteristics, respectively; thus, once common individual and external baseline covariates are taken into account, biological and geographic/behavioral characteristics are unrelated. Condition (ii) implies that, although new viral variants may change transmission probabilities under both vaccine and placebo over time, this change stays in constant proportion, and this proportion is similar for individuals with different characteristics. Further discussion is given in Section 7 and Appendix B.

Within this framework, the goal of inference on waning of VE based on the data from the trial can be stated precisely as inference on $VE(\tau) = 1 - \mathcal{R}^b(\tau)$, $\tau \geq \ell$, so reflecting VE after full efficacy is achieved. It is critical to recognize that, like estimands of interest in most clinical trials, $VE(\tau)$ represents VE at time since vaccination τ under the original conditions of the trial, under which all participants are

blinded. The challenge we address in subsequent sections is how to achieve valid inference on $VE(\tau)$, $\tau \geq \ell$, using data from the modified trial in which blinded participants are unblinded in a staggered fashion, with placebo subjects offered the option to receive vaccine.

We propose a semiparametric model within which we cast this objective. Let $\mathcal{I}_{1\ell}^u(t, \tau) = E\{p(t, S)c_{1\ell}^u(t)\pi_1(t, \tau)\}$, $\tau < \ell$, and $\mathcal{I}_1^u(t, \tau) = E\{p(t, S)c_1^u(t)\pi_1(t, \tau)\}$, $\tau \geq \ell$, be the infection rates in the study population at t if all individuals were to receive vaccine at time $t - \tau$ and be unblinded to that fact. Analogous to (i) above, assume that $\{\pi_1(t, \tau), \pi_0(t)\} \perp\!\!\!\perp \{S, c_{1\ell}^u(t), c_1^u(t)\}|X$, and continue to assume condition (ii). Then, for two values τ_1, τ_2 of τ, it is straightforward that (see Appendix A)

$$\frac{\mathcal{I}_{1\ell}^u(t, \tau_1)}{\mathcal{I}_{1\ell}^u(t, \tau_2)} = \frac{\mathcal{R}^b(\tau_1)}{\mathcal{R}^b(\tau_2)}, \quad \tau_1, \tau_2 < \ell; \qquad \frac{\mathcal{I}_1^u(t, \tau_1)}{\mathcal{I}_1^u(t, \tau_2)} = \frac{\mathcal{R}^b(\tau_1)}{\mathcal{R}^b(\tau_2)}, \quad \tau_1, \tau_2 \geq \ell. \tag{3}$$

Defining $\mathcal{I}_{1\ell}^u(t) = \mathcal{I}_{1\ell}^u(t, 0) = E\{p(t, S)c_{1\ell}^u(t)\pi_1(t, 0)\}$ and $\mathcal{I}_1^u(t) = \mathcal{I}_1^u(t, \ell) = E\{p(t, S)c_1^u(t)\pi_1(t, \ell)\}$, by (3) with $\tau_1 = \tau$ and $\tau_2 = 0$ (ℓ) on the left (right) hand side, the infection rates at t if all individuals in the study population were unblinded and to receive vaccine at time $t - \tau$ are

$$\mathcal{I}_{1\ell}^u(t, \tau) = \mathcal{I}_{1\ell}^u(t)\frac{\mathcal{R}^b(\tau)}{\mathcal{R}^b(0)}, \quad \tau < \ell; \qquad \mathcal{I}_1^u(t, \tau) = \mathcal{I}_1^u(t)\frac{\mathcal{R}^b(\tau)}{\mathcal{R}^b(\ell)}, \quad \tau \geq \ell. \tag{4}$$

Likewise, from (2), the infection rate at t if all individuals in the study population were blinded and to receive vaccine at time $t - \tau$ is

$$\mathcal{I}_1^b(t, \tau) = \mathcal{I}_0^b(t)\mathcal{R}^b(\tau). \tag{5}$$

We now represent the infection rate ratio $\mathcal{R}^b(\tau)$ as

$$\mathcal{R}^b(\tau; \theta) = \exp\{\zeta(\tau)\}\mathrm{I}(\tau < \ell) + \exp\{\theta_0 + g(\tau - \ell; \theta_1)\}\mathrm{I}(\tau \geq \ell), \quad \theta = (\theta_0, \theta_1^T)^T, \tag{6}$$

where $\zeta(\tau)$ is an unspecified function of τ; θ_0 and θ_1 are real- and vector-valued parameters, respectively; and $g(u; \theta_1)$ is a real-valued function of such that $g(0; \theta_1) = 0$ for all θ_1 and $g(u; 0) = 0$. For example, taking $g(u; \theta_1) = \theta_1 u$ yields $\mathcal{R}^b(\tau; \theta) = \exp\{\theta_0 + \theta_1(\tau - \ell)\}$, $\tau \geq \ell$, in which case $\theta_1 = 0$ implies that $VE(\tau) = 1 - \mathcal{R}^b(\tau)$, $\tau \geq \ell$, does not change with time since vaccination, and $\theta_1 > 0$ indicates that $VE(\tau)$ decreases with increasing τ; i.e., exhibits waning. More complex specifications of $g(u; \theta_1)$ using splines (e.g., Fintzi and Follmann, 2021) or piecewise constant functions could be made; e.g., for $v_1 < v_2 \leq L$,

$$g(u; \theta_1) = \theta_{11}\mathrm{I}(v_1 < u \leq v_2) + \theta_{12}\mathrm{I}(u > v_2), \quad \theta_1 = (\theta_{11}, \theta_{12})^T. \tag{7}$$

Under this model, (5) and (4) can be written as

$$\mathcal{I}_1^b(t, \tau) = \mathcal{I}_0^b(t)\left[\exp\{\zeta(\tau)\}\mathrm{I}(\tau < \ell) + \exp\{\theta_0 + g(\tau - \ell; \theta_1)\}\mathrm{I}(\tau \geq \ell)\right],$$
$$\mathcal{I}_{1\ell}^u(t, \tau) = \mathcal{I}_{1\ell}^u(t)\exp\{\zeta(\tau)\}, \quad \tau < \ell, \quad \mathcal{I}_1^u(t, \tau) = \mathcal{I}_1^u(t)\exp\{g(\tau - \ell; \theta_1)\}, \quad \tau \geq \ell. \tag{8}$$

Thus, to estimate $VE(\tau)$ for any τ and make inference on potential waning of VE, we must develop a principled approach to estimation of θ based on the data from the modified trial in which participants are unblinded and those on placebo may cross over to vaccine.

7

4 Statistical Framework

4.1 Motivation

Estimation of $VE(\tau)$, equivalently $\mathcal{R}^b(\tau)$, would be straightforward for any $\tau \geq \ell$ over the entire follow-up period if all participants remained on their assigned treatments throughout the trial. However, subjects randomized to placebo have the option to cross over to vaccine on or after $\mathcal{T}_P$. For $\tau < \mathcal{T}_P$, it is possible to estimate $\mathcal{R}^b(\tau)$ because, due to randomization, for $t < \mathcal{T}_P$ we have representative samples of blinded subjects on vaccine and placebo and thus information on $\mathcal{I}_1^b(t,\tau)$ and $\mathcal{I}_0^b(t)$, so can estimate θ_0 and components of θ_1 identified for such τ; e.g., in (7) depending on the values of v_1 and v_2. At $\mathcal{T}_P \leq t < \mathcal{T}_C$, the data comprise a mixture of blinded and unblinded participants, where, within the latter group, those on placebo may have crossed over to vaccine. Here, information, albeit diminishing during the interval $[\mathcal{T}_P, \mathcal{T}_C)$, on $\mathcal{I}_1^b(t,\tau)$ and $\mathcal{I}_0^b(t)$ is available from those participants not yet unblinded, which contributes to estimation of θ_0 and components of θ_1. Information is also available on $\mathcal{I}_1^u(t,\tau)$ from individuals who were originally randomized to vaccine and provide information on longer τ, and from individuals who recently crossed over to vaccine and provide information on shorter τ. For $t \geq \mathcal{T}_C$, there are no longer blinded participants, so that information is available only on $\mathcal{I}_1^u(t,\tau)$. For these latter groups, for longer $\tau_1 \geq \ell$ and shorter $\tau_2 \geq \ell$, $\mathcal{I}_1^u(t,\tau_1)/\mathcal{I}_1^u(t,\tau_2) = \exp\left[g\{\tau_1 - \ell; \theta_1\} - g\{\tau_2 - \ell; \theta_1\}\right]$, and, because of the mixture of times since vaccination, θ_1 can be fully estimated.

Through the following potential outcomes formulation and under suitable assumptions, in the next several sections we develop an approach to estimation of θ based on the observed data (1) that embodies the foregoing intuitive principles.

4.2 Potential outcomes formulation

Denote by $T_0^*(e,r)$ the potential time to infection on the scale of patient time for an arbitrary individual in the study population if s/he were to enter the trial at calendar time e, receive placebo and be blinded to that fact, and, if not infected by calendar time r, be unblinded and cross over to vaccine at r. Let $T_0^*(e) = T_0^*(e, \infty)$, if s/he is never crossed over to receive vaccine. Similarly, define $T_1^*(e, r)$ to be the potential time to infection (patient time scale) for an arbitrary individual if s/he were to enter the trial at e, receive vaccine and be blinded to that fact, and, if not infected by r, be unblinded at r; and define $T_1^*(e) = T_1^*(e, \infty)$. We make the consistency assumptions that $T_0^*(e, r) = T_0^*(e)$ if $T_0^*(e) < r$ and $T_1^*(e, r) = T_1^*(e)$ if $T_1^*(e) < r$. For $a = 0, 1$, denote the hazard at calendar time t, $t > e$, by

$$\lambda_a(t, e, r) = \lim_{dt \to 0} \text{pr}\{t \leq T_a^*(e, r) + e < t + dt \mid T_a^*(e, r) + e \geq t\}, \quad a = 0, 1, \tag{9}$$

8

where the addition of e induces a shift from patient to calendar time. Denote the set of all potential outcomes as

$$W^* = \{T_0^*(e,r), T_1^*(e,r); e > 0, r > e\}.$$

The development in Section 3 is in terms of infection rates at the individual-specific and population levels. Population-level hazard rates such as (9) are not equivalent to population-level infection rates. However, we argue in Appendix C that, because the probabilities of infection under vaccine and placebo during the course of the trial are small, population-level hazard rates and population-level infection rates are approximately equivalent; this assumption is implicit in the standard primary analysis noted in Section 1. Thus, to reflect this, we use familiar notation and write $\lambda^b(t) = \mathcal{I}_0^b(t)$, $\lambda_\ell^u(t) = \mathcal{I}_{1\ell}^u(t)$, and $\lambda^u(t) = \mathcal{I}_1^u(t)$. Under these conditions, using (8), we can write for $t > e$

$$
\begin{aligned}
\lambda_0(t,e,r) = {} & \lambda^b(t)\mathrm{I}(t < r) + \lambda_\ell^u(t)\exp\{\zeta(t-r)\}\mathrm{I}(t - r < \ell) \\
& + \lambda^u(t)\exp\{g(t - r - \ell; \theta_1)\}\mathrm{I}(t - r \geq \ell),
\end{aligned}
\tag{10}
$$

$$
\begin{aligned}
\lambda_1(t,e,r) = {} & \lambda^b(t)\big[\exp\{\zeta(t-e)\}\mathrm{I}(t - e < \ell) + \exp\{\theta_0 + g(t - e - \ell; \theta_1)\}\mathrm{I}(t - e \geq \ell)\big]\mathrm{I}(t < r) \\
& + \lambda^u(t)\exp\{g(t - e - \ell; \theta_1)\}\mathrm{I}(t \geq r),
\end{aligned}
\tag{11}
$$

where (11) follows because $r \geq \mathcal{T}_P$, $e \leq \mathcal{T}_A$, $\mathcal{T}_P - \mathcal{T}_A > \ell$. Define the counting processes for infection by $N_a^*(t,e,r) = \mathrm{I}\{T_a^*(e,r) + e \leq t\}$ and $N_a^*(t,e) = N_a^*(t,e,\infty)$, and the at-risk processes by $Y_a^*(t,e,r) = \mathrm{I}\{T_a^*(e,r) + e \geq t\}$ and $Y_a^*(t,e) = Y_a^*(t,e,\infty)$, $a = 0,1$ (Fleming and Harrington, 2005). From the above consistency assumptions, if $t < r$, then $N_a^*(t,e,r) = N_a^*(t,e)$, $Y_a^*(t,e,r) = Y_a^*(t,e)$, $a = 0,1$. For $a = 0,1$, let $\Lambda_a(t,e,r) = \int_0^t \lambda_a(u,e,r)\,du$ be the cumulative hazard. Because $E\{dN_a^*(t,e,r)|Y_a^*(t,e,r)\} = d\Lambda_a(t,e,r)Y_a^*(t,e,r)$, $a = 0,1$, it follows that $\{dN_a^*(t,e,r) - d\Lambda_a(t,e,r)Y_a^*(t,e,r)\}$, $a = 0,1$, are mean-zero counting process increments. Thus, any linear combination of these increments over t, e, r can be used to define unbiased estimating functions in W^* of quantities of interest. In Appendix D, we formulate a particular set of estimating functions such that, given iid potential outcomes W_i^*, $i = 1, \ldots, n$, lead to consistent and asymptotically normal estimators for $\{\Lambda^b(t), \Lambda^u(t), \theta^T\}^T$, $\Lambda^k(t) = \int_0^t \lambda^k(u)\,du$, $k = b, u$. Because interest focuses on $VE(\tau)$ for $\tau \geq \ell$, estimation of $\Lambda_\ell^u(t) = \int_0^t \lambda_\ell^u(u)\,du$ and $\zeta(\cdot)$ is not considered.

For fixed t, $0 \leq t \leq L$, the estimating functions for $\Lambda^b(t)$ and $\Lambda^u(t)$ are, respectively,

$$
\begin{aligned}
\mathcal{E}_{\Lambda^b}^*\{W^*; \Lambda^b(t), \theta\} = {} & \mathrm{I}(t < \mathcal{T}_C)\left(\int_0^{\min(t, \mathcal{T}_A)} \{dN_0^*(t,e) - d\Lambda^b(t)Y_0^*(t,e)\}\widetilde{w}_0(t,e)\,de \right. \tag{12} \\
& + \mathrm{I}(t \geq \ell)\int_0^{\min(t-\ell, \mathcal{T}_A)} \big[dN_1^*(t,e) - d\Lambda^b(t)\exp\{\theta_0 + g(t - e - \ell; \theta_1)\mathrm{I}(t - e \geq \ell)\}Y_1^*(t,e)\big]\widetilde{w}_1(t,e)\,de \bigg),
\end{aligned}
$$

$$\mathcal{E}^*_{\Lambda^u}\{W^*; \Lambda^u(t), \theta\} = \text{I}(t \geq \mathcal{T}_P + \ell) \left(\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\min(t-\ell, \mathcal{T}_C)} \left[dN_0^*(t, e, r) \right. \right.$$
$$\left. - d\Lambda^u(t) \exp\{g(t - r - \ell; \theta_1)\text{I}(t - r \geq \ell)\} Y_0^*(t, e, r) \right] w_0(t, e, r) \, dr \, de \right)$$
$$+ \text{I}(t \geq \mathcal{T}_P) \left(\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\min(t, \mathcal{T}_C)} \left[dN_1^*(t, e, r) - d\Lambda^u(t) \exp\{g(t - e - \ell; \theta_1)\} \right. \right. \tag{13}$$
$$\left. \left. \times Y_1^*(t, e, r) \right] w_1(t, e, r) \text{I}(t \geq r) \, dr \, de \right),$$

where $\widetilde{w}_a(t, e)$ and $w_a(t, e, r)$, $a = 0, 1$, are arbitrary nonnegative weight functions, specification of which is discussed later. The estimating function for θ is given by

$$\mathcal{E}^*_\theta\{W^*; \Lambda^b(\cdot), \Lambda^u(\cdot), \theta\}$$
$$= \int_\ell^{\mathcal{T}_C} \int_0^{\min(t-\ell, \mathcal{T}_A)} \begin{pmatrix} 1 \\ g_\theta(t - e - \ell) \end{pmatrix} \left[dN_1^*(t, e) - d\Lambda^b(t) \exp\{\theta_0 + g(t - e - \ell; \theta_1) \right.$$
$$\left. \times \text{I}(t - e \geq \ell)\} Y_1^*(t, e) \right] \widetilde{w}_1(t, e) \, de$$
$$+ \int_{\mathcal{T}_P+\ell}^L \int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\min(t-\ell, \mathcal{T}_C)} \begin{pmatrix} 0 \\ g_\theta(t - r - \ell) \end{pmatrix} \left[dN_0^*(t, e, r) - d\Lambda^u(t) \exp\{g(t - r - \ell; \theta_1)\text{I}(t - r \geq \ell)\} \right.$$
$$\left. \times Y_0^*(t, e, r) \right] w_0(t, e, r) \, dr \, de \tag{14}$$
$$+ \int_{\mathcal{T}_P}^L \int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\min(t, \mathcal{T}_C)} \begin{pmatrix} 0 \\ g_\theta(t - e - \ell) \end{pmatrix} \left[dN_1^*(t, e, r) - d\Lambda^u(t) \exp\{g(t - e - \ell; \theta_1)\} \right.$$
$$\left. \times Y_1^*(t, e, r) \right] w_1(t, e, r) \text{I}(t \geq r) \, dr \, de,$$

where $g_\theta(u) = \partial/\partial\theta_1\{g(u; \theta_1)\}$. Analogous to Yang, Tsiatis, and Blazing (2018), envisioning (12)-(14) as characterizing a system of estimating functions

$$\mathcal{E}^*\{W^*; \Lambda^b(\cdot), \Lambda^u(\cdot), \theta\} = [\mathcal{E}^*_{\Lambda^b}\{W^*; \Lambda^b(t), \theta\}, \mathcal{E}^*_{\Lambda^u}\{W^*; \Lambda^u(t), \theta\}, 0 \leq t \leq L, \mathcal{E}^*_\theta\{W^*; \Lambda^b(\cdot), \Lambda^u(\cdot), \theta\}^T]^T,$$

if we could observe W_i^*, $i = 1 \ldots, n$, we would estimate $d\Lambda^b(\cdot), d\Lambda^u(\cdot), \theta$ by solving the estimating equations $\sum_{i=1}^n \mathcal{E}^*(W_i^*; \Lambda^b(\cdot), \Lambda^u(\cdot), \theta)\} = 0$.

4.3 Identifiability assumptions

Of course, the potential outcomes W_i^*, $i = 1, \ldots, n$, are not observed. However, we now present assumptions under which we can exploit the developments in the last section to derive estimating equations yielding estimators based on the observed data (1).

Define the indicator that a participant is observed to be infected at time t by $dN(t) = \text{I}(U = t, \Delta = 1)$, the observed at-risk indicator at t by $Y(t) = \text{I}(E < t \leq U)$, and

$$I_0(t, e) = (1 - A)\text{I}(E = e)\text{I}(R \geq t), \quad I_1(t, e) = A\,\text{I}(E = e)\text{I}(R \geq t),$$
$$I_{01}(t, e, r) = (1 - A)\text{I}(E = e)\{\text{I}(R = r, \Gamma = 1, \Psi = 1) + \text{I}(R = r, \Gamma = 2, \Psi = 1)\}, \tag{15}$$
$$I_{11}(t, e, r) = A\,\text{I}(E = e)\{\text{I}(R = r, \Gamma = 1) + \text{I}(R = r, \Gamma = 2)\}.$$

10

$I_a(t, e) = 1$ indicates that a subject entering the trial at time e and randomized to placebo ($a = 0$) or vaccine ($a = 1$) has not yet been infected or unblinded by t. For $t > r$, $I_{01}(t, e, r) = 1$ indicates that a subject randomized to placebo at entry time e is unblinded (either by request or at a PDCV) at time r and crosses over to vaccine at r, and $I_{11}(t, e, r) = 1$ if a subject randomized to vaccine at entry time e is unblinded at r. Make the consistency assumptions

$$I_a(t, e)dN(t) = I_a(t, e)dN_a^*(t, e), \quad I_a(t, e)Y(t) = I_a(t, e)Y_a^*(t, e), \quad a = 0, 1,$$

$$I_{01}(t, e, r)dN(t) = I_{01}(t, e, r)dN_0^*(t, e, r), \quad I_{01}(t, e, r)Y(t) = I_{01}(t, e, r)Y_0^*(t, e, r), \tag{16}$$

$$I_{11}(t, e, r)dN(t) = I_{11}(t, e, r)dN_1^*(t, e, r), \quad I_{11}(t, e, r)Y(t) = I_{11}(t, e, r)Y_1^*(t, e, r).$$

We now make assumptions similar in spirit to those adopted in observational studies. By randomization,

$$A \perp\!\!\!\perp (X, E, W^*), \tag{17}$$

where we subsume the site indicator S in X, and let $p_A = \mathrm{pr}(A = 1)$. It is realistic to assume that the mix of baseline covariates changes over the accrual period; e.g., during the trial, because of lagging accrual of elderly subjects and subjects from underrepresented groups, an effort was made to increase participation of these groups in the latter part of the accrual period. Accordingly, we allow the distribution of entry time E to depend on X, and denote its conditional density as $f_{E|X}(e|x)$. We make the no unmeasured confounders assumption

$$E \perp\!\!\!\perp W^* \,|\, X. \tag{18}$$

Define the hazard functions of unblinding in the periods between the Pfizer EUA and the start of PDCVs and after the start of PDCVs, respectively, as

$$\lambda_{R,1}(r|X, A, E, W^*) = \lim_{dr \to 0} \mathrm{pr}(r \le R < r + dr, \Gamma = 1|R \ge r, X, A, E, W^*), \quad \mathcal{T}_P \le r < \mathcal{T}_U$$

$$\lambda_{R,2}(r|X, A, E, W^*) = \lim_{dr \to 0} \mathrm{pr}(r \le R < r + dr, \Gamma = 2|R \ge r, X, A, E, W^*), \quad \mathcal{T}_U \le r < \mathcal{T}_C,$$

where $\lambda_{R,j}(r|X, A, E, W^*) = 0$ for $r \ge \mathcal{T}_U$ ($j = 1$) and $r \ge \mathcal{T}_C$ ($j = 2$). Because the accrual period was short relative to the length of follow-up, we take these unblinding hazard functions to not depend on E, although including such dependence is straightforward; and, similar to a noninformative censoring assumption, to not depend on W^* and write

$$\lambda_{R,j}(r|X, A, E, W^*) = \lambda_{R,j}(r|X, A), \quad j = 1, 2. \tag{19}$$

Define $\mathcal{K}_R(r|X, A) = \exp[-\{\Lambda_{R,1}(r|X, A) + \Lambda_{R,2}(r|X, A)\}]$, $\Lambda_{R,j}(r|X, A) = \int_{\mathcal{T}_j}^r \lambda_{R,j}(u|X, A)\, du$, $\mathcal{T}_j = \mathcal{T}_P$ ($j = 1$) or $\mathcal{T}_j = \mathcal{T}_U$ ($j = 2$). Because $\lambda_{R,1}(r|X, A)$ and $\lambda_{R,2}(r|X, A)$ are defined on the nonoverlapping

intervals $[\mathcal{T}_P, \mathcal{T}_U)$ and $[\mathcal{T}_U, \mathcal{T}_C)$, respectively, with $\mathcal{K}_{R,j}(r|X, A) = \exp\{-\Lambda_{R,j}(r|X, A)\}$, $j = 1, 2$,

$$
\begin{aligned}
\mathcal{K}_R(r|X, A) &= 1, & r &< \mathcal{T}_P, \\
&= \mathcal{K}_{R,1}(r|X, A), & \mathcal{T}_P &\leq r < \mathcal{T}_U, \\
&= \mathcal{K}_{R,1}(\mathcal{T}_U|X, A)\mathcal{K}_{R,2}(r|X, A), & \mathcal{T}_U &\leq r < \mathcal{T}_C, \\
&= 0, & r &\geq \mathcal{T}_C.
\end{aligned}
$$

Finally, define $f_{R,j}(r|X, A) = \mathcal{K}_R(r|X, A)\lambda_{R,j}(r|X, A)$, $j = 1, 2$.

Let $\mathrm{pr}(\Psi = 1|X, E, \Gamma, R, W^*)$ be the probability that a placebo participant unblinded at R agrees to receive the Moderna vaccine. Similar to (19), we assume this probability does not depend on E, W^*; moreover, because the unblinding interval $[\mathcal{T}_P, \mathcal{T}_C)$ is very short relative to the length of follow-up, we assume it does not depend on R but does depend on the unblinding dynamics at R. Thus, write

$$
\mathrm{pr}(\Psi = 1|X, E, \Gamma, R, W^*) = \mathrm{pr}(\Psi = 1|X, \Gamma) = p_\Psi(X, \Gamma). \tag{20}
$$

4.4 Observed data estimating equations

We now outline, under the assumptions (16)-(20), which we take to hold henceforth, how we can develop unbiased estimating equations based on the observed data yielding consistent and asymptotically normal estimators for $d\Lambda^b(\cdot), d\Lambda^u(\cdot), \theta$. The basic premise is to use inverse probability weighting (IPW) to probabilistically represent potential outcomes in terms of the observed data to mimic the estimating functions (12)-(14).

Considering (15), define the inverse probability weights

$$
h_0(t, e|X) = (1 - p_A)f_{E|X}(e|X)\mathcal{K}_R(t|X, A = 0), \quad h_1(t, e|X) = p_A\, f_{E|X}(e|X)\mathcal{K}_R(t|X, A = 1),
$$

$$
\begin{aligned}
h_{01}(e, r|X) = (1 - p_A)f_{E|X}(e|X) \\
\times \{f_{R,1}(r|X, A = 0)p_\Psi(X, \Gamma = 1) + f_{R,2}(r|X, A = 0)p_\Psi(X, \Gamma = 2)\},
\end{aligned}
$$

$$
h_{11}(e, r|X) = p_A\, f_{E|X}(e|X)\{f_{R,1}(r|X, A = 1) + f_{R,2}(r|X, A = 1)\}.
$$

We show in Appendix E that

$$
E\left\{\frac{I_0(t, e)dN(t)}{h_0(t, e|X)} \bigg| X, W^*\right\} = dN_0^*(t, e), \quad E\left\{\frac{I_0(t, e)Y(t)}{h_0(t, e|X)} \bigg| X, W^*\right\} = Y_0^*(t, e) \tag{21}
$$

$$
E\left\{\frac{I_1(t, e)dN(t)}{h_1(t, e|X)} \bigg| X, W^*\right\} = dN_1^*(t, e), \quad E\left\{\frac{I_1(t, e)Y(t)}{h_1(t, e|X)} \bigg| X, W^*\right\} = Y_1^*(t, e), \tag{22}
$$

$$
E\left\{\frac{I_{01}(t, e, r)dN(t)}{h_{01}(e, r|X)} \bigg| X, W^*\right\} = dN_0^*(t, e, r), \quad E\left\{\frac{I_{01}(t, e, r)Y(t)}{h_{01}(e, r|X)} \bigg| X, W^*\right\} = Y_0^*(t, e, r), \tag{23}
$$

$$
E\left\{\frac{I_{11}(t, e, r)dN(t)}{h_{11}(e, r|X)} \bigg| X, W^*\right\} = dN_1^*(t, e, r), \quad E\left\{\frac{I_{11}(t, e, r)Y(t)}{h_{11}(e, r|X)} \bigg| X, W^*\right\} = Y_1^*(t, e, r). \tag{24}
$$

To obtain observed data analogs to the estimating functions (12)-(14), based on the equalities in (21)-(24), we substitute the IPW expressions in the conditional expectations on the left hand sides. Using (15) and (21)-(22), the analog to (12) is given by

$$
\begin{aligned}
\mathcal{E}_{\Lambda^b}\{O; \Lambda^b(t), \theta\} = {}& \mathrm{I}(t < \mathcal{T}_C) \left(\int_0^{\min(t, \mathcal{T}_A)} \frac{I_0(t, e)}{h_0(t, e|X)} \{dN(t) - d\Lambda^b(t) Y(t)\} \widetilde{w}_0(t, e) \, de \right. \\
& + \mathrm{I}(t \geq \ell) \int_0^{\min(t-\ell, \mathcal{T}_A)} \frac{I_1(t, e)}{h_1(t, e|X)} \Big[dN(t) - d\Lambda^b(t) \exp\{\theta_0 + g(t - e - \ell; \theta_1) \\
& \left. \hspace{5cm} \times \mathrm{I}(t - e \geq \ell)\} Y(t) \Big] \widetilde{w}_1(t, e) \, de \right) \\
= {}& \mathrm{I}(t < \mathcal{T}_C) \left(\frac{(1 - A)\mathrm{I}(R \geq t)}{h_0(t, E|X)} \{dN(t) - d\Lambda^b(t) Y(t)\} \widetilde{w}_0(t, E) \right. \\
& \left. + \frac{A\mathrm{I}(E + \ell \leq t \leq R)}{h_1(t, E|X)} \Big[dN(t) - d\Lambda^b(t) \exp\{\theta_0 + g(t - E - \ell; \theta_1)\} Y(t) \Big] \widetilde{w}_1(t, E) \right).
\end{aligned}
\tag{25}
$$

Likewise, using (23)-(24), the analog to (13) is

$$
\begin{aligned}
\mathcal{E}_{\Lambda^u}\{O; \Lambda^u(t), \theta\} = {}& \mathrm{I}(t \geq \mathcal{T}_P + \ell) \left(\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\min(t-\ell, \mathcal{T}_C)} \frac{I_{01}(t, e, r)}{h_{01}(e, r|X)} \Big[dN(t) \right. \\
& \left. \hspace{3cm} - d\Lambda^u(t) \exp\{g(t - r - \ell; \theta_1) \mathrm{I}(t - r \geq \ell)\} Y(t) \Big] w_0(t, e, r) \, dr \, de \right) \\
& + \mathrm{I}(t \geq \mathcal{T}_P) \left(\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\min(t, \mathcal{T}_C)} \frac{I_{11}(t, e, r)}{h_{11}(e, r|X)} \Big[dN(t) - d\Lambda^u(t) \exp\{g(t - e - \ell; \theta_1)\} \right. \\
& \left. \hspace{3cm} \times Y(t) \Big] w_1(t, e, r) \mathrm{I}(t \geq r) \, dr \, de \right) \\
= {}& \mathrm{I}(t \geq \mathcal{T}_P + \ell) \left(\frac{(1 - A)\mathrm{I}(t - R \geq \ell)\{\mathrm{I}(\Gamma = 1, \Psi = 1) + \mathrm{I}(\Gamma = 2, \Psi = 1)\}}{h_{01}(E, R|X)} \right. \\
& \left. \hspace{3cm} \times \Big[dN(t) - d\Lambda^u(t) \exp\{g(t - R - \ell; \theta_1)\} Y(t) \Big] w_0(t, E, R) \right) \\
& + \mathrm{I}(t \geq \mathcal{T}_P) \left(\frac{A\mathrm{I}(t > R)\{\mathrm{I}(\Gamma = 1) + \mathrm{I}(\Gamma = 2)\}}{h_{11}(E, R|X)} \right. \\
& \left. \hspace{3cm} \times \Big[dN(t) - d\Lambda^u(t) \exp\{g(t - E - \ell; \theta_1)\} Y(t) \Big] w_1(t, E, R) \right).
\end{aligned}
\tag{26}
$$

A entirely similar representation $\mathcal{E}_\theta\{O; \Lambda^b(\cdot)\Lambda^u(\cdot), \theta\}$ of (14) in terms of the observed data can be deduced and is suppressed for brevity.

To simplify notation, based on (25), (26), and the analogous expression for (14), define

$$d\widetilde{N}^b(t) = dN(t) \left\{ \frac{(1-A)\mathrm{I}(R \geq t)\widetilde{w}_0(t, E)}{h_0(t, E|X)} + \frac{A\mathrm{I}(E + \ell \leq t \leq R)\widetilde{w}_1(t, E)}{h_1(t, E|X)} \right\}$$

$$\widetilde{Y}^b(t) = Y(t) \left[\frac{(1-A)\mathrm{I}(R \geq t)\widetilde{w}_0(t, E)}{h_0(t, E|X)} + \frac{A\mathrm{I}(E + \ell \leq t \leq R)\widetilde{w}_1(t, E)}{h_1(t, E|X)} \exp\{\theta_0 + g(t - E - \ell; \theta_1)\} \right]$$

$$d\widetilde{N}^u(t) = dN(t) \left[\frac{(1-A)\mathrm{I}(t - R \geq \ell)\{\mathrm{I}(\Gamma = 1, \Psi = 1) + \mathrm{I}(\Gamma = 2, \Psi = 1)\}w_0(t, E, R)}{h_{01}(E, R|X)} \right.$$
$$\left. + \frac{A\mathrm{I}(t > R)\{\mathrm{I}(\Gamma = 1) + \mathrm{I}(\Gamma = 2)\}w_1(t, E, R)}{h_{11}(E, R|X)} \right]$$

$$\widetilde{Y}^u(t) = Y(t) \left[\frac{(1-A)\mathrm{I}(t - R \geq \ell)\{\mathrm{I}(\Gamma = 1, \Psi = 1) + \mathrm{I}(\Gamma = 2, \Psi = 1)\}w_0(t, E, R)}{h_{01}(E, R|X)} \right.$$
$$\times \exp\{g(t - R - \ell; \theta_1)$$
$$\left. + \frac{A\mathrm{I}(t > R)\{\mathrm{I}(\Gamma = 1) + \mathrm{I}(\Gamma = 2)\}w_1(t, E, R)}{h_{11}(E, R|X)} \exp\{g(t - E - \ell; \theta_1)\right].$$

Define also

$$Z^b(t) = A \begin{pmatrix} 1 \\ g_\theta(t - E - \ell) \end{pmatrix}, \quad Z^u(t) = A \begin{pmatrix} 0 \\ g_\theta(t - E - \ell) \end{pmatrix} + (1 - A) \begin{pmatrix} 0 \\ g_\theta(t - R - \ell) \end{pmatrix}.$$

Then it is straightforward that the observed-data estimating functions are

$$\mathcal{E}_{\Lambda^b}\{O; \Lambda^b(t), \theta\} = d\widetilde{N}^b(t) - d\Lambda^b(t)\widetilde{Y}^b(t), \quad \mathcal{E}_{\Lambda^u}\{O; \Lambda^u(t), \theta\} = d\widetilde{N}^u(t) - d\Lambda^u(t)\widetilde{Y}^u(t),$$

$$\mathcal{E}_\theta\{O; \Lambda^b(\cdot)\Lambda^u(\cdot), \theta\} = \int_0^{\mathcal{T}_C} Z^b(t)\{d\widetilde{N}^b(t) - d\Lambda^b(t)\widetilde{Y}^b(t)\} + \int_{\mathcal{T}_P}^L Z^u(t)\{d\widetilde{N}^u(t) - d\Lambda^u(t)\widetilde{Y}^u(t)\}.$$

Letting $\widetilde{N}_i^b(t)$, $\widetilde{N}_i^u(t)$, $\widetilde{Y}_i^b(t)$, $\widetilde{Y}_i^u(t)$, $Z_i^b(t)$, and $Z_i^u(t)$ denote evaluation at O_i in (1), the foregoing developments lead to the set of observed-data estimating equations

$$\sum_{i=1}^n \{d\widetilde{N}_i^b(t) - d\Lambda^b(t)\widetilde{Y}_i^b(t) = 0, \quad \sum_{i=1}^n \{d\widetilde{N}_i^u(t) - d\Lambda^u(t)\widetilde{Y}_i^u(t) = 0, \tag{27}$$

$$\sum_{i=1}^n \left[\int_0^{\mathcal{T}_C} Z_i^b(t)\{d\widetilde{N}_i^b(t) - d\Lambda^b(t)\widetilde{Y}_i^b(t)\} + \int_{\mathcal{T}_P}^L Z_i^u(t)\{d\widetilde{N}_i^u(t) - d\Lambda^u(t)\widetilde{Y}_i^u(t)\} \right] = 0. \tag{28}$$

For fixed θ, the estimators for $d\Lambda^b(t)$ and $d\Lambda^u(t)$ are the solutions to the equations in (27) given by

$$d\widehat{\Lambda}^b(t) = \left\{ \sum_{i=1}^n \widetilde{Y}_i^b(t) \right\}^{-1} \sum_{i=1}^n d\widetilde{N}_i^b(t), \quad d\widehat{\Lambda}^u(t) = \left\{ \sum_{i=1}^n \widetilde{Y}_i^u(t) \right\}^{-1} \sum_{i=1}^n d\widetilde{N}_i^u(t). \tag{29}$$

Substituting these expressions in (28) yields, after some algebra, the equation

$$\sum_{i=1}^n \left[\int_0^{\mathcal{T}_C} \{Z_i^b(t) - \overline{Z}^b(t)\}d\widetilde{N}_i^b(t) + \int_{\mathcal{T}_P}^L \{Z_i^u(t) - \overline{Z}^u(t)\}d\widetilde{N}_i^u(t) \right] = 0, \tag{30}$$

$$\overline{Z}^b(t) = \left\{ \sum_{i=1}^n \widetilde{Y}_i^b(t) \right\}^{-1} \sum_{i=1}^n Z_i^b(t)\widetilde{Y}_i^b(t), \quad \overline{Z}^u(t) = \left\{ \sum_{i=1}^n \widetilde{Y}_i^u(t) \right\}^{-1} \sum_{i=1}^n Z_i^u(t)\widetilde{Y}_i^u(t).$$

14

5 Practical Implementation and Inference

Choice of the weight functions $\widetilde{w}_0(t,e)$, $\widetilde{w}_1(t,e)$, $w_0(t,e,r)$, and $w_1(t,e,r)$ is arbitrary but can play an important role in performance of the resulting estimators. We recommend taking a fixed value $\widetilde{x}$ of X, e.g., the sample mean, and setting $\widetilde{w}_a(t,e) = h_a(t,e|\widetilde{x})$ and $w_a(t,e,r) = h_{a1}(e,r|\widetilde{x})$, $a = 0,1$, where the latter does not depend on t. The resulting weights $h_a(t,e|\widetilde{x})/h_j(t,e|X)$ and $h_{a1}(e,r|\widetilde{x})/h_{a1}(e,r|X)$, $a = 0,1$, are referred to as stabilized weights (Robins, Hernán, and Brumback, 2000), as they mitigate the effect of small inverse probability weights that can give undue influence to a few observations. Note that dependence of the inverse probability weights on p_A cancels in construction of stabilized weights. Moreover, if there is no confounding, in that $\lambda_{R,j}(r|X,A)$, $j = 1,2$ in (19), $f_{E|X}(e|X)$, and $p_\Psi(X,\Gamma)$ do not depend on X, the stabilized weights are identically equal to one.

If the "survival probabilities" for R, $\mathcal{K}_{R,j}(r|X,A)$, and the densities $f_{R,j}(r|X,A)$, $j = 1,2$, and $f_{E|X}(e|X)$ in the inverse probability weights, which appear in the expressions in the estimating equation (30), were known, (30) could be solved to yield an estimator for θ and in particular θ_1 characterizing VE waning. As these quantities are unknown, models must be posited for them, leading to estimators that can be substituted in (30). We propose the use of Cox proportional hazards models for $\lambda_{R,j}(r|X,A)$, $j = 1,2$, in (19), which can be fitted using the data $\{X_i, A_i, R_i, \mathrm{I}(\Gamma_i = j)\}$, $i = 1\ldots,n$; and for the hazard of entry time E given X, which can be fitted using (E_i, X_i), $i = 1,\ldots,n$. A binary, e.g., logistic, regression model can be used to represent $p_\Psi(X,\Gamma)$ and fitted using (X_i, Γ_i, Ψ_i) for i such that $A_i = 0$.

For individual i, the stabilized weights involve the quantities $f_{R,j}(R_i|\widetilde{x},a)/f_{R,j}(R_i|X_i,a)$, $j = 1,2$, $a = 0,1$, and $f_{E|X}(E_i|\widetilde{x})/f_{E|X}(E_i|X_i)$. With proportional hazards models as above with predictors $\phi_j(X,\beta_j)$, say, it is straightforward that $f_{E|X}(E_i|\widetilde{x})/f_{E|X}(E_i|X_i)$ and

$$f_{R,j}(R_i|\widetilde{x},a)/f_{R,j}(R_i|X_i,a) = [\exp\{\phi_j(\widetilde{x},\beta_j)\}\mathcal{K}_R(R_i|\widetilde{x},a)]/[\exp\{\phi_j(X_i,\beta_j)\}\mathcal{K}_R(R_i|X_i,a)],$$

where in each case the baseline hazard cancels from numerator and denominator. for Thus, the estimated stabilized weights involve only the estimated cumulative hazard functions and estimators for the β_j, each of which is root-n consistent and asymptotically normal.

As sketched in Appendix F, with stabilized weights set equal to one or estimated, the estimating equation (30) can be solved easily via a Newton-Raphson algorithm. A heuristic argument demonstrating that $\widehat{\theta}$ is asymptotically normal leading to an expression for its approximate sampling variance using the sandwich technique is given in Appendix F.

6 Simulations

We report on simulation studies demonstrating performance of the methods, each involving 1000 Monte Carlo replications, based roughly on the Moderna trial. We took $p_A = 0.5$ and $\mathcal{T}_A = 12$, $\mathcal{T}_P = 19$, $\mathcal{T}_U = 21$, and $\mathcal{T}_C = 31$, where all times are in weeks, and consider an analysis at calendar time $L = 52$ weeks, with $n = 30,000$. In all cases, $g(u, \theta_1) = \theta_1 I(u > v)$ where $v = 20$ weeks and $\theta_0 = \log(0.05)$, corresponding to VE $= 95\%$ prior to time v, so that, depending on θ_1, VE potentially wanes following v. We consider $\theta_1 = \log(7)$, corresponding to VE $= 65\%$ after time v, and $\theta_1 = 0$, corresponding to no waning.

Because the trial and unblinding process are ongoing, we were not able to base our generative scenarios on data from the trial. Owing to the complexity of the trial and multiple potential sources of confounding, to facilitate exploration of a range of conditions while controlling computational complexity and intensity, we focused on several basic scenarios meant to represent varying degrees of confounding consistent with our expectations for the most likely sources of such confounding in the trial. Specifically, we took $f_{E|X}(e|X)$ and $\lambda_{R,2}(r|X, A)$ to not depend on X (or A in the latter case) in any scenario, reflecting mostly random entry and PDCV unblinding processes. In scenarios involving confounding, we took $\lambda_{R,1}(r|X, A)$, corresponding to the period $[\mathcal{T}_P, \mathcal{T}_U)$ in which "requested unblinding" occurred, and the "agreement process" $p_\Psi(X, \Gamma)$ to depend on X, as described below, reflecting our belief that these processes could be associated with participant characteristics.

In the first set of simulations, we consider two cases: (i) no confounding, where all of $\lambda_{R,j}(r|X, A)$, $j = 1, 2$, $f_{E|X}(e|X)$, and $p_\Psi(X, \Gamma)$ do not depend on X; and (ii) confounding, where $\lambda_{R,1}(r|X, A)$ and $p_\Psi(X, \Gamma)$ depend on X as above. In both (i) and (ii), the entry process $E \sim \mathcal{U}(0, \mathcal{T}_A)$, i.e., uniform on $[0, \mathcal{T}_A]$, and the unblinding process during PDCVs was $\mathcal{U}(\mathcal{T}_U, \mathcal{T}_C)$; see below. In each simulation experiment, for each participant in each Monte Carlo data set, we first generated $A \sim \text{Bernoulli}(p_A)$, two baseline covariates $X_1 \sim \text{Bernoulli}(p_{X_1} = 0.5)$ and $X_2 \sim \mathcal{N}(\mu_{X_2} = 45, \sigma_{X_2}^2 = 10^2)$, and E as above. To obtain R, we generated G_1 to be exponential with hazard $\lambda_{R,1}(r|X, A) = \exp[\widetilde{\beta}_{10} + \{\widetilde{\beta}_{11}(X_1 - p_{X_1}) + \widetilde{\beta}_{12}(X_2 - \mu_{X_2})\}(1 - A) + \{\widetilde{\beta}_{13}(X_1 - p_{X_1}) + \widetilde{\beta}_{14}(X_2 - \mu_{X_2})\}A]$, where $\widetilde{\beta}_{10} = \log(0.036)$, corresponding to roughly 7% unblinding during $[\mathcal{T}_P, \mathcal{T}_U)$, and $(\widetilde{\beta}_{11}, \widetilde{\beta}_{12}, \widetilde{\beta}_{13}, \widetilde{\beta}_{14}) = (0, 0, 0, 0, 0)$ for (i), no confounding, and $(-0.8, -0.08, 0.8, 0.08)$ for (ii), confounding. With $R_1 = \mathcal{T}_P + G_1$ and $R_2 \sim \mathcal{U}(\mathcal{T}_U, \mathcal{T}_C)$, we let $\widetilde{\Gamma} = 1 + I(R_1 \geq \mathcal{T}_U)$ and $\widetilde{R} = R_1 I(\widetilde{\Gamma} = 1) + R_2 I(\widetilde{\Gamma} = 2)$. We generated Ψ as $\text{Bernoulli}\{p_\Psi(X, \widetilde{\Gamma})\}$, $p_\Psi(X, \widetilde{\Gamma}) = \text{expit}\{\widetilde{\gamma}_0 + \widetilde{\gamma}_1(X_1 - p_{X_1}) + \widetilde{\gamma}_2(X_2 - \mu_{X_2}) + \widetilde{\gamma}_3\widetilde{\Gamma}\}$, $\text{expit}(u) = (1 + e^{-u})^{-1}$, where $\widetilde{\gamma}_0 = 1.4$, corresponding to approximately 80% agreement to receive the vaccine by unblinded placebo participants, and $(\widetilde{\gamma}_1, \widetilde{\gamma}_2, \widetilde{\gamma}_3) = (0, 0, -0.1)$ for (i) and $= (-0.8, -0.08, -0.1)$ for (ii).

16

To generate U, Δ, we first generated $T_0^*(E, R)$ and $T_1^*(E, R)$ based on (10)-(11), with $\lambda^b(t) = \lambda^b = \exp\{\delta_0 + \delta_1(X_1 - p_{X_1}) + \delta_2(X_2 - \mu_{X_2}) + \mathcal{Z}\}$, where $(\delta_0, \delta_1, \delta_2) = \{\log(0.0006), 0.4, 0.04\}$, leading to approximately a 3% infection rate for placebo participants over L, and $\mathcal{Z} \sim \mathcal{N}(0, 0.04)$,; $\lambda_\ell^u(t) = \lambda_\ell^u = \lambda^b$; $\zeta(t) = 0$; and $\lambda^u(t) = \lambda^u = 1.25\lambda^b$, so that $\lambda_a(t, e, r)$ in (10)-(11), $a = 0, 1$, are piecewise constant hazards. $T_0^*(E, R)$ and $T_1^*(E, R)$ were obtained via inverse transform sampling. We then generated U (calendar time) as $U = E + AT_1^*(E, R) + (1 - A)[\mathrm{I}\{T_0^*(E, R) < \widetilde{R}\}T_0^*(E, R) + \mathrm{I}\{T_0^*(E, R) \geq \widetilde{R}\}\{\Psi T_0^*(E, R) + (1 - \Psi)T_r^*\}$, where $T_r^* = \widetilde{R} + G_2$ for G_2 exponential with hazard λ^b; infection times for unblinded placebo participants who decline vaccine are not used in the analysis. Finally, we set $\Delta = \mathrm{I}(U < L)$, and defined $R = U\mathrm{I}(U \leq \widetilde{R}) + \widetilde{R}\mathrm{I}(U > \widetilde{R})$ and $\Gamma = \widetilde{\Gamma}\mathrm{I}(U > R)$. Although we obtained Ψ for all n participants, Ψ is used only when $A = 0, \Gamma \geq 1$.

For each combination of (i) and (ii) and (a) $\theta_1 = \log(7)$ and (b) $\theta_1 = 0$, we estimated θ and thus $VE(\tau)$ for $\tau \leq v$ and $\tau > v$ two ways: taking the stabilized weights equal to one, so disregarding possible confounding, and with estimated stabilized weights. The latter were obtained by fitting proportional hazards models for entry time E with linear predictor $\nu_1 X_1 + \nu_2 X_2$ and for $\lambda_{R,j}(r|X, A)$, $j = 1, 2$, with linear predictors $\beta_{11}X_1 + \beta_{12}X_2 + \beta_{13}A + \beta_{14}X_1A + \beta_{15}X_2A$ and $\beta_{21}X_1 + \beta_{22}X_2$, respectively; and a logistic regression model for $p_\Psi(X, \Gamma) = \mathrm{expit}\{(\gamma_{10} + \gamma_{11}X_1 + \gamma_{12}X_2)\mathrm{I}(\Gamma = 1) + (\gamma_{20} + \gamma_{21}X_1 + \gamma_{22}X_2)\mathrm{I}(\Gamma = 2)\}$.

Table 2 presents the results for estimation of θ_1, dictating waning; $VE_{\leq 20} = 1 - \exp(\theta_0)$, VE prior to $v = 20$ weeks; and $VE_{>20} = 1 - \exp(\theta_0 + \theta_1)$, VE after $v = 20$ weeks. Because the Monte Carlo distribution of some of these quantities exhibited slight skewness, those for the VE quantities likely due to the exponentiation, we report both Monte Carlo mean and median. Estimation of $VE_{\leq 20}$ shows virtually no bias for both (a) and (b); that for $VE_{>20}$ in case (a) shows minimal bias and virtually none for (b). In all cases, standard errors obtained via the sandwich technique as outlined in Appendix F along with the delta method for the VEs track the Monte Carlo standard deviations. Under both (i) no confounding and (ii) confounding, estimation of the stabilized weights appears to have little consequence for precision of the estimators relative to setting them to equal to one. 95% Wald confidence intervals, exponentiated for the VEs, achieve nominal coverage. For (b) and each combination of stabilized weights set equal to one or estimated and (i), no confounding, and (ii), confounding, we also calculated the empirical Type I error achieved by a Wald test at level of significance 0.05 for VE waning addressing the null and alternative hypotheses $H_0 : \theta_1 \leq 0$ versus $H_1 : \theta_1 > 0$. These values are 0.043 and 0.056 when using stabilized weights set equal to one under (i) and (ii), respectively; the analogous values with estimated weights are 0.046 and 0.050 under (i) and (ii).

In the first set of simulations, the confounding induced by our generative choices led to little to no

Table 2: Simulation results based on 1000 Monte Carlo replications, first scenario. Mean = mean of Monte Carlo estimates, Med = median of Monte Carlo estimates, SD = standard deviation of Monte Carlo estimates, SE = average of standard errors obtained via the sandwich technique/delta method, Cov = empirical coverage of nominal 95% Wald confidence interval (transformed for VE). $VE_{\leq 20} = 1 - \exp(\theta_0)$, VE prior to $v = 20$ weeks; $VE_{>20} = 1 - \exp(\theta_0 + \theta_1)$, VE after $v = 20$ weeks. True values: (a) $\theta_1 = \log(7) = 1.946$, $VE_{\leq 20} = 0.95$, $VE_{>20} = 0.65$; (b) $\theta = 0$, $VE_{\leq 20} = VE_{>20} = 0.95$.

	Stabilized Weights = 1					Stabilized Weights Estimated				
	Mean	Med	SD	SE	Cov	Mean	Med	SD	SE	Cov
(i), no confounding; (a) $\theta_1 = \log(7)$										
θ_1	1.961	1.935	0.310	0.308	0.955	1.983	1.959	0.303	0.310	0.957
$VE_{\leq 20}$	0.950	0.953	0.019	0.019	0.952	0.950	0.952	0.019	0.019	0.953
$VE_{>20}$	0.634	0.663	0.183	0.174	0.956	0.626	0.662	0.188	0.177	0.957
(ii), confounding; (a) $\theta_1 = \log(7)$										
θ_1	2.030	2.013	0.325	0.320	0.949	1.990	1.973	0.346	0.335	0.948
$VE_{\leq 20}$	0.951	0.953	0.019	0.018	0.958	0.951	0.952	0.019	0.019	0.955
$VE_{>20}$	0.614	0.647	0.199	0.185	0.948	0.619	0.665	0.201	0.186	0.941
(i), no confounding; (b) $\theta_1 = 0$										
θ_1	-0.020	-0.019	0.433	0.422	0.954	0.007	0.019	0.421	0.424	0.958
$VE_{\leq 20}$	0.950	0.952	0.020	0.019	0.955	0.950	0.952	0.020	0.019	0.956
$VE_{>20}$	0.947	0.954	0.032	0.030	0.958	0.946	0.953	0.033	0.031	0.954
(ii), confounding; (b) $\theta_1 = 0$										
θ_1	0.053	0.045	0.446	0.436	0.955	0.011	-0.004	0.452	0.450	0.956
$VE_{\leq 20}$	0.951	0.952	0.019	0.019	0.958	0.950	0.952	0.020	0.019	0.955
$VE_{>20}$	0.944	0.951	0.035	0.032	0.957	0.945	0.954	0.036	0.033	0.952

bias in the estimators for θ_1 and the VEs prior to and after 20 weeks. Notably, modeling and fitting of the stabilized weights to adjust for potential confounding shows little effect relative to setting the stabilized weights to one. To the extent that this scenario is a plausible approximation to actual conditions of the trial, it may be that confounding will not be a serious challenge for the analysis of VE waning.

To examine the ability of the methods with estimated stabilized weights to adjust for confounding that potentially could be sufficiently strong to bias results, we carried out additional simulations under settings (a) $\theta_1 = \log(7)$ and (b) $\theta_1 = 0$ with (ii) confounding in which our choices of generative parameters induce a stronger association between the potential infection times and the agreement process. Specifically, we took instead $(\delta_0, \delta_1, \delta_2)^T = \{\log(0.0006), 0.7, 0.07\}^T$ and $(\widetilde{\gamma}_0, \widetilde{\gamma}_1, \widetilde{\gamma}_2, \widetilde{\gamma}_3) = (1.4, -1.0, -0.1, -0.1)$, with all other settings identical to those above.

Table 3: Simulation results based on 1000 Monte Carlo replications, second scenario. Entries are as in Table 2. True values: (a) $\theta_1 = \log(7) = 1.946$, $VE_{\leq 20} = 0.95$, $VE_{>20} = 0.65$; (b) $\theta = 0$, $VE_{\leq 20} = VE_{>20} = 0.95$.

	Stabilized Weights = 1					Stabilized Weights Estimated				
	Mean	Med	SD	SE	Cov	Mean	Med	SD	SE	Cov
(ii), confounding; (a) $\theta_1 = \log(7)$										
θ_1	2.125	2.100	0.315	0.299	0.925	2.009	2.008	0.346	0.325	0.942
$VE_{\leq 20}$	0.952	0.953	0.017	0.016	0.970	0.950	0.952	0.017	0.017	0.964
$VE_{>20}$	0.581	0.611	0.191	0.182	0.950	0.613	0.640	0.179	0.175	0.956
(ii), confounding; (b) $\theta_1 = 0$										
θ_1	0.171	0.149	0.436	0.403	0.921	0.050	0.053	0.447	0.426	0.955
$VE_{\leq 20}$	0.951	0.953	0.173	0.171	0.967	0.950	0.952	0.018	0.017	0.962
$VE_{>20}$	0.937	0.945	0.038	0.034	0.949	0.942	0.949	0.034	0.032	0.950

Table 3 shows the results. The estimators for θ_1 and $VE_{>20}$ are slightly biased when stabilized weights are set equal to one, although coverage probability for the latter is at the nominal level. This feature is mitigated by use of estimated stabilized weights. Coverage probability for θ_1 is somewhat lower than nominal. Under (b), empirical Type I error achieved by a Wald test at level of significance 0.05 of $H_0 : \theta_1 \leq 0$ versus $H_1 : \theta_1 > 0$. is 0.122 when stabilized weights are equal to one, demonstrating the potential for biased inference; Type I error is 0.065 using estimated stabilized weights, leading to a more reliable test.

7 Discussion

We have proposed a conceptual framework based on potential outcomes for study of VE in which assumptions on biological, behavioral, and other phenomena are made transparent. The corresponding statistical framework combines information from blinded and unblinded participants over time. We focus on the setting of the Moderna phase 3 trial, but the principles can be adapted to other settings, including the blinded crossover design of Follmann et al. (2020). The methods provide a mechanism to account for possible confounding.

Through condition (ii) in Section 3, (ii) $E\{\pi_1(t,\tau)|X\}/E\{\pi_0(t)|X\} = q(\tau)$, the methods embed the assumption that VE is similar across current and emerging viral variants. If the analyst is unwilling to adopt an assumption like condition (ii), then it is not possible to rule out that the data from the blinded (prior to $\mathcal{T}_P$) and unblinded (starting at $\mathcal{T}_P$ phases of the trial reflect very different variant mixtures. In this case, calendar time and time since vaccination cannot be disentangled, and thus it is not possible to

evaluate VE solely as a function of time since vaccination. However, it may be possible to evaluate the ratio of infection rates under vaccine at any time t (and thus variant mixture in force at t) after different times since vaccination τ_1 and τ_2, say, during the unblinded phase of the trial, namely, $\mathcal{I}_1^u(t, \tau_1)/\mathcal{I}_1^u(t, \tau_2)$, $t \geq \mathcal{T}_P$. The infection rates can be estimated based on the infection status data at time t from vaccinated individuals who received vaccine at times $t - \tau_1$ and $t - \tau_2$, respectively. These infection rates and their ratio will reflect information about the waning of the vaccine itself under the conditions at time t, and in fact this infection rate ratio can be viewed as the ratio of vaccine efficacies at τ_1 and τ_2. However, because after $\mathcal{T}_C$ information on $\mathcal{I}_0^u(t)$ will no longer be available, it is not possible to deduce VE itself for $t \geq \mathcal{T}_C$. But if data external to the trial became available that provide information on VE at t, even for small τ, it may be possible to integrate this information with that from the infection rates to gain insight into VE as a function of τ.

Acknowledgements

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Appendix A: Demonstration of (2) and (3)

We demonstrate that, under the conditions in Section 3 of the main paper, namely,

(i) $\{\pi_1(t,\tau), \pi_0(t)\} \perp\!\!\!\perp \{S, c^b(t)\}|X$ and $\{\pi_1(t,\tau), \pi_0(t)\} \perp\!\!\!\perp \{S, c^u_{1\ell}(t), c^u_1(t)\}|X$,

(ii) $E\{\pi_1(t,\tau)|X\}/E\{\pi_0(t)|X\} = q(\tau)$,

that (2) of the main paper,

$$\mathcal{R}^b(t,\tau) = \frac{\mathcal{I}^b_1(t,\tau)}{\mathcal{I}^b_0(t)} = \frac{E\{p(t,S)c^b(t)\pi_1(t,\tau)\}}{E\{p(t,S)c^b(t)\pi_0(t)\}} \tag{A.1}$$

does not depend on t, and the second equality in (3) of the main paper,

$$\frac{\mathcal{I}^u_1(t,\tau_1)}{\mathcal{I}^u_1(t,\tau_2)} = \frac{E\{p(t,S)c^u_1(t)\pi_1(t,\tau_1)\}}{E\{p(t,S)c^u_1(t)\pi_1(t,\tau_2)\}} = \frac{\mathcal{R}^b(\tau_1)}{\mathcal{R}^b(\tau_2)}, \quad \tau_1, \tau_2 \geq \ell; \tag{A.2}$$

the first equality in (3) of the main paper follows by an entirely similar argument.

We can write (A.1) using condition (i) as

$$\mathcal{R}^b(t,\tau) = \frac{E\big[E\{p(t,S)c^b(t)|X\}E\{\pi_1(t,\tau)|X\}\big]}{E\big[E\{p(t,S)c^b(t)|X\}E\{\pi_0(t)|X\}\big]}.$$

21

By condition (ii), $E\{\pi_1(t,\tau)|X\} = E\{\pi_0(t)|X\}q(\tau)$; thus, substituting yields

$$\mathcal{R}^b(t,\tau) = \frac{E\big[E\{p(t,S)c^b(t)|X\}E\{\pi_0(t)|X\}\big]q(\tau)}{E\big[E\{p(t,S)c^b(t)|X\}E\{\pi_0(t)|X\}\big]} = q(\tau),$$

so that in fact $q(\tau) = \mathcal{R}^b(\tau)$.

We can write (A.2) as

$$\frac{E\big[E\{p(t,S)c_1^u(t)|X\}E\{\pi_1(t,\tau_1)|X\}\big]}{E\big[E\{p(t,S)c_1^u(t)|X\}E\{\pi_1(t,\tau_2)|X\}\big]}.$$

Under condition (ii), $E\{\pi_1(t,\tau_j)|X\} = E\{\pi_0(t)|X\}q(\tau_j)$, $j = 1,2$; thus, substituting these equalities yields

$$\frac{E\big[E\{p(t,S)c_1^u(t)|X\}E\{\pi_0(t)|X\}q(\tau_1)\big]}{E\big[E\{p(t,S)c_1^u(t)|X\}E\{\pi_0(t)|X\}q(\tau_2)\}\big]} = \frac{q(\tau_1)}{q(\tau_2)} = \frac{\mathcal{R}^b(\tau_1)}{\mathcal{R}^b(\tau_2)},$$

as required.

Appendix B: Discussion of Assumptions

The conceptual framework in Section 3 of the main paper in which we define vaccine efficacy at a particular time since vaccination relies on some assumptions. Of critical importance is the assumption referred to as condition (ii), namely,

$$E\{\pi_1(t,\tau)|X\}/E\{\pi_0(t)|X\} = q(\tau), \tag{B.1}$$

which states that the ratio of transmission probabilities over time within values of X does not change with time and does not depend on characteristics in X but depends only on time since vaccination.

As noted in Section 3 of the main paper, in our conceptualization, we let the individual-specific transmission probabilities $\pi_1(t,\tau)$ and $\pi_0(t)$ depend on t to reflect an evolving mixture of viral variants as mutations of the virus occur over the course of the pandemic, under which the overall virulence of virus to which individuals in the study population may be exposed is changing. From this point of view, we can regard time t as a "proxy" for this changing variant mixture and its virulence as the study progresses. If in fact the overall virulence of the variant mixture does not change or changes only gradually over time, then it may be reasonable to take $\pi_1(t,\tau) = \pi_1(\tau)$ and $\pi_0(t) = \pi_0$. In this case, the ratio $E\{\pi_1(t,\tau)|X\}/E\{\pi_0(t)|X\}$ in (B.1) is a function only of τ and X. If instead the variant mixture does change over the course of the study in a non-trivial way, taking $\pi_1(t,\tau)$ and $\pi(t)$ not to depend on t is untenable. However, if within the mixture of variants present at any time t we are willing to assume that the ratio of transmission probabilities between vaccine and placebo stays in constant proportion for all variants, it again is reasonable to assume that $E\{\pi_1(t,\tau)|X\}/E\{\pi_0(t)|X\}$ does not depend on t so is a function only of τ and X.

Under either of these perspectives, for (B.1) to hold, we furthermore must be willing to assume that $E\{\pi_1(t,\tau)|X\}/E\{\pi_0(t)|X\}$ does not depend on X (in addition to not depending on t) and thus depends only on τ. Adopting (B.1) is similar in spirit to making the assumptions embodied in many popular models; e.g., a constant odds ratio over categories in the proportional odds model or a constant hazard ratio over time in the proportional hazards model. If (B.1) is violated in that $E\{\pi_1(t,\tau)|X\}/E\{\pi_0(t)|X\}$ does depend on X (but not on t), the implication for the proposed methods is that, in estimating VE assuming it depends only on τ, one is estimating roughly a weighted average of VE as a function of τ over values of X in a manner similar to the Mantel-Haenzel method; such an interpretation is also commonly invoked when the proportional odds or hazards assumptions do not hold.

If the analyst is unwilling to adopt an assumption like that in (B.1), then it is not possible to rule out that the data from the blinded (prior to $\mathcal{T}_P$) and unblinded (starting at $\mathcal{T}_P$, when unblinding requests commenced following the Pfizer EUA) phases of the trial reflect very different variant mixtures. In this case, calendar time and time since vaccination cannot be disentangled, and thus it is not possible to evaluate vaccine efficacy solely as a function of time since vaccination. In this setting, however, it may be possible to evaluate the ratio of infection rates under vaccine at any time t (and thus variant mixture in force at t) after different times since vaccination $\tau_1 \geq \ell$ and $\tau_2 \geq \ell$, say, during the unblinded phase of the trial, namely,

$$\mathcal{I}_1^u(t,\tau_1)/\mathcal{I}_1^u(t,\tau_2), \quad t \geq \mathcal{T}_P.$$

The infection rates in this ratio presumably can be estimated based on the infection status data at time t from vaccinated individuals who received vaccine at times $t - \tau_1$ and $t - \tau_2$, respectively. These infection rates and their ratio will reflect information about the waning of the vaccine itself under the conditions at time t, and in fact this infection rate ratio can be viewed as the ratio of vaccine efficacies at different values τ_1 and τ_2. However, because after $\mathcal{T}_C$ information on $\mathcal{I}_0^u(t)$ will no longer be available, it is not possible to deduce vaccine efficacy itself for $t \geq \mathcal{T}_C$. But if data external to the trial became available that provide information on vaccine efficacy at t, even for small τ it may be possible to integrate this information with that from the infection rates to gain insight into vaccine efficacy itself as a function of τ.

Appendix C: Approximate Equivalence of Hazard Rate and Infection Rate

As an example, consider $\lambda_0(t, e) = \lambda_0(t, e, \infty)$ defined in (9) of the main paper. From Section 3 of the main paper, the individual-specific infection rate for an arbitrary subject in the study population at site S who receives placebo and is never unblinded ($r = \infty$) is given by $p(t, S)c^b(t)\pi_0(t)$. This quantity is a random variable defined for the population Ω with probability $\{P(\omega) : \omega \in \Omega\}$, where we view ω as an individual in Ω. Thus, the infection rate for $\omega \in \Omega$ is $\iota_0(t)(\omega) = p\{t, S(\omega)\}c^b(t)(\omega)\pi_0(t)(\omega)$, and the population-level infection rate is given by

$$E\{\iota_0(t)\} = \int_\Omega \iota_0(t)(\omega) \, dP(\omega).$$

In contrast, the hazard at time t is defined by

$$\lambda_0(t, e) = -\frac{d}{dt} \log \left[\mathrm{pr}\{T_0^*(e) + e \geq t\} \right],$$

where

$$\mathrm{pr}\{T_0^*(e) + e \geq t\} = \int_\Omega \mathrm{pr}\{T_0^*(e)(\omega) + e \geq t\} \, dP(\omega).$$

If ω is at risk of infection at time t, then this individual's hazard of becoming infected at t is given by $\iota_0(t)(\omega)$. Thus,

$$\mathrm{pr}\{T_0^*(e)(\omega) + e \geq t\} = \exp\left\{ -\int_e^t \iota_0(u)(\omega) \, du \right\}.$$

We make the rare infection assumption

$$\int_0^L \iota_0(t)(\omega) \, du < \epsilon \quad \text{a.s.} \tag{C.1}$$

Now

$$\lambda_0(t, e) = \frac{\int_\Omega G(t)(\omega)\iota_0(t)(\omega) \, dP(\omega)}{\int_\Omega G(t)(\omega) \, dP(\omega)},$$

where, using the rare infection assumption,

$$G(t)(\omega) = \exp\left\{ -\int_e^t \iota_0(u)(\omega) \, du \right\} \geq \exp(-\epsilon) > 1 - \epsilon \quad \text{a.s.}$$

Because

$$\int_\Omega G(t)(\omega)\iota_0(t)(\omega) \, dP(\omega) \leq \int_\Omega \iota_0(t)(\omega) \, dP(\omega)$$

and $G(t)(\omega) > 1 - \epsilon$ a.s.,

$$\lambda_0(t, e) \leq \frac{\int_\Omega \iota_0(t)(\omega) \, dP(\omega)}{1 - \epsilon}.$$

Moreover, because

$$\int_\Omega G(t)(\omega)\iota_0(t)(\omega)\,dP(\omega) > (1-\epsilon)\int_\Omega \iota_0(t)(\omega)\,dP(\omega)$$

and $\int_\Omega G(t)(\omega)\,dP(\omega) \le 1$,

$$\lambda_0(t,e) \ge (1-\epsilon)\int_\Omega \iota_0(t)(\omega)\,dP(\omega).$$

Thus,

$$(1-\epsilon) < \frac{\lambda_0(t,e)}{\int_\Omega \iota_0(t)(\omega)\,dP(\omega)} < (1-\epsilon)^{-1}.$$

Consequently, under the rare infection assumption (C.1), the population-level infection rate and the population-level hazard rate are of the same order of magnitude.

Appendix D: Derivation of Estimating Functions (12)-(14)

We present derivations leading to the estimating functions (12)-(14) based on potential outcomes given in Section 4.2 of the main paper. Because interest focuses on $\tau \ge \ell$, from (10) and (11) of the main paper, we are concerned only with $\Lambda^b(t)$, $\Lambda^u(t)$, and θ. Accordingly, to determine appropriate linear combinations of the mean-zero counting process increments $\{dN_a^*(t,e,r) - d\Lambda_a(t,e,r)Y_a^*(t,e,r)\}$, $a = 0,1$, we must deduce relevant values of t, e, and r, where $e \le \mathcal{T}_A$ and $\mathcal{T}_P \le r < \mathcal{T}_C$ by design. For $a = 0$, from (10) of the main paper, the relevant values are $t < r$ or $t \ge \ell + r$ and $e \le \min(t,r)$. For $a = 1$, from (11) of the main paper, $e + \ell \le t \le r$ and $t > r$.

Consider for fixed $0 \le t \le L$, $a = 0,1$, integrals of the form

$$\iint \{dN_a^*(t,e,r) - d\Lambda_a(t,e,r)Y_a^*(t,e,r)\}\, w_a(t,e,r)\, dr\, de, \tag{D.1}$$

where $w_a(t,e,r)$ is a non-negative weight function, $a = 0,1$. We determine the limits of integration for (D.1) by considering three time periods.

When $t < \mathcal{T}_P$, at which point all trial participants are still blinded, so that $t < r$, (D.1) for $a = 0$ becomes, using (10) of the main paper and the consistency assumptions below (11) of the main paper,

$$\int_0^{\min(t,\mathcal{T}_A)} \int_{\mathcal{T}_P}^{\mathcal{T}_C} \{dN_0^*(t,e) - d\Lambda^b(t)Y_0^*(t,e)\}\, w_0(t,e,r)\, dr\, de$$

$$= \int_0^{\min(t,\mathcal{T}_A)} \{dN_0^*(t,e) - d\Lambda^b(t)Y_0^*(t,e)\}\, \widetilde{w}_0(t,e)\, de, \tag{D.2}$$

where for $t < \mathcal{T}_P$

$$\widetilde{w}_0(t,e) = \int_{\mathcal{T}_P}^{\mathcal{T}_C} w_0(t,e,r)\, dr.$$

For $a = 1$, $\ell \leq t < \mathcal{T}_P$ shows that (D.1) becomes, using (11) of the main paper,

$$\int_0^{\min(t-\ell,\mathcal{T}_A)} \int_{\mathcal{T}_P}^{\mathcal{T}_C} \left[dN_1^*(t,e) - d\Lambda^b(t) \exp\{\theta_0 + g(t - e - \ell; \theta_1)\} Y_1^*(t,e) \right] w_1(t,e,r) \, dr \, de$$

$$= \int_0^{\min(t-\ell,\mathcal{T}_A)} \left[dN_1^*(t,e) - d\Lambda^b(t) \exp\{\theta_0 + g(t - e - \ell; \theta_1)\} Y_1^*(t,e) \right] \widetilde{w}_1(t,e) \, de, \qquad \text{(D.3)}$$

where for $t < \mathcal{T}_P$

$$\widetilde{w}_1(t,e) = \int_{\mathcal{T}_P}^{\mathcal{T}_C} w_1(t,e,r) \, dr.$$

Next consider $\mathcal{T}_P \leq t < \mathcal{T}_C$; at times in this interval, some participants are still blinded while others have become unblinded. We consider both $t < r$, so before unblinding, and $t \geq r$, after unblinding at time r. First consider (D.1) with $a = 0$. For $t < r$, (D.1) becomes

$$\int_0^{\mathcal{T}_A} \int_t^{\mathcal{T}_C} \{dN_0^*(t,e) - d\Lambda^b(t) Y_0^*(t,e)\} w_0(t,e,r) \, dr \, de$$

$$= \int_0^{\mathcal{T}_A} \{dN_0^*(t,e) - d\Lambda^b(t) Y_0^*(t,e)\} \widetilde{w}_0(t,e) \, de, \qquad \text{(D.4)}$$

where for $\mathcal{T}_P \leq t < \mathcal{T}_C$

$$\widetilde{w}_0(t,e) = \int_t^{\mathcal{T}_C} w_0(t,e,r) \, dr.$$

Similarly, for $a = 1$, $t < r$, (D.1) becomes

$$\int_0^{\mathcal{T}_A} \left[dN_1^*(t,e) - d\Lambda^b(t) \exp\{\theta_0 + g(t - e - \ell; \theta_1)\} Y_1^*(t,e) \right] \widetilde{w}_1(t,e) \, de, \qquad \text{(D.5)}$$

where for $\mathcal{T}_P \leq t < \mathcal{T}_C$

$$\widetilde{w}_1(t,e) = \int_t^{\mathcal{T}_C} w_1(t,e,r) \, dr.$$

Continuing to consider $\mathcal{T}_P + \ell \leq t < \mathcal{T}_C$, now take $t \geq r$. For $a = 0$, (D.1) becomes

$$\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{t-\ell} \left[dN_0^*(t,e,r) - d\Lambda^u(t) \exp\{g(t - r - \ell; \theta_1) \mathrm{I}(t - r \geq \ell)\} Y_0^*(t,e,r) \right] w_0(t,e,r) \, dr \, de, \qquad \text{(D.6)}$$

For $a = 1$, (D.1) becomes

$$\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^t \left[dN_1^*(t,e,r) - d\Lambda^u(t) \exp\{g(t - e - \ell; \theta_1)\} Y_1^*(t,e,r) \right] w_1(t,e,r) \mathrm{I}(t \geq r) \, dr \, de, \qquad \text{(D.7)}$$

Finally, consider $t \geq \mathcal{T}_C$; these are times where all participants are unblinded. Thus, when $a = 0$, (D.1) equals

$$\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\min((t-\ell,\mathcal{T}_C)} \left[dN_0^*(t,e,r) - d\Lambda^u(t) \exp\{g(t - r - \ell; \theta_1) \mathrm{I}(t - r \geq \ell)\} Y_0^*(t,e,r) \right] w_0(t,e,r) \, dr \, de,$$

$$\text{(D.8)}$$

and when $a = 1$ equals

$$\int_0^{\mathcal{T}_A} \int_{\mathcal{T}_P}^{\mathcal{T}_C} \left[dN_1^*(t,e,r) - d\Lambda^u(t) \exp\{g(t - e - \ell; \theta_1)\} Y_1^*(t,e,r) \right] w_1(t,e,r) \mathrm{I}(t \geq r) \, dr \, de. \tag{D.9}$$

Combining (D.2)-(D.5) yields estimating function $\mathcal{E}_{\Lambda^b}\{W^*; \Lambda^b(t), \theta\}$ in (12) of the main paper. Combining (D.6)-(D.9) yields $\mathcal{E}_{\Lambda^u}\{W^*; \Lambda^u(t), \theta\}$ in (13) of the main paper. Estimating function $\mathcal{E}_\theta\{W^*; \Lambda^b(\cdot)\Lambda^u(\cdot), \theta\}$ arises through similar considerations, integrating over t and differentiating with respect to θ_0 and θ_1.

Appendix E: Demonstration of (21)-(24)

We make the assumptions (16)-(20) in Section 4.3 of the main paper. Here, we show the first equalities in (21) and (23), i.e.,

$$E\left\{ \frac{I_0(t,e) dN(t)}{h_0(t,e|X)} \,\middle|\, X, W^* \right\} = dN_0^*(t,e) \tag{E.1}$$

and

$$E\left\{ \frac{I_{01}(t,e,r) dN(t)}{h_{01}(e,r|X)} \,\middle|\, X, W^* \right\} = dN_0^*(t,e,r). \tag{E.2}$$

Demonstration of the other equalities in (21)-(24) follows by analogous arguments.

We first show (E.1). By the consistency assumption (16) in the main paper, the left hand side of (E.1) is equal to

$$E\left\{ \frac{I_0(t,e) dN_0^*(t,e)}{h_0(t,e|X)} \,\middle|\, X, W^* \right\} = \frac{dN_0^*(t,e)}{h_0(t,e|X)} E\{I_0(t,e)|X, dN_0^*(t,e) = 1, W^*\}.$$

The result follows if we show that

$$E\{I_0(t,e)|X, dN_0^*(t,e) = 1, W^*\} = h_0(t,e|X). \tag{E.3}$$

By (15) of the main paper, the left hand side of (E.3) is computed as

$$\mathrm{pr}\{E = e|X, dN_0^*(t,e) = 1, W^*\} \tag{E.4}$$
$$\times \mathrm{pr}\{A = 0|X, E, dN_0^*(t,e) = 1, W^*\} \tag{E.5}$$
$$\times \mathrm{pr}\{R > t|X, A = 0, dN_0^*(t,e) = 1, W^*\}, \tag{E.6}$$

where we have used the assumption discussed above (19) in the main paper in (E.6). By (17) of the main paper, (E.5) is equal to $\mathrm{pr}(A = 0) = 1 - p_A$. By (17) and (18) of the main paper, (E.4) is equal to $f_{E|X}(e|X)$. The proof will be complete by showing that (E.6) is equal to $\mathcal{K}_R(t|X, A = 0)$.

To demonstrate this, we consider $t < \mathcal{T}_P$, $\mathcal{T}_p \leq t < \mathcal{T}_U$, $\mathcal{T}_U \leq t < \mathcal{T}_C$, and $t \geq \mathcal{T}_C$ in turn. Clearly (E.6) is equal to 1 for $t < \mathcal{T}_P$. Because the estimating function using $I_0(t,e)$ is defined only for $t < \mathcal{T}_C$,

we need not consider $t \geq \mathcal{T}_C$. Thus, we need only consider the cases $\mathcal{T}_p \leq t < \mathcal{T}_U$ and $\mathcal{T}_U \leq t < \mathcal{T}_C$. For $\mathcal{T}_P \leq t < \mathcal{T}_U$, we write (E.6) as a product integral as in Anderson et al. (1993) and use an argument similar to that in (8.72)-(8.77) of Tsiatis et al. (2020):

$$\prod_{\mathcal{T}_P \leq w < t} [1 - \mathrm{pr}\{w \leq R < w + dw | R \geq w, X, A = 0, dN_0^*(t, e) = 1, W^*\}]$$

$$= \prod_{\mathcal{T}_P \leq w < t} [1 - \mathrm{pr}\{w \leq R < w + dw, \Gamma = 1 | R \geq w, X, A = 0, dN_0^*(t, e) = 1, W^*\}] \qquad \text{(E.7)}$$

$$= \prod_{\mathcal{T}_P \leq w < t} [1 - \lambda_{R,1}\{w | X, A = 0, dN_0^*(t, e) = 1, W^*\} dw]$$

$$= \prod_{\mathcal{T}_P \leq w < t} \{1 - \lambda_{R,1}(w | X, A = 0) \, dw\} \qquad \text{(E.8)}$$

$$= \exp\left\{-\int_{\mathcal{T}_P}^{t} \lambda_{R,1}(w | X, A = 0) \, dw\right\} = \mathcal{K}_{R,1}(t | X, A = 0) = \mathcal{K}_R(t | X, A = 0),$$

where (E.7) follows because, if $dN_0^*(t, e) = 1$ and $A = 0$, then the individual could not have been infected before time t, and thus for $\mathcal{T}_P \leq t < \mathcal{T}_U$, the only way R could fall between w and $w + dw$ is if s/he were unblinded during this period, in which case $\Gamma = 1$. (E.8) holds because of assumption (19) of the main paper. Thus, (E.6) holds for $\mathcal{T}_P \leq t < \mathcal{T}_U$. Finally, for $\mathcal{T}_U \leq t < \mathcal{T}_C$, write (E.6) as

$$\mathrm{pr}\{R \geq \mathcal{T}_U | X, A = 0, dN_0^*(t, e) = 1, W^*\} \qquad \text{(E.9)}$$

$$\times \mathrm{pr}\{R > t | R \geq \mathcal{T}_U, X, A = 0, dN_0^*(t, e) = 1, W^*\}. \qquad \text{(E.10)}$$

From the previous argument, (E.9) is equal to $\mathcal{K}_{R,1}(\mathcal{T}_U | X, A = 0)$, and (E.10) can be written as a product integral, namely,

$$\prod_{\mathcal{T}_U \leq w < t} [1 - \mathrm{pr}\{w \leq R < w + dw | R \geq w, X, A = 0, dN_0^*(t, e) = 1, W^*\}],$$

where, using an argument analogous to that above, (E.10) can be shown to be equal to $\mathcal{K}_{R,2}(t | X, A = 0)$. Thus the product of (E.9) and (E.10) is equal to $\mathcal{K}_{R,1}(\mathcal{T}_U | X, A = 0)\mathcal{K}_{R,2}(t | X, A = 0) = \mathcal{K}_R(t | X, A = 0)$ for $\mathcal{T}_U \leq t < \mathcal{T}_C$, completing the proof.

We now show (E.2). By the consistency assumption (16) in the main paper, the left hand side of (E.2) is

$$E\left\{\frac{I_{01}(t, e, r) dN_0^*(t, e, r)}{h_{01}(e, r | X)} \, \middle| \, X, W^*\right\} = \frac{dN_0^*(t, e, r)}{h_{01}(e, r | X)} E\{I_{01}(t, e, r) | X, dN_0^*(t, e, r) = 1, W^*\}.$$

The result will follow if we can show that

$$E\{I_{01}(t, e, r) | X, dN_0^*(t, e, r) = 1, W^*\} = h_{01}(e, r | X). \qquad \text{(E.11)}$$

By (15) of the main paper, the left hand side of (E.11) is computed as

$$\text{pr}\{E = e|X, dN_0^*(t, e, r) = 1, W^*\} \tag{E.12}$$

$$\times \text{pr}\{A = 0|X, E, dN_0^*(t, e, r) = 1, W^*\} \tag{E.13}$$

$$\times \Big[\text{pr}\{R = r, \Gamma = 1|X, A = 0, dN_0^*(t, e, r) = 1, W^*\} \tag{E.14}$$

$$\times \text{pr}\{\Psi = 1|X, A = 0, \Gamma = 1, dN_0^*(t, e, r) = 1, W^*\} \tag{E.15}$$

$$+ \text{pr}\{R = r, \Gamma = 2|X, A = 0, dN_0^*(t, e, r) = 1, W^*\} \tag{E.16}$$

$$\times \text{pr}\{\Psi = 1|X, A = 0, \Gamma = 2, dN_0^*(t, e, r) = 1, W^*\} \Big]. \tag{E.17}$$

As in the proof of (E.1), (E.13) is equal to $(1 - p_A)$, and (E.12) is equal to $f_{E|X}(e|X)$. By definition, R is only defined for values of r between $\mathcal{T}_P$ and $\mathcal{T}_C$. For $\mathcal{T}_P \leq r < \mathcal{T}_U$, Γ must be equal to 1, in which case the product of (E.16) and (E.17) is equal to zero. For $\mathcal{T}_U \leq r < \mathcal{T}_C$, Γ must equal 2, in which case the product of (E.14) and (E.15) is equal to zero. By assumption (20) of the main paper, (E.15) is equal to $p_\Psi(X, A = 0, \Gamma = 1)$, whereas (E.14) can be written as a product integral

$$\prod_{\mathcal{T}_P \leq w < r} [1 - \text{pr}\{w \leq R < w + dw|R \geq w, X, A = 0, dN_0^*(t, e, r) = 1, W^*\}]$$

$$\times \text{pr}\{r \leq R \leq r + dr, \Gamma = 1|R \geq r, X, A = 0, dN_0^*(t, e, r) = 1, W^*\}$$

$$= \prod_{\mathcal{T}_P \leq w < r} [1 - \text{pr}\{w \leq R < w + dw, \Gamma = 1|R \geq w, X, A = 0, dN_0^*(t, e, r) = 1, W^*\}]$$

$$\times \text{pr}\{r \leq R \leq r + dr, \Gamma = 1|R \geq r, X, A = 0, dN_0^*(t, e, r) = 1, W^*\} \tag{E.18}$$

$$= \prod_{\mathcal{T}_P \leq w < r} [1 - \lambda_{R,1}\{w|X, A = 0, dN_0^*(t, e, r) = 1, W^*\}dw]$$

$$\times \lambda_{R,1}\{r|X, A = 0, dN_0^*(t, e, r) = 1, W^*\}dr$$

$$= \prod_{\mathcal{T}_P \leq w < r} \{1 - \lambda_{R,1}(w|X, A = 0)\,dw\}\lambda_{R,1}(r|X, A = 0)\,dr \tag{E.19}$$

$$= \exp\left\{-\int_{\mathcal{T}_P}^r \lambda_{R,1}(w|X, A = 0)\,dw\right\}\lambda_{R,1}(r|X, A = 0)\,dr = f_{R,1}(r|X, A = 0),$$

where (E.18) follows because, if $dN_0^*(t, e, r) = 1$ and $A = 0$, then the individual could not have been infected before time r. This implies that the only way R could fall between w and $w + dw$, for $w < r$, is if unblinding occurred in this period, in which case $\Gamma = 1$. (E.19) holds because of assumption (19) of the main paper. Thus, (E.11) holds for $\mathcal{T}_P \leq r < \mathcal{T}_U$. Analogous arguments can be used to show that, when $\mathcal{T}_U \leq t < \mathcal{T}_C$, the product of (E.16) and (E.17) is equal to $f_{R,2}(r|X, A = 0)p_\Psi(X, A = 0, \Gamma = 2)$, thus demonstrating that (E.11) holds for $\mathcal{T}_U \leq r < \mathcal{T}_C$, completing the proof.

Appendix F: Implementation and Large Sample Properties

We present a heuristic argument to establish the large-sample properties of the estimator $\widehat{\theta}$ solving (30) of the main paper, namely,

$$\sum_{i=1}^{n}\left[\int_{0}^{\mathcal{T}_C}\{Z_i^b(t)-\overline{Z}^b(t)\}d\widetilde{N}_i^b(t)+\int_{\mathcal{T}_P}^{L}\{Z_i^u(t)-\overline{Z}^u(t)\}d\widetilde{N}_i^u(t)\right]=0, \tag{F.1}$$

$$\overline{Z}^b(t)=\left\{\sum_{i=1}^{n}\widetilde{Y}_i^b(t)\right\}^{-1}\sum_{i=1}^{n}Z_i^b(t)\widetilde{Y}_i^b(t),\quad \overline{Z}^u(t)=\left\{\sum_{i=1}^{n}\widetilde{Y}_i^u(t)\right\}^{-1}\sum_{i=1}^{n}Z_i^u(t)\widetilde{Y}_i^u(t).$$

The estimating equation (F.1) can be written equivalently as

$$\sum_{i=1}^{n}\left[\int_{0}^{\mathcal{T}_C}\{Z_i^b(t)-\overline{Z}^b(t)\}\{d\widetilde{N}_i^b(t)-d\Lambda^b(t)\widetilde{Y}_i^b(t)\}\right.$$

$$\left.+\int_{\mathcal{T}_P}^{L}\{Z_i^u(t)-\overline{Z}^u(t)\}\{d\widetilde{N}_i^u(t)-d\Lambda^u(t)\widetilde{Y}_i^u(t)\}\right]=0, \tag{F.2}$$

which follows because

$$\sum_{i=1}^{n}\{Z_i^k(t)-\overline{Z}^k(t)\}\widetilde{Y}_i^k(t)=0,\quad k=b,u.$$

Letting $\mu^k(t)$ be the limit in probability of $\overline{Z}^k(t)$ $k=b,u$, then the left hand side of (F.2) can be written as

$$\sum_{i=1}^{n}\left[\int_{0}^{\mathcal{T}_C}\{Z_i^b(t)-\mu^b(t)\}\{d\widetilde{N}_i^b(t)-d\Lambda^b(t)\widetilde{Y}_i^b(t)\}\right.$$

$$\left.+\int_{\mathcal{T}_P}^{L}\{Z_i^u(t)-\mu^u(t)\}\{d\widetilde{N}_i^u(t)-d\Lambda^u(t)\widetilde{Y}_i^u(t)\}\right] \tag{F.3}$$

$$-\sum_{i=1}^{n}\left[\int_{0}^{\mathcal{T}_C}\{\overline{Z}^b(t)-\mu^b(t)\}\{d\widetilde{N}_i^b(t)-d\Lambda^b(t)\widetilde{Y}_i^b(t)\}\right.$$

$$\left.+\int_{\mathcal{T}_P}^{L}\{\overline{Z}^u(t)-\mu^u(t)\}\{d\widetilde{N}_i^u(t)-d\Lambda^u(t)\widetilde{Y}_i^u(t)\}\right]=0. \tag{F.4}$$

Because $E\{d\widetilde{N}_i^k(t)-d\Lambda^k(t)\widetilde{Y}_i^k(t)\}=0$, and $\{\overline{Z}^k(t)-\mu^k(t)\}$ converges in probability to zero $k=b,u$, (F.4) is a small order term that can be ignored in the sense that $n^{-1/2}\times(F.4)$ converges in probability to zero. Thus, solving (F.2) is asymptotically equivalent to setting (F.3) equal to zero. Letting $\theta^{(0)}$ denote the true value of θ under the assumption that the semiparametric model (6) of the main paper is correctly specified, then (F.3) is a sum of mean-zero independent and identically distributed (iid) terms

$$\psi(O_i;\theta)=\int_{0}^{\mathcal{T}_C}\{Z_i^b(t)-\mu^b(t)\}\{d\widetilde{N}_i^b(t)-d\Lambda^b(t)\widetilde{Y}_i^b(t)\}$$

$$+\int_{\mathcal{T}_P}^{L}\{Z_i^u(t)-\mu^u(t)\}\{d\widetilde{N}_i^u(t)-d\Lambda^u(t)\widetilde{Y}_i^u(t)\}, \tag{F.5}$$

where $E\{\psi(O_i; \theta^{(0)})\} = 0$. Thus, the estimator $\widehat{\theta}$ solving the asymptotically equivalent estimating equation

$$\sum_{i=1}^{n} \psi(O_i; \theta) = 0$$

satisfies, by a standard Taylor series expansion,

$$0 = \sum_{i=1}^{n} \psi(O_i, \widehat{\theta}) \approx \sum_{i=1}^{n} \psi(O_i, \theta^{(0)}) + \left\{ \sum_{i=1}^{n} \frac{\partial \psi(O_i, \theta_0)}{\partial \theta^T} \right\} (\widehat{\theta} - \theta^{(0)}).$$

As a consequence,

$$n^{1/2}(\widehat{\theta} - \theta^{(0)}) = \left[-E \left\{ \frac{\partial \psi(O_i, \theta^{(0)})}{\partial \theta^T} \right\} \right]^{-1} n^{-1/2} \sum_{i=1}^{n} \psi(O_i, \theta^{(0)}) + o_P(1), \tag{F.6}$$

which implies that $\widehat{\theta}$ is asymptotically normal with mean zero and covariance matrix

$$\left[-E \left\{ \frac{\partial \psi(O_i, \theta^{(0)})}{\partial \theta^T} \right\} \right]^{-1} \text{var}\{\psi(O_i, \theta^{(0)})\} \left(\left[-E \left\{ \frac{\partial \psi(O_i, \theta^{(0)})}{\partial \theta^T} \right\} \right]^{-1} \right)^T, \tag{F.7}$$

where $\text{var}\{\psi(O_i, \theta^{(0)})\} = E\{\psi(O_i, \theta^{(0)})\psi(O_i, \theta^{(0)})^T\}$.

An estimator for the asymptotic variance (F.7) can be obtained as follows. The term $\text{var}\{\psi(O_i, \theta^{(0)})\}$ can be estimated by

$$\widehat{\text{var}}\{\psi(O_i, \theta^{(0)})\} = n^{-1} \sum_{i=1}^{n} \widehat{\psi}_i(\widehat{\theta}) \widehat{\psi}_i(\widehat{\theta})^T,$$

where $\widehat{\psi}_i(\widehat{\theta})$ is an estimator for $\psi(O_i, \theta^{(0)})$ obtained by substituting (i) $\overline{Z}^k(t)$ for $\mu^k(t)$, $k = b, u$; (ii) $d\widehat{\Lambda}^k(t)$ in (29) of the main paper for $d\Lambda^k(t)$, $k = b, u$; and (iii) $\widehat{\theta}$ for $\theta^{(0)}$. An estimator for

$$E \left\{ \frac{\partial \psi(O_i, \theta^{(0)})}{\partial \theta^T} \right\}$$

is obtained by substitutions (i)–(iii) in this expression and averaging over i, leading to

$$\widehat{E} \left\{ \frac{\partial \psi(O_i, \theta^{(0)})}{\partial \theta^T} \right\} = -n^{-1} \sum_{i=1}^{n} \left\{ \int_0^{\mathcal{T}_C} V^b(t) \, d\widetilde{N}_i^b(t) + \int_{\mathcal{T}_P}^{L} V^u(t) \, d\widetilde{N}_i^u(t) \right\}, \tag{F.8}$$

where

$$V^k(t) = \frac{\sum_{i=1}^{n} \{Z_i^k(t) - \overline{Z}^k(t)\}\{Z_i^k(t) - \overline{Z}^k(t)\}^T \widetilde{Y}_i^k(t)}{\sum_{i=1}^{n} \widetilde{Y}_i^k(t)}, \quad k = b, u.$$

The resulting sandwich estimator for the large sample covariance matrix of $\widehat{\theta}$ is then given by

$$\left[\widehat{E} \left\{ \frac{\partial \psi(O_i, \theta^{(0)})}{\partial \theta^T} \right\} \right]^{-1} \widehat{\text{var}}\{\psi(O_i, \theta^{(0)})\} \left[\widehat{E} \left\{ \frac{\partial \psi(O_i, \theta^{(0)})}{\partial \theta^T} \right\} \right]^{-1}. \tag{F.9}$$

The foregoing developments take the inverse probability weights and thus the stabilized weights to be known. If models for $\lambda_{R,j}(r|X,A)$, $j = 1, 2$, $f_{E|X}(e|X)$, and $p_\Psi(X, \Gamma)$ are posited and fitted and substituted in (F.1), then the large sample distribution of $n^{1/2}(\widehat{\theta} - \theta^{(0)})$ would be considerably more complicated. In simulations, we have observed that standard errors and confidence intervals based on (F.6) and (F.9) reflect the true sampling variation in that their numerical values are consistent with the Monte Carlo sampling variation and confidence intervals achieve the nominal level of coverage. An alternative strategy to obtaining approximate standard errors and confidence intervals would be to use a nonparametric bootstrap.

The result (F.6) suggests a Newton-Raphson iterative scheme for solving the estimating equation (F.1). Letting $\theta_{(0)}$ be an initial value for θ and $\theta_{(m)}$ be the value at the mth iteration, compute the update by

$$\theta_{(m+1)} = \theta_{(m)} - \left[\widehat{E} \left\{ \frac{\partial \psi(O_i, \theta_{(m)})}{\partial \theta^T} \right\} \right]^{-1} \widehat{\psi}_i(\theta_{(m)}).$$

This scheme is iterated until some convergence criterion is satisfied.

Appendix References

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