Estimation of the Odds Ratio in a Proportional Odds Model with Censored Time-lagged Outcome in a Randomized Clinical Trial

Anastasios A. Tsiatis*, Marie Davidian**, and Shannon T. Holloway***

Department of Statistics, North Carolina State University, Raleigh, NC, USA.

*email: tsiatis@ncsu.edu
**email: davidian@ncsu.edu
***email: sthollow@ncsu.edu

Summary: In many randomized clinical trials of therapeutics for COVID-19, the primary outcome is an ordinal categorical variable, and interest focuses on the odds ratio (active agent vs. control) under the assumption of a proportional odds model. Although at the final analysis the outcome will be determined for all subjects, at an interim analysis, the status of some participants may not yet be determined, e.g., because ascertainment of the outcome may not be possible until some pre-specified follow-up time. Accordingly, the outcome from these subjects can be viewed as censored. A valid interim analysis can be based on data only from those subjects with full follow up; however, this approach is inefficient, as it does not exploit additional information that may be available on those for whom the outcome is not yet available at the time of the interim analysis. Appealing to the theory of semiparametrics, we propose an estimator for the odds ratio in a proportional odds model with censored, time-lagged categorical outcome that incorporates additional baseline and time-dependent covariate information and demonstrate that it can result in considerable gains in efficiency relative to simpler approaches. A byproduct of the approach is a covariate-adjusted estimator for the odds ratio based on the full data that would be available at a final analysis.

Key words: Augmented inverse probability weighting; Censored ordinal categorical outcome; Covariate adjustment; COVID-19 treatment; Estimating function; Marked point process

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1. Introduction

The pandemic due to the novel coronavirus SARS CoV-2 has led to an intensive effort to identify and develop treatments for COVID-19, coordinated through the public-private partnership Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV, 2021). Within ACTIV, candidate therapeutics are prioritized and evaluated in clinical trials orchestrated through coordinated master protocols that incorporate a common control arm.

The ACTIV-3b: Therapeutics for Severely Ill Inpatients With COVID-19 (TESICO) Phase 3 master protocol (ClinicalTrials.gov NCT04843761) is focused on evaluation of multiple agents to improve outcomes for patients with acute respiratory failure associated with COVID-19. In a double-blind trial within this protocol, patients hospitalized with acute respiratory distress syndrome (ARDS) are randomized to study agents or placebo and followed for 90 days after study entry. The primary outcome is based on the number of days patients are out of the hospital without need for oxygen over the 90 day period. Because these patients are severely ill, there is a nonnegligible probability of death. Accordingly, the primary outcome is defined as an ordinal categorical variable with death as the worst category (Category 6). The remaining five categories reflect recovery status of the patient at Day 90 following randomization. Categories 1–3 are defined by the number of consecutive days off oxygen. For Category 4, a patient must be out of the hospital at Day 90 but either at home on oxygen or not at home (so continuing to receive care elsewhere). Category 5 patients are hospitalized or in hospice care at Day 90. Table I summarizes the definitions of the categories and the assumed distributions of the outcome for an investigational agent and placebo/control. The primary treatment effect estimand is defined in the master protocol as the odds ratio (OR) of improvement in recovery status at Day 90 for an investigational agent versus placebo under the assumption of a proportional odds model (Agresti, 2019). Under the assumed distributions in Table I, the sample size of 640 was chosen to obtain $n = 602$.
evaluable subjects so as to achieve 80% power to detect an OR of 1.5 using a two-sided test with type 1 error 0.05, accounting for loss to follow-up or withdrawn consent.

[Table 1 about here.]

The trial is monitored by a US government-convened Data and Safety Monitoring Board (DSMB) focused on studies of COVID-19 prevention and therapeutics of which the first author is a member, and interim analyses are to be conducted and reviewed by the DSMB. If all participants are followed for the full 90 days, as would be the case at the conclusion of the trial, the categorical outcome will be known for all, and a standard analysis based on fitting of the proportional odds model can be carried out to draw inference on the OR of interest. However, at the time of an interim analysis, not all subjects will have complete follow up: Because of staggered entry, some will have progressed through the entire 90 day follow-up period, and some may have not yet entered the trial. The status of participants who die during the 90 days (Category 6) will be known immediately at the time of death, but the statuses of subjects not on study for the full 90 days at the time of the analysis will not be known. Thus, information on Category 6 will accumulate more quickly than that on the other outcome categories. A naive analysis based on this differential outcome information could lead to biased inference on the OR; thus, an approach to taking this feature into appropriate account is required.

A simple way to circumvent this potential for biased inference is to carry out the standard analysis based on only the data from those participants who have been on study for the full 90 days. Under this convention, information on deaths occurring for subjects not on study for 90 days would be excluded. Clearly, however, this approach represents an inefficient use of the available data. There may be information from patients who have not died but have not been followed for the full 90 days that could be exploited to increase precision; e.g., if at the time of analysis a participant is at day 45 of follow up and still in the hospital, then it
would be known that his/her status at 90 days can be only in Categories 3–6. The standard analysis would not take advantage of such additional information.

The primary outcome in TESICO is an example of a time-lagged response or marked point process (Huang and Louis, 1998), characterized by the categorical outcome, $Cat$, say, referred to as the mark, and the time from entry into the study $T$ at which the outcome is ascertained, the point process. In TESICO, if the outcome is Category 6, so $Cat = 6$, then $T$ is the time of death; if $Cat = 1, \ldots, 5$, $T = 90$ days. In this article, we take this point of view and develop an estimator for the OR in a proportional odds model with censored, time-lagged categorical outcome. Although we motivate and discuss the methodology in the context of TESICO, it is applicable in any randomized trial where ascertainment of the categorical outcome of interest is possibly censored at the time of analysis.

In Section 2 we define notation and assumptions, and we discuss inference on the OR under the proportional odds model based on full, uncensored data from an estimating equation perspective in Section 3. We then exploit the theory of semiparametrics as in Lu and Tsiatis (2011) in Section 4 to characterize a class of estimating equations through which consistent inference on the OR based on censored, time-lagged categorical outcome data can be achieved; this formulation also leads to an approach to covariate-adjusted inference when the full data are available. In Section 5 we present a practical strategy for implementation of the proposed methods, and we report in Section 6 on a suite of simulation studies demonstrating their performance and in particular their ability to yield unbiased estimators for the OR with enhanced efficiency relative to simpler approaches.

2. **Statistical framework**

Assume that the follow-up time at which status will have been ascertained on any participant is $T_F$; $T_F = 90$ in TESICO. Let $A$ denote a participant’s randomized treatment assignment, taking values 0 (placebo) and 1 (investigational agent), and let $Cat$ denote the category
corresponding to the participant’s status, taking values 1, . . . , c, where c corresponds to death; c = 6 in TESICO. Let T be the time at which status is ascertained, so that T = time of death if Cat = c, and if Cat < c, T = time ≤ T_F at which Cat is determined, which can be different for different categories in general. In TESICO, all non-fatal outcomes are not fully determined until T_F, so T = T_F if Cat = 1, . . . , c − 1. Baseline covariate information also may be recorded on each participant prior to initiation of assigned treatment, including demographic and physiological characteristics, information on severity of illness, and so on.

Letting logit(p) = log{p/(1 − p)}, the proportional odds model assumes that

\[ \logit\{\Pr(\text{Cat} \leq j \mid A)\} = \alpha_j + \beta A, \quad j = 1, \ldots, c - 1. \]  (1)

Under (1), the treatment effect of interest is expressed as the treatment-specific odds ratio \( \exp(\beta) \), where \( \beta \) is the log odds ratio. Consequently, the null hypothesis of no effect of the investigational agent is \( H_0 : \beta = 0 \). In TESICO, the clinically important effect represented by OR = 1.5 corresponds to the alternative hypothesis \( H_A : \beta = \log(1.5) \).

For a trial involving \( n \) participants randomized to the investigational agent with probability \( \Pr(A = 1) = \pi \), if all \( n \) participants were to have complete follow up to time \( T_F \), as would be the case at the time of the final analysis, the full data that would be available for inference on \( \beta \) can be summarized as independent and identically distributed (iid)

\[ F_i = (X_i, A_i, \text{Cat}_i, T_i), \quad i = 1, \ldots, n. \]  (2)

Here, the categorical outcome is known for all \( n \) subjects, and standard methodology for fitting model (1) can be used to estimate \( \alpha = (\alpha_1, \ldots, \alpha_{c-1})^T \) and \( \beta \) and test \( H_0 \); we discuss inference based on the full data (2) in Section 3. Because this inference references only the conditional distribution of \( \text{Cat} \) given \( A \), the data on \( X \) and \( T \) are not required or used. As demonstrated by Benkeser et al. (2021) in the context of COVID-19 therapeutics trials, an alternative covariate-adjusted analysis in which \( X \) is taken into account could yield substantial precision gains; we discuss covariate adjustment in Section 4.
At the time of an interim analysis, some participants will not have complete follow up to time $T_F$. Denote by $C$ the potential censoring time equal to, e.g., the time from study entry to the time of the interim analysis. If a subject has died prior to the time of the interim analysis, then $Cat = c$ is observed, and $T = \text{time of death} \leq C$. Otherwise, if at the time of interim analysis $Cat$ is not yet determined, then $T > C$. Thus, let $U = \min(T, C)$ be the time on study at the time of the analysis and $\Delta = I(T \leq C)$. $Cat$ is observed only if $\Delta = 1$.

In addition to baseline covariates $X$, intermediate, time-dependent information may have been collected through time $U$, while a participant is on study. For example, an indicator of whether or not a patient is in the hospital at $U$ and, if out of the hospital, for how long, will be available. At $u$ time units after study entry, this information can be summarized as a vector of time-dependent covariates $L(u)$, and denote the history of such time-dependent covariates as $\bar{L}(u) = \{L(s); 0 \leq s \leq u\}$. As we demonstrate in the sequel, although such post-randomization information cannot be used as part of the primary final analysis based on the full data (2), it may be advantageous at an interim analysis.

We summarize the observed data available on $n$ participants at the time of an interim analysis as

$$O_i = \{X_i, A_i, U_i, \Delta_i, \Delta_i Cat_i, \bar{L}(U_i)\}, \quad i = 1, \ldots, n.$$ (3)

The statistical challenge, which we address in Section 4, is estimation of the log odds ratio $\beta$ in the proportional odds model (1) based on the observed data (3).

3. Inference based on the full data

In Section 4, we appeal to the theory of semiparametrics to develop an approach to estimation of $\beta$ using the observed data (3) via solution of an estimating equation that exploits information in the baseline and time-dependent covariates $X$ and $\bar{L}(\cdot)$ to enhance efficiency. Following the theory, this observed-data estimating equation is formulated based on a suitably-chosen estimating equation using the full data (2); more precisely, using the subset of the full data
(A_i, Cat_i), i = 1, \ldots, n. Accordingly, we begin by considering an estimator for β obtained by solving an estimating equation based on these full data. That is, we identify a $c$-dimensional estimating function $\mathcal{M}(F; \alpha, \beta)$ satisfying $E_{\alpha, \beta}\{\mathcal{M}(F; \alpha, \beta)\} = 0$ for all $\alpha, \beta$, where this notation indicates expectation taken with respect to the distribution of $F$ evaluated at $\alpha, \beta$, such that solution of the estimating equation

$$
\sum_{i=1}^{n} \mathcal{M}(F_i; \alpha, \beta) = 0
$$

(4)

in $\alpha$ and $\beta$ yields consistent and asymptotically normal estimators $\hat{\alpha}_F$ and $\hat{\beta}_F$, say.

As is well-established (Tsiatis, 2006), generically, there is a correspondence between consistent and asymptotically normal estimators for a finite-dimensional parameter $\theta$ in a statistical model based on data $F_i$, $i = 1, \ldots, n$, and influence functions. Namely, assuming that the statistical model is correctly specified, and letting $\theta_0$ be the true value of $\theta$ generating the data, for a consistent and asymptotically normal estimator $\hat{\theta}$, there exists a function $\varphi(F)$ with $E\{\varphi(F)\} = 0$, referred to as the influence function for $\hat{\theta}$, such that

$$
n^{1/2}(\hat{\theta} - \theta_0) = n^{-1/2} \sum_{i=1}^{n} \varphi(F_i) + o_p(1),
$$

(5)

where $o_p(1)$ is a term that converges in probability to zero, and $E\{\varphi(F)\varphi(F)^T\} < \infty$ is nonsingular. It follows that $n^{1/2}(\hat{\theta} - \theta_0)$ converges in distribution to a mean-zero normal random vector with covariance matrix $E\{\varphi(F)\varphi(F)^T\}$. Estimating functions can be deduced from influence functions, as discussed below.

Identifying $\theta = (\alpha^T, \beta)^T$ and assuming that the proportional odds model (11) holds with true values $\alpha_0$ and $\beta_0$, we now propose a full-data estimating function $\mathcal{M}(F; \alpha, \beta)$ leading to an estimating equation as in (11) and obtain the associated influence function for the resulting estimators $\hat{\theta} = (\hat{\alpha}_F^T, \hat{\beta}_F)^T$. Because our main focus is estimation of $\beta$, based on these, we then deduce the associated estimating function and influence function for the resulting estimator $\hat{\beta}_F$ alone. These quantities play a prominent role in the developments in Section 4.
Let \( R_j = I(C_{\text{at}} \leq j), \ j = 1, \ldots, c - 1 \). The proportional odds model (1) assumes that

\[
E(R_j \mid A) = \expit(\alpha_j + \beta A), \quad j = 1, \ldots, c - 1,
\]

where \( \expit(u) = e^u / (1 + e^u) \). As is well known, from Chapter 4 of Tsiatis (2006), all estimating functions for \((\alpha^T, \beta)^T\) leading to consistent and asymptotically normal estimators can be characterized as

\[
G(A) = \begin{pmatrix}
R_1 - \expit(\alpha_1 + \beta A) \\
\vdots \\
R_{c-1} - \expit(\alpha_{c-1} + \beta A)
\end{pmatrix},
\]

where \( G(A) \) is an arbitrary \((c \times c - 1)\) matrix of functions of \( A \). The optimal choice of \( G(A) \) leading to the most precise estimation asymptotically is given by \( D^T(A; \alpha, \beta) V^{-1}(\alpha, \beta) \), where \( D(A; \alpha, \beta) \) is the \((c - 1 \times c)\) gradient matrix of the elements of \( R_j - \expit(\alpha_j + \beta A), \ j = 1, \ldots, c - 1 \), with respect to \( \alpha \) and \( \beta \), and \( V(\alpha, \beta) \) is the conditional covariance matrix of \( R_j - \expit(\alpha_j + \beta A), \ j = 1, \ldots, c - 1 \), given \( A \); this choice corresponds to the maximum likelihood estimators given by Agresti (2019).

We propose basing the developments in Section 4 on taking \( D(A; \alpha, \beta) \) as above and choosing \( V(\alpha, \beta) \) according to the so-called “working independence” assumption, which leads to the full-data estimating function

\[
M(F; \alpha, \beta) = \begin{pmatrix}
R_1 - \expit(\alpha_1 + \beta A) \\
\vdots \\
R_{c-1} - \expit(\alpha_{c-1} + \beta A) \\
A \sum_{j=1}^{c-1} \{ R_j - \expit(\alpha_j + \beta A) \}
\end{pmatrix}
\]

(6)

Although this is not the efficient choice, it has been observed that the loss of efficiency relative to the optimal choice is minimal, and, importantly, basing the approach in Section 4 on (6) leads to more straightforward implementation.

Appealing to standard theory of M-estimation (Stefanski and Boos, 2002), it is straightforward that the influence function for the estimators solving the estimating equation (1)
with estimating function $\mathcal{M}(F; \alpha, \beta)$ as in (6) is given by
\[
- \left[ E \left\{ \frac{\partial \mathcal{M}(F; \alpha, \beta)}{\partial \alpha^T(\alpha^T, \beta)} \right\}_{\alpha=\alpha_0, \beta=\beta_0} \right]^{-1} \mathcal{M}(F; \alpha_0, \beta_0),
\]
(7)
where $\partial \mathcal{M}(F; \alpha, \beta)/\partial \alpha^T(\alpha^T, \beta) (c \times c)$ is the gradient matrix comprising partial derivatives of $\mathcal{M}(F; \alpha, \beta)$ with respect to $\alpha$ and $\beta$.

Let
\[
p_{j0} = \operatorname{expit}(\alpha_j), \quad p_{j1} = \operatorname{expit}(\alpha_j + \beta) \quad \text{and} \quad \check{p}_j = \pi p_{j1}(1 - p_{j1}) + (1 - \pi)p_{j0}(1 - p_{j0}),
\]
and let $p_{j0}^0$, $p_{j1}^0$, and $\check{p}_j^0$ denote these quantities evaluated at $\alpha_0, \beta_0$. Then it is shown in Appendix A that the influence function for $\hat{\beta}_F$ only is
\[
\{V(\alpha_0, \beta_0)\}^{-1} m(F; \alpha_0, \beta_0),
\]
(9)
where
\[
V(\alpha, \beta) = \sum_{j=1}^{c-1} \frac{\pi (1 - \pi)p_{j1}(1 - p_{j1})p_{j0}(1 - p_{j0})}{\check{p}_j}
\]
(10)
and
\[
m(F; \alpha, \beta) = \sum_{j=1}^{c-1} \frac{A(R_j - p_{j1})(1 - \pi)p_{j0}(1 - p_{j0}) - (1 - A)(R_j - p_{j0})\pi p_{j1}(1 - p_{j1})}{\check{p}_j}.
\]
(11)
It can be verified that $E_{\alpha, \beta}\{m(F; \alpha, \beta)\} = 0$. These results suggest that a consistent and asymptotically normal estimator for $\beta$ that is asymptotically equivalent to $\hat{\beta}_F$, with influence function (9), solves the estimating equation $\sum_{i=1}^n m(F_i; \alpha_0, \beta) = 0$; two estimators $\hat{\beta}^{(1)}$ and $\hat{\beta}^{(2)}$ are asymptotically equivalent if $n^{1/2}(\hat{\beta}^{(1)} - \hat{\beta}^{(2)})$ converges in probability to zero. Of course, $\alpha_0$ is unknown; however, we argue in Appendix A that a consistent and asymptotically normal estimator for $\beta$ that is asymptotically equivalent to $\hat{\beta}_F$ can be obtained by substituting for $\alpha_0$ any $n^{1/2}$-consistent estimator $\hat{\alpha}$ and solving the estimating equation
\[
\sum_{i=1}^n m(F_i; \hat{\alpha}, \beta) = 0,
\]
(12)
and the resulting estimator $\hat{\beta}$ for $\beta$ has influence function (9), from which the asymptotic variance of $\hat{\beta}$ can be derived.
4. Inference based on the observed data

Armed with the full data estimating function \( m(F; \alpha, \beta) \) in (11), we are now in a position to characterize a class of estimating functions yielding estimators for \( \beta \) based on the observed data (3). Letting “\( \perp \)” denote “independent of,” we make the following two assumptions:

(i) \( X \perp \perp A \),
(ii) \( C \perp \perp \{ X, T, Cat, \bar{L}(T) \} \mid A \),

where (i) is immediate because of randomization, and (ii) states that censoring is independent of the other data conditional on \( A \).

Under (i) and (ii) and the assumed proportional odds model, with no further assumptions, we follow Lu and Tsiatis (2011), who invoked the theory of semiparametrics and reasoning analogous to the above. Given a particular full-data estimating function \( m(F; \alpha, \beta) \), which we take to be that in (11) here, all consistent and asymptotically normal estimators for \( \beta \) based on the observed data (3) are characterized by estimating functions of the form

\[
m^*(O; \alpha, \beta) = \frac{\Delta m(F; \alpha, \beta)}{K(U, A)} - (A - \pi)f(X) + \int dM_c(u, A) h\{u, X, A, \bar{L}(u)\}. \tag{13}
\]

In (13), \( K(u, a) = \text{pr}(C \geq u \mid A = a) \), \( u \geq 0 \), \( a = 0, 1 \), is the treatment-specific survival distribution for the censoring variable \( C \);

\[
dM_c(u, a) = \{dN_c(u) - d\Lambda_c(u, a)Y(u)\}I(A = a),
\]

where \( N_c(u) = I(U \leq u, \Delta = 0) \) and \( Y(u) = I(U \geq u) \) are the censoring counting and at-risk processes, and \( \Lambda_c(u, a) = -\log\{K(u, a)\} \) is the cumulative hazard function for censoring; and \( f(X) \) is an arbitrary function of \( X \) and \( h\{u, X, A, \bar{L}(u)\} \) is an arbitrary function of \( u, X, A, \) and \( \bar{L}(u) \). If \( K(u, a) \) were known, then, analogous to (12), we could obtain an observed-data estimator for \( \beta \) as the solution to the estimating equation

\[
\sum_{i=1}^{n} m^*(O_i; \hat{\alpha}, \beta) = 0, \tag{14}
\]

where \( \hat{\alpha} \) is an \( n^{1/2} \)-consistent estimator for \( \alpha \). Estimators arising from solving (14) with an estimating function like those in the class of estimating functions in (13) are referred to as aug-
mented inverse probability complete case (AIPWCC) estimators. If \( f(\cdot) \) and \( h\{\cdot, X, A, \bar{L}(\cdot)\} \)
are chosen to be equal to zero, then the resulting estimator whose estimating function is the
first term on the right hand side of (13) is an inverse probability weighted complete case (IPWCC) estimator. The second and third “augmentation” terms on the right hand side of (13) have mean zero under (i) and (ii) and serve to increase efficiency relative to the IPWCC estimator by exploiting information in \( X \) and \( \bar{L}(u) \). Namely, for each participant \( i \), the first augmentation term recovers information from participants randomized to the treatment to which \( i \) was not randomized through the baseline covariates \( X \), and the second term recovers information lost due to censoring through \( X \) and the time-dependent covariates \( \bar{L}(u) \).

In practice, \( K(u, a) \), which appears in the leading term and second augmentation term of (13), is not known. We propose estimating \( K(u, a) \) by treatment-specific Kaplan-Meier estimators \( \hat{K}(u, a) \), for the censoring distributions, so for \( a = 0, 1 \) based on the data \( \{U_i, 1 - \Delta_i\} \) from participants \( i \) for whom \( A_i = a \). Substituting \( \hat{K}(u, a) \) in (14), consider AIPWCC estimators for \( \beta \) that solve estimating equations of the form

\[
\sum_{i=1}^{n} \tilde{m}(F_i; \alpha, \beta) - \sum_{i=1}^{n} \left[ \Delta_i m(F_i; \hat{\alpha}, \beta) \over \hat{K}(U_i, A_i) \right] - (A_i - \pi) f(X_i) + \int d\hat{M}_{c,i}(u, A_i) h\{u, X_i, A_i, \bar{L}_i(u)\} = 0,
\]

(15)

where \( d\hat{M}_{c,i}(u, a) = \{dN_{c,i}(u) - d\hat{\Lambda}_c(u, a)Y_i(u)\} I(A_i = a) \), \( N_{c,i}(u) = I(U_i \leq u, \Delta_i = 0) \), \( Y_i(u) = I(U_i \geq u) \), and \( \hat{\Lambda}_c(u, a) = -\log\{\hat{K}(u, a)\} \). From (5), the asymptotic variance of an estimator follows from its influence function. Because of the substitution of \( \hat{K}(u, a) \), in contrast to the full-data case, where the influence function (9) is directly proportional to the full-data estimating function (11), the influence functions for estimators for \( \beta \) solving (15) involve terms in addition to \( \tilde{m}(F; \alpha_0, \beta_0) \). Accordingly, to facilitate straightforward derivation of the asymptotic variance of the estimators, using results from other works (Zhao and Tsiatis, 1997; Bang and Tsiatis, 2000; Lu and Tsiatis, 2011), we instead consider estimating equations that yield AIPWCC estimators for \( \beta \) that are asymptotically equivalent to those
solving \((15)\) but are based directly on the influence functions associated with \((15)\). These estimators are characterized by estimating functions of the form

\[
\frac{\Delta m(F; \alpha, \beta)}{K(U, A)} + \int \frac{dM_c(u, A)\mu(m, u, A; \alpha, \beta)}{K(u, A)} - (A - \pi)f(X) \\
+ \int dM_c(u, A) \left[ h\{u, X, A, \bar{L}(u)\} - \mu(h, u, A) \right],
\]

\[
\mu(m, u, a; \alpha, \beta) = E\{m(F; \alpha, \beta) | T \geq u, A = a\}, \quad \mu(h, u, a) = E[h\{u, X, a, \bar{L}(u)\} | T \geq u, A = a].
\]

Estimating functions in \((16)\) are distinguished by different specifications of the functions \(f(\cdot)\) and \(h\{\cdot, X, A, \bar{L}(\cdot)\}\). Application of the theory of semiparametrics (Tsiatis, 2006) and results from Lu and Tsiatis (2011) show that the optimal choices of \(f(\cdot)\) and \(h\{\cdot, X, A, \bar{L}(\cdot)\}\) leading to the estimator for \(\beta\) with smallest asymptotic variance among all AIPWCC estimators solving estimating equations using \((16)\) are given by

\[
f^{opt}(X; \alpha, \beta) = E\{m(F; \alpha, \beta) | X, A = 1\} - E\{m(F; \alpha, \beta) | X, A = 0\},
\]

\[
h^{opt}\{u, X, A, \bar{L}(u); \alpha, \beta\} = \frac{E\{m(F; \alpha, \beta) | T \geq u, X, A, \bar{L}(u)\}}{K(u, A)}.
\]

The conditional expectations in \((17)\) and \((18)\) that define the optimal choices are unknown in general. Estimation of \(f^{opt}(X; \alpha, \beta)\) and \(h^{opt}\{u, X, A, \bar{L}(u); \alpha, \beta\}\) based on the observed data involves positing models for these conditional expectations, which is clearly challenging. Accordingly, analogous to the approach taken by Zhang, Tsiatis, and Davidian (2008) and Lu and Tsiatis (2011), we consider approximating these functions by linear combinations of basis functions. Specifically, we consider a linear subspace spanned by basis functions \(f_1(X), \ldots, f_M(X)\); namely, with \(f_0(X) \equiv 1\), we approximate \(f^{opt}(X; \alpha, \beta)\) by

\[
\sum_{m=0}^{M} \psi_m f_m(X).
\]

Similarly, for \(a = 0, 1\) and specified basis functions \(h_\ell\{u, X, \bar{L}(u)\}, \ell = 1, \ldots, L\), we approximate \(h^{opt}\{u, X, a, \bar{L}(u); \alpha, \beta\}\) by

\[
I(A = a) \sum_{\ell=1}^{L} \phi_{a,\ell} h_\ell\{u, X, \bar{L}(u)\}, \quad a = 0, 1.
\]

Although these representations are only approximations to the complex optimal choices,
experience in other contexts (Zhang et al., 2008; Lu and Tsiatis, 2011) shows that the 
resulting augmentation terms lead to considerable efficiency gains over taking \( f(\cdot) \) and 
h\{\cdot, X, A, \bar{L}(\cdot)\} equal to zero.

Substituting these linear representations in (16) leads to the estimating functions 
\[
m(O; \alpha, \beta) = \frac{\Delta m(F; \alpha, \beta)}{K(U, A)} + \int \frac{dM_c(u, A)\mu(m, u, A; \alpha, \beta)}{K(u, A)} - (A - \pi) \sum_{m=0}^{M} \psi_m f_m(X) \\
+ \int dM_c(u, A) \sum_{\ell=1}^{L} \phi_{A,\ell} \left[ h_{\ell}\{u, X, \bar{L}(u)\} - \mu(h_{\ell}, u, A) \right].
\]  

Deducing the optimal estimating function among those of form (19) that leads to the 
resulting augmentation terms lead to considerable efficiency gains over taking 
values \( \psi^{opt}_m \), \( m = 0, \ldots, M \), and \( \phi^{opt}_{a,\ell} \), \( a = 0, 1, \ell = 1, \ldots, L \), that minimize the variance 
of \( m(O; \alpha_0, \beta_0) \) and thus of the corresponding influence function. From the form of (19), 
minimizing the variance is a linear least squares problem, discussed in Section 5.

Based on these developments, we propose to estimate \( \beta \) by solving estimating equations 
characterized by the estimating function \( m(O; \alpha, \beta) \) in (19). In particular, substituting esti-
mators for \( \pi, K(U, A), \mu(m, u, A; \alpha, \beta), \) and \( \mu(h_{\ell}, u, A) \), the proposed AIPWCC estimator \( \hat{\beta} \) 
solves in \( \beta \) the estimating equation 
\[
\sum_{i=1}^{n} \tilde{m}(O_i; \tilde{\alpha}, \beta) = \sum_{i=1}^{n} \left( \frac{\Delta_i m(F_i; \tilde{\alpha}, \beta)}{\tilde{K}(U_i, A_i)} + \int \frac{d\tilde{M}_{c,i}(u, A_i)\tilde{\mu}(m, u, A_i; \tilde{\alpha}, \beta)}{\tilde{K}(u, A_i)} - (A_i - \tilde{\pi}) \sum_{m=0}^{M} \psi_m f_m(X_i) \\
+ \int d\tilde{M}_{c,i}(u, A_i) \sum_{\ell=1}^{L} \phi_{A,i,\ell} \left[ h_{\ell}\{u, X_i, \bar{L}(u)\} - \tilde{\mu}(h_{\ell}, u, A_i) \right] \right) = 0,
\]  
where \( \tilde{\pi} = n^{-1} \sum_{i=1}^{n} A_i, \) 
\[
d\tilde{M}_{c,i}(u, a) = \{dN_{c,i}(u) - d\tilde{\Lambda}_c(u, a)Y_i(u)\} I(A_i = a) \\
= \left[ dN_{c,i}(u) - \left\{ \sum_{k=1}^{n} \frac{dN_{c,k}(u)I(A_k = a)}{\sum_{k=1}^{n} Y_k(u)I(A_k = a)} \right\} Y_i(u) \right] I(A_i = a),
\]
\[
\frac{\hat{\mu}(m, u, a; \alpha, \beta)}{\tilde{K}(u, a)} = \left\{ \sum_{i=1}^{n} Y_i(u)I(A_i = a) \right\}^{-1} \sum_{i=1}^{n} \left\{ \frac{\Delta_i m(F_i; \tilde{\alpha}, \beta)}{\tilde{K}(U_i, a)} Y_i(u)I(A_i = a) \right\},
\]
\[
\hat{\mu}(h_\ell, u, a) = \left\{ \sum_{i=1}^{n} Y_i(u) I(A_i = a) \right\}^{-1} \sum_{i=1}^{n} [h_\ell(u, X_i, \bar{L}_i(u)) Y_i(u) I(A_i = a)].
\]

From (19), \( \hat{m}(O_i; \hat{\alpha}, \beta) \) involves substitution of these estimated quantities. However, in contrast to (15), because \( \hat{m}(O_i; \hat{\alpha}, \beta) \) has the form of \( m(O; \alpha, \beta) \) in (19), which when evaluated at \( (\alpha_0^T, \beta_0^T) \) is proportional to the influence function for the “ideal” estimator that could be obtained by solving estimating equations characterized by \( m(O; \alpha, \beta) \) if \( \pi, K(U, A), \mu(m, u, A; \alpha, \beta), \) and \( \mu(h_\ell, u, A) \) were known, it follows from semiparametric theory that \( \hat{\beta} \) shares the same influence function. Specifically, the theory guarantees that \( \hat{\beta} \) is asymptotically equivalent to the “ideal” estimator, with asymptotic variance that can be estimated from the form of (20); because the estimating function is based directly on the influence function, there is no effect of substituting estimators on the large sample properties.

The foregoing developments subsume the case where the full data are in fact available, as at the conclusion of the trial. Here, \( \Delta_i = 1, \bar{K}(U_i, A_i) = 1, \) and \( d\hat{M}_{c,i}(u, A_i) = 0, i = 1, \ldots, n, \) and (20) becomes

\[
\sum_{i=1}^{n} \left\{ m(F_i; \hat{\alpha}, \beta) - (A_i - \hat{\pi}) \sum_{m=0}^{M} \psi_m f_m(X_i) \right\} = 0. \tag{21}
\]

The estimating equation (21) is of the form of those of Zhang et al. (2008) for covariate-adjusted inference; see also Zhang and Zhang (2021). Thus, the proposed methodology leads to a covariate-adjusted estimator for the OR based on the full data that has the potential to increase the precision of inference. We discuss this further in Sections 5-7.

5. Practical implementation

Given a \( n^{1/2} \)-consistent estimator \( \hat{\alpha} \), the proposed estimator \( \hat{\beta} \) can be obtained by solving the estimating equation (20) directly; e.g., by a Newton-Raphson iterative algorithm. This procedure must incorporate estimation of the optimal choices of the parameters \( \psi_m, m = 0, \ldots, M, \) and \( \phi_{a,\ell}, a = 0, 1, \ell = 1, \ldots, L. \) As noted above, the estimators for these parameters should minimize the variance of \( m(O; \alpha_0, \beta_0) \), which suggests estimating \( \psi_m^{opt}, m = 0, \ldots, M, \)
and $\phi_{a,\ell}^{opt}$, $a = 0, 1, \ell = 1, \ldots, L$, by linear regression, with “dependent variable”

$$\hat{J}_i(\beta) = \frac{\Delta_i m(F_i; \bar{\alpha}, \beta)}{\hat{K}(U_i, A_i)} + \int \frac{d\hat{M}_{c,i}(u, A_i)\hat{\mu}(m, u, A_i; \bar{\alpha}, \beta)}{\hat{K}(u, A_i)}$$

(22)

and “covariates” $(A_i - \bar{\pi}) f_m(X_i)$, $m = 0, \ldots, M$, $I(A_i = 0) \int d\hat{M}_{c,i}(u, 0)[h_\ell\{u, X_i, \bar{L}_i(u)\} - \hat{\mu}(h_\ell, u, 0)]$, and $I(A_i = 1) \int d\hat{M}_{c,i}(u, 1)[h_\ell\{u, X_i, \bar{L}_i(u)\} - \hat{\mu}(h_\ell, u, 1)]$, $\ell = 1, \ldots, L$. Thus, because the “dependent variable” depends on $\beta$, within the algorithm, this regression would be carried out at each internal iteration with the “dependent variable” evaluated at the current iterate for $\hat{\beta}$.

We have found that the following alternative two-step strategy yields comparable results but is simpler to implement.

1. Obtain initial estimates $\hat{\alpha}$ and $\hat{\beta}_{init}$, say, by solving an IPWCC version of the full-data estimating equations with estimating function (6); namely, solve jointly in $\alpha$ and $\beta$ the $c$ equations

$$\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i, A_i)} \{R_{ji} - \expit(\alpha_j + \beta A_i)\} = 0, \quad j = 1, \ldots, c - 1,$$

$$\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i, A_i)} A_i \sum_{j=1}^{c-1} \{R_{ji} - \expit(\alpha_j + \beta A_i)\} = 0.$$

2. Obtain least squares estimators $\hat{\psi}_m$, $m = 0, \ldots, M$, and $\hat{\phi}_{a,\ell}$, $a = 0, 1, \ell = 1, \ldots, L$, by regressing the “dependent variable” in (22) evaluated at $\hat{\beta}_{init}$, $\hat{J}_i(\hat{\beta}_{init})$, on the “covariates” above, where, in $\hat{J}_i(\hat{\beta}_{init})$, from (11),

$$m(F; \bar{\alpha}, \hat{\beta}_{init}) = \sum_{j=1}^{c-1} \frac{A(R_j - \hat{p}_{j1})(1 - \bar{\pi})\hat{p}_{j0}(1 - \hat{p}_{j0}) - (1 - A)(R_j - \hat{p}_{j0})\bar{\pi}\hat{p}_{j1}(1 - \hat{p}_{j1})}{\hat{p}_{j}};$$

and $\hat{p}_{j0}$, $\hat{p}_{j1}$, and $\hat{p}_j$, $j = 1, \ldots, c - 1$, are the quantities in (8) evaluated at $\hat{\alpha}$ and $\hat{\beta}_{init}$. Then obtain the “predicted values”

$$\text{Pred}_i = (A_i - \bar{\pi}) \sum_{m=0}^{M} \hat{\psi}_m f_m(X_i) + \int d\hat{M}_{c,i}(u, A_i) \sum_{\ell=1}^{L} \hat{\phi}_{A_i,\ell} \left[h_\ell\{u, X_i, \bar{L}_i(u)\} - \hat{\mu}(h_\ell, u, A_i)\right].$$

Finally, obtain the AIPWCC estimator $\hat{\beta}$ as the one-step update

$$\hat{\beta} = \hat{\beta}_{init} - \{\nabla(\hat{\alpha}, \hat{\beta}_{init})\}^{-1} n^{-1} \sum_{i=1}^{n} \text{Pred}_i,$$

(23)
where, from (10),

\[ V(\hat{\alpha}, \hat{\beta}_{\text{init}}) = c^{-1} \sum_{j=1}^{c-1} \frac{\hat{\pi}(1 - \hat{\pi})\hat{\beta}_{j1}(1 - \hat{\beta}_{j1})\hat{\beta}_{j0}(1 - \hat{\beta}_{j0})}{\hat{\beta}_j}. \]

The asymptotic variance for \( \hat{\beta} \) can be estimated by

\[ \{V(\hat{\alpha}, \hat{\beta}_{\text{init}})\}^{-2} \sum_{i=1}^{n} \{\hat{Y}_i(\hat{\beta}_{\text{init}}) - Pred_i\}^2. \] (24)

A variation on this approach is to iterate step (2) a fixed number of times or to “convergence.” We have found in simulations that iterating does not yield significant improvement relative to carrying out steps (1) and (2) a single time. In Appendix B, we sketch a heuristic justification for the one-step updated estimator \( \hat{\beta} \) in (23).

The full-data covariate-adjusted analysis based on (21) can be implemented using the two-step strategy with \( \Delta_i = 1 \), \( \hat{K}(U_i, A_i) = 1 \), and \( d\hat{M}_{c,i}(u, A_i) = 0 \), \( i = 1, \ldots, n \), substituted in steps (1) and (2). Here, then, in step (2), \( \hat{Y}_i(\hat{\beta}_{\text{init}}) = m(F; \hat{\alpha}, \hat{\beta}_{\text{init}}) \) is regressed only on the “covariates” \( (A_i - \hat{\pi})f_m(X_i) \) to obtain \( \hat{\psi}_m, m = 0, \ldots, M \), and the “predicted values” are \( Pred_i = (A_i - \hat{\pi})\sum_{m=0}^{M} \hat{\psi}_m f_m(X_i) \), which are substituted in (23) to yield the covariate-adjusted one-step updated estimator with asymptotic variance estimated by (24).

6. Simulation studies

We conducted a suite of simulation experiments under scenarios resembling the situation of the TESICO study introduced in Section 1. Each simulation involved 5000 Monte Carlo replications, and in all cases for each of \( n = 602 \) simulated subjects, \( A \) was generated as Bernoulli with \( \text{pr}(A = 1) = \pi = 0.5 \), where \( a = 0 (1) \) corresponds to placebo (investigational agent). To simulate full and observed data from scenarios in which the proportional odds model (11) holds, we generated \( \Gamma \) such that the distribution of \( \Gamma \) given \( A = 0 \) was \( U(0,1) \), and the distribution of \( \Gamma \) given \( A = 1 \) followed a proportional odds model with logit\{pr(\Gamma \leq u \mid A = 1)\} = logit\{pr(\Gamma \leq u \mid A = 0)\} + \beta \), where \( \beta = \log(\text{OR}) \). This was accomplished by generating \( \Upsilon \sim U(0,1) \) and taking \( \Gamma = (1 - A)\Upsilon + A\Upsilon(1/\text{OR})/(1 - \Upsilon + \Upsilon(1/\text{OR})) \).
In our initial experiment, Scenario 1 below, we assumed six categories with probabilities as presented in Table I and took the true value of the odds ratio $\text{OR} = 1.5$. For a given simulated subject, we generated the categorical outcome $\text{Cat}$ according to which interval $\Gamma$ fell as determined by the cutpoints $[0.00, 0.12, 0.35, 0.52, 0.62, 0.67, 1.00]$, which from Table I are determined by the cumulative probabilities for Categories 1–6 for placebo. Thus, by the construction of $\Gamma$, the probabilities of falling into each category for a subject with $A = 0$ are as in Table I for placebo, and those for a subject with $A = 1$ are as shown for the investigational agent. Categories 1–3 are based on the number of consecutive days at home and off oxygen at day 90; thus, if $\Gamma < 0.52$, we defined time in hospital as $H = 90\Gamma/0.52$, and the number of days at home and off oxygen as $90 - H$. In TESICO, participants can leave and then return to the hospital, so that their category status will not be known until day 90. For simplicity in the simulations, we did not allow that possibility; however, the proposed methods are not predicated on this simplification. If $\Gamma < 0.52$, we took $T = 90$. If $0.52 \leq \Gamma < 0.62$ or $0.62 \leq \Gamma < 0.67$, corresponding to Categories 4 and 5, again $T = 90$. If $\Gamma \geq 0.67$, corresponding to death, $T =$ time of death, which was generated as $T_0 \sim U(a_0, b_0)$ if $A = 0$ and $T_1 \sim U(a_1, b_1)$ if $A = 1$. With these conventions, $T = 90I(\Gamma < 0.67) + \{(1 - A)T_0 + AT_1\}I(\Gamma \geq 0.67)$. In all scenarios, we took $(a_0, b_0) = (0, 30)$ and $(a_1, b_1) = (20, 50)$.

To create a baseline covariate $X$ satisfying (i), we generated $X \sim N\{\gamma(Y - 0.5), 1\}$, so that $X$ is independent of $A$, correlated with outcome, and does not affect the proportional odds model. We considered two time-dependent covariates, so that $L(u) = \{L_1(u), L_2(u)\}$. Defining $T = H I(\Gamma < 0.52) + 90 I(\Gamma \geq 0.52)$, $L_1(u) = I(T < u)$, indicating whether or not the subject was still in the hospital at time $u$, and $L_2(u) = (90 - T)L_1(u)$, corresponding to the number of days the subject was expected to be out of the hospital at day 90. We took the censoring time $C \sim U(0, \zeta)$, where $\zeta > 90$, and $U = \min(T, C)$, $\Delta = I(T \leq C)$. In all scenarios, $\gamma = 1.5$, and $\zeta = 135$, which led to roughly 50% censored outcomes.
For each Monte Carlo data set, we estimated \( \beta \) and thus \( \text{OR} = \exp(\beta) \) several ways. For each subject, we generated both full data \( F = (X, A, \text{Cat}, T) \) as in (2) and observed data \( O = \{X, A, U, \Delta, \Delta\text{Cat}, \bar{L}(U)\} \) as in (3). The former allows us to study the ideal full-data analysis with no censoring that could be conducted at the end of the study as a (unattainable at an interim analysis) benchmark and thus evaluate the extent to which the proposed AIPWCC estimator for \( \beta \), and thus that for \( \text{OR} = \exp(\beta) \), can recover information and approach the efficiency of the ideal full-data maximum likelihood estimator \( \hat{\beta}_{\text{ideal}} \). This estimator is based only on \((A, \text{Cat})\), so does not incorporate information in \( X \) to increase precision. Thus, as further benchmarks, we also considered three covariate-adjusted estimators for \( \beta \): The maximum likelihood estimator \( \hat{\beta}_{\text{ideal,adj}} \) for \( \beta \) in the conditional model \( \log\{\text{pr}(\text{Cat} \leq j \mid X, A)\} = \alpha_j + \beta A + \gamma X \); the estimator \( \hat{\beta}_{LOR} \) for the average of category-specific log-odds ratios of Benkeser et al. (2021), which when the proportional odds assumption holds estimates the OR of interest; and the one-step AIPWCC estimator \( \hat{\beta}_{AIPW1,\text{full}} \) solving (21) discussed at the end of Section 5. Based on the observed data, we estimated \( \beta \) five ways:

1. Using the “naive” maximum likelihood estimator \( \hat{\beta}_{\text{naive}} \) based on the data \((A_i, \text{Cat}_i)\) for \( i \) with \( \Delta_i = 1 \) only, which over-represents accumulating deaths;
2. Using the maximum likelihood estimator \( \hat{\beta}_{90} \) based on data for all subjects who have had at least 90 days of follow up at the time of the analysis; with administrative censoring, we observe \( C \), and these data are \((A_i, \text{Cat}_i)\) for \( i \) with \( C_i \geq 90 \);
3. Using the IPWCC estimator \( \hat{\beta}_{init} \), denoted here as \( \hat{\beta}_{IPW} \);
4. Using the one-step AIPWCC estimator \( \hat{\beta}_{AIPW1} \) that uses only the augmentation term involving baseline covariate information \( X \), so taking \( \phi_{a,\ell} = 0, a = 0, 1, \ell = 1, \ldots, L \), and estimating only \( \psi_m, m = 0, \ldots, M \), to gain efficiency;
5. Using the one-step AIPWCC estimator \( \hat{\beta} \), which we denote here as \( \hat{\beta}_{AIPW2} \), which uses both baseline and time-dependent covariate information to gain efficiency.
For $\hat{\beta}_{\text{ideal}}, \hat{\beta}_{\text{ideal,adj}}, \hat{\beta}_{\text{naive}},$ and $\hat{\beta}_{90},$ estimates and standard errors were obtained using the \texttt{polr} function in the R package \texttt{MASS} (Venables and Ripley, 2002). For $\hat{\beta}_{\text{LOR}},$ estimates and standard errors (back-calculated from confidence intervals) were obtained using the R package \texttt{drord} (Benkeser, 2021). Those for the proposed IPWCC and AIPWCC estimators (3)-(5) were obtained using the R package \texttt{tLagPropOdds} developed by the authors.

For Scenario 1, where data were generated according to the foregoing scheme with OR $= 1.5,$ results for estimation of $\text{OR} = \exp(\beta)$ are presented in Table 2. Because of the exponentiation, not unexpectedly, although the empirical distributions of the 5000 estimates of $\beta$ appear normal, those for estimates of $\exp(\beta)$ exhibit slight skew due to a few large values; accordingly, we present both Monte Carlo mean and median. If the full data were available, inference based on the benchmark estimator $\exp(\hat{\beta}_{\text{ideal}})$ is unbiased as expected, with confidence interval achieving the nominal 95% level. The adjusted estimator $\exp(\hat{\beta}_{\text{ideal,adj}})$ is upwardly biased; this behavior is not unexpected, as the proportional odds model is nonlinear, so the conditional and marginal estimators do not coincide. The covariate-adjusted full-data estimators $\exp(\hat{\beta}_{\text{LOR}})$ and $\exp(\hat{\beta}_{\text{AIPW1,full}})$ exhibit virtually identical performance and offer a roughly 15% efficiency gain over $\exp(\hat{\beta}_{\text{ideal}})$ with confidence intervals achieving the nominal level. For the attainable observed-data estimators, the $\exp(\hat{\beta}_{\text{naive}})$ yields substantially biased inference, as expected. The estimator $\exp(\hat{\beta}_{90})$ based on data from subjects with $C_i \geq 90$ only is consistent and yields valid confidence intervals; however, it exhibits an over-two-fold efficiency loss relative to the fully augmented estimator $\exp(\hat{\beta}_{\text{AIPW2}}),$ which exploits information from both baseline and time-dependent covariates. The IPWCC and AIPWCC estimators all yield unbiased inference and yield valid confidence intervals; however, $\exp(\hat{\beta}_{\text{IPW}})$ and $\exp(\hat{\beta}_{\text{AIPW1}})$ show nontrivial efficiency loss relative to the fully augmented estimator $\exp(\hat{\beta}_{\text{AIPW2}}).$ Relative to the unachievable benchmark estimator $\exp(\hat{\beta}_{\text{ideal}}),$ the observed-data estimator $\exp(\hat{\beta}_{90})$ shows a three-fold efficiency loss, which is expected under the
generative censoring distribution that yields only $1/3$ of participants having full 90-day follow up, and even greater inefficiency relative to $\exp(\hat{\beta}_{LOR})$ and $\exp(\hat{\beta}_{AIPW1,full})$. The proposed augmented estimator $\exp(\hat{\beta}_{AIPW2})$ recovers a substantial proportion of this efficiency loss, showing only a 35% loss relative to $\exp(\hat{\beta}_{ideal})$. The sample size for TESICO was chosen to yield approximately 80% power to detect $OR = 1.5$ with a two-sided test of $H_0$: $OR = 1.0$ at level of significance 0.05 at the final analysis; i.e., based on $\hat{\beta}_{ideal}$; we discuss empirical power results for Scenario 1 momentarily.

Scenario 2 is identical to Scenario 1, except that $H_0$ holds, so that the true odds ratio $OR = 1.0$. From Table 2 relative performance of the estimators is qualitatively similar to that under Scenario 1. The tests of $H_0$ achieve the nominal level except when based on the “naive” estimator $\hat{\beta}_{naive}$, which is again biased. The test based on $\hat{\beta}_{ideal}$ achieves power very near 80%, as planned, and, not surprisingly, the tests based on $\hat{\beta}_{ideal,adj}$, $\hat{\beta}_{LOR}$, and $\hat{\beta}_{AIPW1,full}$, which incorporate baseline covariate information and are unbiased under $H_0$, are more powerful. Among the tests based on observed data, that based on $\hat{\beta}_{90}$, which makes use only of data on participants with at least 90 days of follow up at the time of the analysis achieves only 36% power, whereas exploiting covariate information from subjects for whom the outcome is censored at the time of the analysis results in substantial power gains.

Scenarios 3 and 4 are the same as Scenarios 1 and 2 except that we generated data assuming a larger number (10) of categories. Categories 1–7 are based on the number of consecutive days at home and off oxygen at day 90 and thus reflect partitioning the time interval from 0 to 90 days more finely than in Scenarios 1–2, so that the categorical outcome $Cat$ is determined according to which interval $\Gamma$ falls as determined by the cutpoints $[0.00, 0.06, 0.12, 0.22, 0.31, 0.39, 0.46, 0.52, 0.62, 0.67, 1.00]$. Categories 8 and 9 correspond to $0.52 \leq \Gamma < 0.62$ or $0.62 \leq \Gamma < 0.67$, and $\Gamma \geq 0.67$, corresponds to Category 10 (death). From Table 2 performance of the estimators is qualitatively similar to that in Scenarios 1 and 2.
Here, with a larger number of categories, \( \exp(\hat{\beta}_{AIPW1,full}) \) slightly outperforms \( \exp(\hat{\beta}_{LOR}) \), which is not unexpected, as the latter does not exploit the proportional odds assumption.

[Table 2 about here.]

We carried out simulations under two additional scenarios under which the proportional odds assumption does not hold. We report on one of these here; see Appendix C for results of the second, for which the generative data mechanism is different from those in this section.

In Scenario 5, we adopted the same conditions as in Scenario 1, except that we generated data from a proportional hazards model, where

\[
\Pr(Cat \leq j) = 1 - \delta_j \exp(\xi), \ j = 1, \ldots, c - 1, \ 
\]

say. From Table 1 for TESICO, \( \Pr(Cat \leq 3) = 0.52 \) under placebo, and, with \( OR = 1.5 \), \( \Pr(Cat \leq 3) = 0.619 \) for the investigational agent. Accordingly, we chose \( \xi \) so that \( \Pr(Cat \leq 3) \) under the proportional hazards model is equal to these same probabilities for placebo and investigational agent, leading to \( \exp(\xi) = 1.315 \). To generate data from this proportional hazards model, we generated \( \Gamma \) as

\[
\Gamma = (1 - A)\Upsilon + A\{1 - \Upsilon \exp(-\xi)\}, \ 
\]

where \( \Upsilon \sim U(0, 1) \). All other aspects of the generative model were identical to the above. Based on \( 10^6 \) simulated subjects, we computed the approximate category-specific odds ratios for Categories 1–5 as (1.34, 1.42, 1.50, 1.58, 1.62); and we estimated \( \beta \) in the proportional odds model using \( \hat{\beta}_{\text{ideal}} \), obtaining a value of 1.48, which we use to approximate the limit in probability of \( \hat{\beta}_{\text{ideal}} \), the true parameter being estimated. The results, shown in Table 3, are qualitatively similar to those in the other scenarios, reflecting robustness to model misspecification.

[Table 3 about here.]

7. Discussion

We have proposed an approach to inference on the odds ratio in an assumed proportional odds model from a randomized clinical trial with censored time-lagged categorical outcome, as would be the case at the time of an interim analysis. The methods exploit baseline and
time-varying information from participants for whom the outcome of interest is censored at the time of the analysis to achieve what can be substantial efficiency gains over inference based on the usual estimator for the odds ratio using only subjects with complete follow up at the time of the analysis. Although the methodology is motivated in the context of COVID-19 therapeutics trials, it is applicable to any setting with primary analysis based on the proportional odds assumption for which the ordinal categorical outcome of interest may not be ascertained for all subjects at the time of an interim analysis.

The methods can be extended to more than two treatments, including the case where the treatments are determined by a factorial arrangement of multiple agents, analogous to the approach in Zhang et al. (2008). The developments are multivariate generalizations of those in Sections 3 and 4 and Appendices A and B and are sketched in Appendix D.

We have taken as a starting point the assumption of a proportional odds model in accordance with the primary analyses defined in several ACTIV COVID-19 therapeutics protocols, including TESICO. Given that the interim analyses in these studies will be based on this assumption as defined in these protocols, our objective is to provide more efficient methodology under this assumption to enable more timely decisions. If the proportional odds assumption does not hold, then, as is well known, the estimator for the odds ratio under this assumption estimates some weighted combination of category-specific odds ratios, in a manner similar to the Mantel-Haenszel method; an analogous interpretation holds when the assumption of proportional hazards for a time-to-event endpoint is violated. Although such a weighted average may not be directly interpretable, its value likely reflects, at least approximately, the strength of the treatment effect of interest. In their comprehensive study demonstrating the benefits of covariate adjustment to improve the precision of inference on treatment effects in a range of COVID-19 therapeutics trials, Benkeser et al. (2021) propose alternative treatment effect estimands for ordinal categorical outcomes that are
not predicated on a parametric assumption such as that of proportional odds and that they suggest may be more interpretable by domain scientists. The authors focus on the case where the full data are available, as at the time of a final analysis, and propose semiparametric covariate-adjusted estimators targeting these estimands; see also Zhang and Zhang (2021). It would be possible to derive the full-data influence functions for these estimators and, by developments similar to those presented here, derive corresponding observed-data influence functions and estimators in the case of censored, time-lagged categorical outcome.

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Data Availability Statement

Data sharing is not applicable to this article, as no datasets are generated or analysed in this paper. The methods developed in the paper are proposed to enable future analyses of data from ongoing clinical trials from which the required data are not yet fully accrued.

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Supporting Information

An R package, tLagPropOdds, implementing the methodology is available at the Comprehensive R Archive Network (CRAN) at https://cran.r-project.org/package=tLagPropOdds.

Appendix A: Full data influence function for estimator for β

It is straightforward to show that

\[-E_{\alpha,\beta}\left\{ \frac{\partial M(F;\alpha,\beta)}{\partial T(\alpha^T,\beta)} \right\} = \begin{pmatrix} B_{11} & B_{12} \\ B_{12}^T & B_{22} \end{pmatrix}, \tag{A.1} \]

where \(B_{11} = \text{diag}(\bar{p}_1,\ldots,\bar{p}_{c-1})\), \(B_{12} = \pi \{ p_{11}(1-p_{11}),\ldots,p_{c-1,1}(1-p_{c-1,1}) \}^T\), and \(B_{22} = \pi \sum_{j=1}^{c-1} p_{j1}(1-p_{j1}) \). The influence function for the estimator \(\hat{\beta}_F\) for \(\beta\) is the last row of the inverse of (A.1) evaluated at \(\alpha_0,\beta_0\) post-multiplied by \(M(F;\alpha_0,\beta_0)\). Using formulae for the inverse of a partitioned matrix, the last row of the inverse is given by

\[-\{V(\alpha_0,\beta_0)\}^{-1} \begin{pmatrix} \frac{\pi p_{11}^0(1-p_{11}^0)}{\bar{p}_1^0}, \ldots, \frac{\pi p_{c-1,1}^0(1-p_{c-1,1}^0)}{\bar{p}_{c-1}^0}, 1 \end{pmatrix}^T, \tag{A.2} \]

where \(V(\alpha,\beta)\) is defined in (10). Post-multiplying by \(M(F;\alpha_0,\beta_0)\), it follows by routine algebra that the influence function for \(\hat{\beta}_F\) is given by \(V(\alpha_0,\beta_0)^{-1}m(F;\alpha_0,\beta_0)\) as in (9), where \(m(F;\alpha_0,\beta_0)\) is defined in (11).

We now argue heuristically that the estimator \(\hat{\beta}\) for \(\beta\) solving the estimating equation (12) with estimating function \(m(F;\hat{\alpha},\beta)\) and \(\hat{\alpha}\) any \(n^{1/2}\)-consistent estimator for \(\alpha\) is consistent and asymptotically normal and has the influence function in (9), where by \(n^{1/2}\)-consistent we mean that \(n^{1/2}(\hat{\alpha} - \alpha_0)\) is bounded in probability. It can be shown that

\[E\left\{ \frac{\partial m(F;\alpha,\beta)}{\partial \beta} \bigg|_{\alpha=\alpha_0,\beta=\beta_0} \right\} = -V(\alpha_0,\beta_0), \tag{A.2} \]

\[E\left\{ \frac{\partial m(F;\alpha,\beta)}{\partial \alpha_j} \bigg|_{\alpha=\alpha_0,\beta=\beta_0} \right\} = -\frac{\pi (1-\pi)p_{j1}^0(1-p_{j1}^0)p_{j0}^0(1-p_{j0}^0)}{\bar{p}_j^0} + \frac{\pi (1-\pi)p_{j1}^0(1-p_{j1}^0)p_{j0}^0(1-p_{j0}^0)}{\bar{p}_j^0} = 0 \tag{A.3} \]
for \( j = 1, \ldots, c - 1 \). By a standard Taylor series expansion and under regularity conditions

\[
n^{-1/2} \sum_{i=1}^{n} m(F_i; \hat{\alpha}, \hat{\beta}) \approx n^{-1/2} \sum_{i=1}^{n} m(F_i; \alpha_0, \beta_0) + \left\{ n^{-1} \sum_{i=1}^{n} \left. \frac{\partial m(F_i; \alpha, \beta)}{\partial \beta} \right|_{\alpha=\alpha_0, \beta=\beta_0} \right\} n^{1/2} (\hat{\beta} - \beta_0) \\
+ \left\{ n^{-1} \sum_{i=1}^{n} \left. \frac{\partial m(F_i; \alpha, \beta)}{\partial \alpha} \right|_{\alpha=\alpha_0, \beta=\beta_0} \right\} n^{1/2} (\hat{\alpha} - \alpha_0).
\]

(A.4)

The averages in braces in the second and third terms on the right hand side converge in probability to their expectations, which for the third term is equal to zero from (A.3).

Substituting these expectations, which are given in (A.2) and (A.3), and rearranging, it is straightforward to show that \( \hat{\beta} \) has influence function (9), demonstrating the result and implying that \( \hat{\beta}_F \) and \( \hat{\beta} \) are asymptotically equivalent. This result can also be deduced directly from semiparametric theory with \( \alpha \) viewed as a nuisance parameter using (A.2) and (A.3) and appealing to the developments in Chapter 3 of Tsiatis (2006).

**Appendix B: Heuristic justification for the one-step updated estimator**

We first find the influence function for \( \hat{\beta}_{\text{init}} \) solving the estimating equations in step (1) of the two-step algorithm, so solving in \( \beta \)

\[
\sum_{i=1}^{n} \frac{\Delta_i m(F_i; \hat{\alpha}, \beta)}{\hat{K}(U_i, A_i)} = 0.
\]

By a Taylor series expansion, we obtain

\[
n^{1/2} (\hat{\beta}_{\text{init}} - \beta_0) \approx \left\{ -n^{-1} \sum_{i=1}^{n} \left. \frac{\Delta_i m(F_i; \hat{\alpha}, \beta)}{\hat{K}(U_i, A_i)} \right|_{\beta=\beta_0} \right\}^{-1} n^{-1/2} \sum_{i=1}^{n} \frac{\Delta_i m(F_i; \hat{\alpha}, \beta_0)}{\hat{K}(U_i, A_i)}.
\]

(B.1)

The first term on the right hand side of (B.1) can be shown to converge in probability to \( \{ \mathcal{V}(\alpha_0, \beta_0) \}^{-1} \), and the second term can be written as

\[
n^{-1/2} \sum_{i=1}^{n} \frac{\Delta_i m(F_i; \hat{\alpha}, \beta_0)}{\hat{K}(U_i, A_i)} + n^{-1/2} \sum_{i=1}^{n} \left\{ \frac{\Delta_i}{\hat{K}(U_i, A_i)} - \frac{\Delta_i}{\hat{K}(U_i, A_i)} \right\} m(F_i; \hat{\alpha}, \beta_0).
\]

(B.2)
Taking a Taylor series of the first term of (B.2) in \( \hat{\alpha} \) about \( \alpha_0 \), using results in Zhao and Tsiatis (1997) to express the second term in (B.2) as

\[
n^{-1/2} \sum_{i=1}^{n} \frac{dM_{c,i}(u, A_i)}{K(u, A_i)} \mu(m, u, A_i; \alpha_0, \beta_0) + o_p(1),
\]

and using the fact that

\[
n^{-1} \sum_{i=1}^{n} \frac{\Delta_i}{K(U_i, A_i)} \frac{\partial m(F; \hat{\alpha}, \beta)}{\partial \alpha} \bigg|_{\alpha=\alpha_0, \beta=\beta_0} \xrightarrow{p} E \left\{ \frac{\partial m(F; \hat{\alpha}, \beta)}{\partial \beta} \bigg|_{\beta=\beta_0} \right\} = 0,
\]

the influence function can be shown to be

\[
\{V(\alpha_0, \beta_0)\}^{-1} \left\{ \frac{\Delta m(F; \alpha_0, \beta_0)}{K(U, A)} + \int dM_c(u, A) \mu(m, u, A; \alpha_0, \beta_0) \right\}.
\]

(B.3)

Now consider the one-step update in (23) and write it equivalently as

\[
n^{1/2}(\hat{\beta} - \beta_0) = n^{1/2}(\hat{\beta}_{init} - \beta_0) - \{V(\hat{\alpha}, \hat{\beta}_{init})\}^{-1}n^{-1/2} \sum_{i=1}^{n} P_{redi}.
\]

(B.4)

From the definition of \( P_{redi} \),

\[
n^{-1/2} \sum_{i=1}^{n} P_{redi} = n^{-1/2} \sum_{i=1}^{n} \left( A_i - \pi \right) \sum_{m=0}^{M} \psi_m^ opt f_m(X_i)
\]

\[+ \int dM_{c,i}(u, A_i) \sum_{\ell=1}^{L} \phi_{A_i, \ell}^ opt \left[ h_\ell \{ u, X_i, \bar{L}_i(u) \} - \bar{\mu}(h_\ell, u, A_i) \right] \xrightarrow{p} o_p(1),
\]

and \( \{V(\hat{\alpha}, \hat{\beta}_{init})\}^{-1} \xrightarrow{p} \{V(\alpha_0, \beta_0)\}^{-1} \). Consequently, from (B.4), the influence function of the one-step estimator \( \hat{\beta} \) is

\[
\{V(\alpha_0, \beta_0)\}^{-1} \left( \frac{\Delta m(F; \alpha_0, \beta_0)}{K(U, A)} + \int dM_c(u, A) \mu(m, u, A; \alpha_0, \beta_0) - (A - \pi) \sum_{m=0}^{M} \psi_m^ opt f_m(X) \right.
\]

\[\left. - \int dM_c(u, A) \sum_{\ell=1}^{L} \phi_{A, \ell}^ opt \left[ h_\ell \{ u, X, \bar{L}(u) \} - \mu(h_\ell, u, A) \right] \right),
\]

which is the influence function of estimators solving the optimal estimating equation of form (20).

**Appendix C: Additional simulation results**

Here, we report on an additional simulation scenario under which the proportional odds assumption does not hold, which we refer to as Scenario 6. We generated data according to a different mechanism that creates the outcome prospectively rather than through a latent
variable ($\Upsilon$) as in the scenarios discussed in the main paper, again with six categories, with $\text{Cat} = 6$ corresponding to death within 90 days. As in the main paper, we simulated 5000 Monte Carlo data sets, each involving $n = 602$ simulated subjects.

We took the hazard rate for leaving the hospital for placebo to be constant and equal to $\lambda_{H0} = 0.0149$ for the first 90 days and the hazard rate for death for placebo within the first 40 days to be $\lambda_{D0} = 0.0139$; these values were chosen to correspond to the probability of leaving the hospital by 90 days without dying to be 0.52 and the probability of dying prior to leaving the hospital within 40 days to be 0.33. To characterize Categories 1 to 3, we defined cutpoints $c_1 = 9.16$ and $c_2 = 39.19$ so that the probabilities of leaving the hospital without dying by $c_1$ or $c_2$ were 0.12 and 0.35, respectively. Under this scenario, about 15% of placebo subjects are still hospitalized and alive at 90 days. For placebo subjects remaining in the hospital at 90 days, we assigned them to Categories 4 and 5 with probabilities $p_{40} = 2/3$ and $1 - p_{40}$, so that 10% and 5% were in Categories 4 and 5, respectively. We generated subjects under treatment such that the hazard for leaving the hospital was $\lambda_{H1} = \lambda_{H0} \exp(\xi)$ for the first 90 days, $\xi = \log(1/0.775)$, so that the hazard increased relative to placebo. Likewise, we took the hazard of death within the first 90 days to be $\lambda_{D1} = \lambda_{D0} \exp(-\xi)$, so that the hazard decreased relative to placebo. Finally, we took the probabilities of assignment to Categories 4 and 5 to be $p_{41}$ and $(1 - p_{41})$, where $\logit(p_{41}) = \logit(p_{40}) + \xi$, increasing the probability of being in Category 4.

To generate a subject, we first generated $A$ as Bernoulli with $\pi = 0.5$ and generated $U_H, U_D$, and $U_4$ to be independent $U(0,1)$. We then generated for each of $a = 0, 1$ $\chi_{Ha} = -\log(U_H)/\lambda_{Ha}$, so as exponential with hazard rate $\lambda_{Ha}$; and $\chi_{Da} = -\log(U_D)/\lambda_{Da}$, so as exponential with hazard rate $\lambda_{Da}$. Note that $\chi_{Ha}, a = 0, 1$, are correlated; and similarly for $\chi_{Da}$. Then, if $\chi_{Da} < \min(\chi_{Ha}, 40)$, we set $\text{Cat}_a = 6$, and $T_a = \chi_{Da}$. Otherwise, if $\chi_{Da} \leq \min(\chi_{Ha}, 40)$, we set $\text{Cat}_a = 1$ if $\chi_{Ha} < 9.16$, $\text{Cat}_a = 2$ if $9.16 \leq \chi_{Ha} < 39.19$, or $\text{Cat}_a = 3$ if...
39.19 \leq \chi_{Ha} < 90, and \, T_a = \chi_{Ha}. If \ \chi_{Ha} > 90, we generated \, B_{4a} = I(U_4 \leq p_{4a}), so that \, B_{4a}
are correlated, and set \, Cat_a = 4 or \, Cat_a = 5 as \, B_a = 1 or 0, respectively, and \, T_a = 90. We
then obtained \, Cat = ACat_1 + (1 - A)Cat_0 \, and \, T = 90I(Cat < 6) + \{AT_1 + (1 - A)T_0\}I(Cat = 6).
Based on 10^6 simulated subjects, this generative model results in approximate category-
specific odds ratios of (1.33, 1.48, 1.60, 1.56, 1.47) corresponding to categories \,(1, \ldots, 5).

To create a baseline covariate \, X satisfying assumption (i) in Section 4 of the main paper,
we took \, X \sim \mathcal{N}\{\gamma(Cat_0 - 3.5), 1\}, so that \, X \, is independent of \, A and correlated with outcome
by virtue of the mechanism above, , with \, \gamma = 0.25. We took the censoring time \, C \sim U(0, \zeta),
where \, \zeta = 135, and \, U = \min(T, C), \, \Delta = I(T \leq C), corresponding to about 50% censoring.
Finally, we created two time-dependent covariates, so that \, L(u) = \{L_1(u), L_2(u)\}, by defining
\, \mathcal{T} = \{AT_1 + (1 - A)T_0\}I(Cat \leq 3) + 90I(Cat > 3) \, and setting \, L_1(u) = I(\mathcal{T} < u), indicating
whether or not the subject was still in the hospital at time \, u, and \, L_2(u) = (90 - \mathcal{T})L_1(u),
corresponding to the number of days the subject was expected to be out of the hospital at
day 90.

Because the proportional odds assumption does not hold, as in Scenario 5 in the main
paper, we approximated the limit in probability of \, \hat{\beta}_{ideal}, the true parameter being estimated,
by simulating 10^6 subjects and obtaining the Monte Carlo average of estimates \, \hat{\beta}_{ideal}, 1.49.

Table 4 presents the results. As for Scenario 5 in the main paper under a true proportional
hazards assumption, the results reflect robustness to model misspecification.

[Table 4 about here.]

APPENDIX D: EXTENSION TO MORE THAN TWO TREATMENTS

We consider the case of \, K \geq 2 treatments. The full data \, F_i \, in (2) and observed data \, O_i \, in (3)
are the same except that \, A \, takes on values \, a = 0, \ldots, K - 1, where 0 indicates placebo and
1, \ldots, K - 1 indicate investigational agents. Subjects are randomized to the \, K \, treatments
with probabilities \( \text{pr}(A = a) = \pi_a \), where \( \sum_{a=0}^{K-1} \pi_a = 1 \). The proportional odds model is now

\[
\logit \{ \text{pr}(\text{Cat} \leq j \mid A) \} = \alpha_j + \beta_1 I(A = 1) + \cdots + \beta_{K-1} I(A = K-1), \quad j = 1, \ldots, c-1,
\]

(D.1)

where, for the \( a \)th investigational agent, \( a = 1, \ldots, K-1 \), the treatment effect is expressed as the treatment-specific odds ratio \( \exp(\beta_a) \); and \( \alpha_j, j = 1, \ldots, c-1 \), are as in (I). Defining now \( \beta = (\beta_1, \ldots, \beta_{K-1})^T \), identify \( \theta \) in (I) as \( \theta = (\alpha^T, \beta^T)^T \), with true values \( \theta_0 = (\alpha_0^T, \beta_0^T)^T \).

Analogous to (I), consider the full-data estimating function for \( \theta \) based on the “working independence” assumption given by

\[
\mathcal{M}(F; \alpha, \beta) = \begin{pmatrix}
R_1 - \expit\{\alpha_1 + \beta_1 I(A = 1) + \cdots + \beta_{K-1} I(A = K-1)\} \\
\vdots \\
R_{c-1} - \expit\{\alpha_{c-1} + \beta_1 I(A = 1) + \cdots + \beta_{K-1} I(A = K-1)\} \\
I(A = 1) \sum_{j=1}^{c-1} \{R_j - \expit(\alpha_j + \beta_1)\} \\
\vdots \\
I(A = K-1) \sum_{j=1}^{c-1} \{R_j - \expit(\alpha_j + \beta_{K-1})\}
\end{pmatrix}_{(c-1+K-1 \times 1)}.
\]

(D.2)

As before, denote by \( \hat{\theta}^F = (\hat{\alpha}^T, \hat{\beta}^T)^T \) the estimators obtained by solving (I) with \( \mathcal{M}(F; \alpha, \beta) \) as in (D.2). Analogous to (I), the influence function for \( \hat{\theta}^F \) is then

\[
-\left[ E \begin{pmatrix}
\frac{\partial \mathcal{M}(F; \alpha, \beta)}{\partial \beta^T(\alpha^T, \beta^T)} \\
\frac{\partial \mathcal{M}(F; \alpha, \beta)}{\partial \alpha^T(\alpha^T, \beta^T)}
\end{pmatrix}_{\alpha = \alpha_0, \beta = \beta_0} \right]^{-1} \mathcal{M}(F; \alpha_0, \beta_0),
\]

(D.3)

and, analogous to (A.1), the gradient matrix in (D.3) satisfies

\[
-E_{\alpha, \beta} \begin{pmatrix}
\frac{\partial \mathcal{M}(F; \alpha, \beta)}{\partial \alpha^T(\alpha^T, \beta^T)} \\
\frac{\partial \mathcal{M}(F; \alpha, \beta)}{\partial \beta^T(\alpha^T, \beta^T)}
\end{pmatrix} = \begin{pmatrix}
B_{11} & B_{12} \\
B_{12}^T & B_{22}
\end{pmatrix}, \quad (c - 1 + K - 1 \times c - 1 + K - 1),
\]

where now, as in (H), \( p_{j0} = \expit(\alpha_j), p_{ja} = \expit(\alpha_j + \beta_a) \), and \( \bar{p}_j = \sum_{a=0}^{K-1} \pi_a p_{ja}(1 - p_{ja}), j = 1, \ldots, c-1, a = 1, \ldots, K-1 \); and \( B_{11} = \text{diag}(\bar{p}_1, \ldots, \bar{p}_{c-1}) \) as before, \( B_{12} \) is the \((c - 1 \times K - 1)\) matrix with \((j, a)\) element given by \( \pi_a p_{ja}(1 - p_{ja}) \), and \( B_{22} = \text{diag}\{\pi_1 \sum_{j=1}^{c-1} p_{j1}(1 - p_{j1}), \ldots, \pi_{K-1} \sum_{j=1}^{c-1} p_{jK-1}(1 - p_{jK-1})\} \) \((K - 1 \times K - 1)\). As in Section 3, add a superscript 0 to these quantities to denote evaluation at \( \alpha_0, \beta_0 \). The \((K - 1 \times 1)\) influence function for
is then given by the last $K - 1$ rows of (D.3) with these definitions, which, using formulæ for the inverse of a partitioned matrix, can be written as $-\{V_\beta \}$ and $I$ form

$$V(\alpha, \beta) = B_{22} - B_{12}^T B_{11}^{-1} B_{12}, \quad m(F; \alpha, \beta) = (B_{12}^T B_{11}^{-1}, \mathcal{I}_{K-1}) \mathcal{M}(F; \alpha, \beta),$$  

(D.4)

and $\mathcal{I}_{K-1}$ denotes a $(K - 1 \times K - 1)$ identity matrix.

The analogs for general $K$ of the observed-data estimating functions in (13) are of the form

$$m^*(O; \alpha, \beta) = \frac{\Delta m(F; \alpha, \beta)}{K(U, A)} - \sum_{a=0}^{K-1} \{I(A = a) - \pi_a\} f^{(a)}(X) + \int dM_c(u, A) h\{u, X, A, \bar{L}(u)\},$$  

(D.5)

where now $m^*(O; \alpha, \beta)$ is $(K - 1 \times 1)$, and

$$f^{(a)}(X) = \begin{pmatrix} f_1^{(a)}(X) \\ \vdots \\ f_{K-1}^{(a)}(X) \end{pmatrix}, \quad a = 0, \ldots, K-1, \quad h\{u, X, A, \bar{L}(u)\} = \begin{pmatrix} h_1\{u, X, A, \bar{L}(u)\} \\ \vdots \\ h_{K-1}\{u, X, A, \bar{L}(u)\} \end{pmatrix}.$$  

The optimal choices of $f^{(a)}(\cdot)$ and $h\{\cdot, X, A, \bar{L}(\cdot)\}$ are, analogous to (17) and (18),

$$f^{(a)}_{\text{opt}}(X; \alpha, \beta) = E\{m(F; \alpha, \beta) \mid X, A = a\}, \quad a = 0, \ldots, K-1,$$

$$h^{\text{opt}}\{u, X, A, \bar{L}(u); \alpha, \beta\} = \frac{E\{m(F; \alpha, \beta) \mid T \geq u, X, A, \bar{L}(u)\}}{K(u, A)}.$$  

With $K = 2$, so that $f^{(a)}(X), a = 0, 1$ are scalar quantities and with $\pi_1 = \pi$ and $\pi_0 = 1 - \pi$, note that in (D.3), $\sum_{a=0}^{1} \{I(A = a) - \pi_a\} f^{(a)}(X) = (A - \pi) \{f^{(1)}(X) - f^{(0)}(X)\} = (A - \pi) f(X),$  

say, as in (13).

As for $K = 2$, because modeling the conditional expectations above is challenging, we approximate them by linear combinations of basis functions. Here, for each $a = 0, \ldots, K-1$, we consider the linear subspace spanned by basis functions $f_1(X), \ldots, f_M(X)$ and, with $f_0(X) \equiv 1$, approximate the $r$th element of $f^{(a)}_{\text{opt}}(X), r = 1, \ldots, K-1$, by

$$\sum_{m=0}^{M} \psi_{ar,m} f_m(X), \quad a = 0, \ldots, K-1.$$  

Because $\sum_{a=0}^{K-1} \{I(A = a) - \pi_a\} = 0$, and because we are taking linear combinations of
\( f_0(X), \ldots, f_M(X) \), generalizing the above when \( K = 2 \), it suffices to consider

\[
\sum_{a=1}^{K-1} \{I(A = a) - \pi_a\} \sum_{m=0}^{M} \psi_{ar,m} f_m(X)
\]

for the \( r \)th element of the first augmentation term in (D.5); i.e., we consider linear combinations of \( f_0(X), \ldots, f_M(X) \) only for \( a = 1, \ldots, K - 1 \). Similarly, for \( a = 0, \ldots, K - 1 \) and specified basis functions \( h_\ell \{u, X, \bar{L}(u)\}, \ell = 1, \ldots, L \), we approximate the \( r \)th element of \( h^{opt} \{u, X, \bar{L}(u); \alpha, \beta\} \) by

\[
I(A = a) \sum_{\ell=1}^{L} \phi_{ar,\ell} h_\ell \{u, X, \bar{L}(u)\}, \quad r = 1, \ldots, K - 1.
\]

Therefore, analogous to (20), the proposed AIPWCC estimator \( \hat{\beta} \) solves in \( \beta \) the estimating equation

\[
\sum_{i=1}^{n} \hat{m}_r(O_i; \hat{\alpha}, \beta) = \sum_{i=1}^{n} \left( \begin{array}{c}
\hat{m}_1(O_i; \hat{\alpha}, \beta) \\
\vdots \\
\hat{m}_{K-1}(O_i; \hat{\alpha}, \beta)
\end{array} \right),
\]

where for \( r = 1, \ldots, K - 1 \)

\[
\sum_{i=1}^{n} \hat{m}_r(O_i; \hat{\alpha}, \beta) = \sum_{i=1}^{n} \left( \frac{\Delta_i m_r(F_i; \hat{\alpha}, \beta)}{\hat{K}(U_i, A_i)} + \int \frac{d\hat{M}_{c,i}(u, A_i) \hat{\mu}_r(m, u, A_i; \hat{\alpha}, \beta)}{\hat{K}(u, A_i)} \right.
\]

\[
- \sum_{a=1}^{K-1} \{I(A_i = a) - \hat{\pi}_a\} \sum_{m=0}^{M} \psi_{ar,m} f_m(X_i)
\]

\[
+ \int d\hat{M}_{c,i}(u, A_i) \sum_{\ell=1}^{L} \phi_{A_i,\ell} \left[ h_\ell \{u, X_i, L_i(u)\} - \hat{\mu}(h_\ell, u, A_i) \right]
\bigg),
\]

\( \hat{\pi}_a = n^{-1} \sum_{i=1}^{n} I(A_i = a), \ a = 1, \ldots, K - 1 \), and

\[
\frac{\hat{\mu}_r(m, u, a; \alpha, \beta)}{\hat{K}(u, a)} = \left\{ \sum_{i=1}^{n} Y_i(u) I(A_i = a) \right\}^{-1} \sum_{i=1}^{n} \left\{ \frac{\Delta_i m_r(F_i; \hat{\alpha}, \beta)}{\hat{K}(U_i, a)} Y_i(u) I(A_i = a) \right\};
\]

and all other quantities are as in Section 4.

Analogous to the two-treatment case, estimators for the optimal choices \( \psi^{opt}_{ar,m}, a = 1, \ldots, K - 1, m = 0, \ldots, M \), and \( \phi^{opt}_{ar,\ell}, a = 0, \ldots, K - 1, \ell = 1, \ldots, L \), can be obtained by least squares regression, element-by-element for \( r = 1, \ldots, K - 1 \). Namely, for each \( r = 1, \ldots, K - 1 \)
separately, regress the “dependent variable”

\[ \hat{Y}_{ir}(\beta) = \frac{\Delta, m_r(F_i; \hat{\alpha}, \beta)}{K(U_i, A_i)} + \int \frac{d\hat{M}_{c,i}(u, A_i)}{K(u, A_i)} \mu_r(m, u, A_i; \hat{\alpha}, \beta) \]

on “covariates” \{I(A_i = a) - \hat{\pi}_a\} f_m(X_i), m = 0, \ldots, M, a = 1, \ldots, K - 1, and I(A_i = a) \int d\hat{M}_{c,i}(u, a)[h_\ell(u, X_i, \tilde{L}_i(u)) - \hat{\mu}(h_\ell, u, a)], \ell = 1, \ldots, L, a = 0, \ldots, K - 1.

The foregoing developments lead to the following generalization of the two-step strategy in Section 5:

1. Obtain initial estimates \( \hat{\alpha} \) and \( \hat{\beta}_{\text{init}} \), say, by solving an IPWCC version of the full-data estimating equations with estimating function (D.2); namely, solve jointly in \( \alpha \) and \( \beta \) the \((c - 1 + K - 1)\) equations

\[
\sum_{i=1}^{n} \frac{\Delta_i}{K(U_i, A_i)} \left[ R_{ji} - \expit\{\alpha_1 + \beta_1I(A_i = 1) + \cdots + \beta_{K-1}I(A_i = K - 1)\} \right] = 0, \\
\quad j = 1, \ldots, c - 1,
\]

\[
\sum_{i=1}^{n} \frac{\Delta_i}{K(U_i, A_i)} I(A_i = a) \sum_{j=1}^{c-1} \left[ R_{ji} - \expit\{\alpha_1 + \beta_1I(A_i = 1) + \cdots + \beta_{K-1}I(A_i = K - 1)\} \right] = 0, \\
\quad a = 1, \ldots, K - 1.
\]

2. Obtain least squares estimators \( \hat{\psi}_{ar,m}, a = 1, \ldots, K - 1, m = 0, \ldots, M, \) and \( \hat{\phi}_{ar,\ell}, a = 0, \ldots, K - 1, \ell = 1, \ldots, L, \) for each \( r = 1 \ldots, K - 1 \) by regressing \( \hat{Y}_{ir}(\hat{\beta}_{\text{init}}) \) on the “covariates” above, separately for each \( r \). Then obtain the “predicted values” \( \text{Pred}_i = (\text{Pred}_{i1}, \ldots, \text{Pred}_{iK-1})^T \), where

\[
\text{Pred}_{ir} = \sum_{a=1}^{K-1} \left\{ I(A_i = a) - \hat{\pi}_a \right\} \sum_{m=0}^{M} \hat{\psi}_{ar,m} f_m(X_i) \\
\quad + \int \frac{d\hat{M}_{c,i}(u, A_i)}{K(u, A_i)} \sum_{\ell=1}^{L} \hat{\phi}_{A_r,\ell}[h_\ell(u, X_i, \tilde{L}_i(u)) - \hat{\mu}(h_\ell, u, A_i)];
\]

and obtain the AIPWCC estimator \( \hat{\beta} \) as the one-step update

\[
\hat{\beta} = \hat{\beta}_{\text{init}} - \{\nabla(\hat{\alpha}, \hat{\beta}_{\text{init}})\}^{-1} n^{-1} \sum_{i=1}^{n} \text{Pred}_i.
\]
where \( V(\alpha, \beta) \) is defined in (D.4). The asymptotic variance for \( \hat{\beta} \) can be estimated by
\[
\{V(\hat{\alpha}, \hat{\beta}_{\text{init}})\}^{-1} \sum_{i=1}^{n} \{\hat{Y}_i(\hat{\beta}_{\text{init}}) - \text{Pred}_i\}\{\hat{Y}_i(\hat{\beta}_{\text{init}}) - \text{Pred}_i\}^T \{V(\hat{\alpha}, \hat{\beta}_{\text{init}})\}^{-1},
\]
where \( \hat{Y}_i(\hat{\beta}_{\text{init}}) = \{\hat{Y}_{i1}(\hat{\beta}_{\text{init}}), \ldots, \hat{Y}_{iK-1}(\hat{\beta}_{\text{init}})\}^T \).

Table 5 shows results of simulation experiments with \( K = 3 \) analogous to those under Scenarios 1 and 2 in Section 6, each involving 5000 Monte Carlo replications with \( n = 903 \) subjects and \( \pi_0 = \pi_1 = \pi_2 = 1/3 \), with \( A \) generated as multinomial with these probabilities.

We generated \( \Gamma \) such that the distribution of \( \Gamma \) given \( A = 0 \) was \( U(0, 1) \) and those of \( \Gamma \) given \( A = a, a = 1, 2 \) followed a proportional odds model as in (D.1) with logit \( \{\text{pr}(\Gamma \geq u | A = a)\} = \logit\{\text{pr}(\Gamma \geq u | A = 0)\} + \beta_a \), where \( \beta_a = \log(\text{OR}_a) \), \( a = 1, 2 \), and \( \text{OR}_1 = 1.5 \) and \( \text{OR}_2 = 1.2 \) under Scenario 1 and \( \text{OR}_1 = \text{OR}_2 = 1.0 \) under Scenario 2. This was accomplished by taking \( \Gamma = I(A = 0) \Upsilon + I(A = 1) \Upsilon(1/\text{OR}_1)/\{1 - \Upsilon + \Upsilon(1/\text{OR}_1)\} + I(A = 2) \Upsilon(1/\text{OR}_2)/\{1 - \Upsilon + \Upsilon(1/\text{OR}_2)\} \). We assumed the six categories in Table 1 of the main paper and generated \( H \) and \( T \) as described in Section 6, except that when \( \Gamma \geq 0.67 \), corresponding to death, we generated \( T = \text{time of death} \) by generating \( T_a \sim U(a_0, b_a) \), \( a = 0, 1, 2 \), \( (a_0, b_0) = (0, 30) \), \( (a_1, b_1) = (20, 50) \), \( (a_2, b_2) = (25, 60) \) and taking \( T = 90I(\Gamma < 0.67) + \{I(A = 0)T_0 + I(A = 1)T_1 + I(A = 2)T_2\}I(\Gamma \geq 0.67) \). The time-independent and time-dependent covariates \( X \) and \( L_1(u), L_2(u) \) and the censoring time \( C \) were generated as in Section 6. For brevity, Table 5 shows results for estimation of \( \beta_1 \) and \( \beta_2 \) using methods c-e in Section 6 i.e., using the IPWCC estimator \( \hat{\beta}_{\text{IPW}} \) and the one-step AIPWCC estimators \( \hat{\beta}_{\text{AIPW}1} \) and \( \hat{\beta}_{\text{AIPW}2} \) using only the augmentation term involving baseline covariates (so with \( \phi_{ar, \ell} = 0 \), \( a = 0, 1, 2 \), \( \ell = 1, \ldots, L \), \( r = 1, \ldots, K - 1 \)) and using both augmentation terms. Overall, the results are qualitatively similar to those in Section 6 and demonstrate the good performance of the methods and the considerable efficiency gains possible via the fully augmented estimator \( \hat{\beta}_{\text{AIPW}2} \).
**Table 1**

*Assumed distributions of primary outcome categories in the TESICO study. Entries are expressed as percentages.*

| Category | Status at 90 days                                                                 | Investigational agent | Control |
|----------|----------------------------------------------------------------------------------|-----------------------|---------|
| 1        | At home and off oxygen, number of days $\geq 77$                                 | 17.0                  | 12.0    |
| 2        | At home and off oxygen, number of days 49-76                                     | 27.7                  | 23.0    |
| 3        | At home and off oxygen, number of days 1-48                                       | 17.2                  | 17.0    |
| 4        | Not hospitalized AND either at home on oxygen OR not at home                       | 9.1                   | 10.0    |
| 5        | Hospitalized for medical care OR in hospice care                                  | 4.3                   | 5.0     |
| 6        | Dead                                                                             | 24.7                  | 33.0    |
| **Total**|                                                                                  | 100.00                | 100.00  |
Table 2
Simulation results, \( n = 602 \), true proportional odds model. Entries are based on estimates of \( OR = \exp(\beta) \) using the indicated estimator. MC mean is the mean of 5000 Monte Carlo estimates; MC median is the median of 5000 Monte Carlo estimates; MC SD is the Monte Carlo standard deviation, Ave MC SE is the mean of Monte Carlo standard estimates, MC Cov is the Monte Carlo coverage of a nominal 95% Wald-type confidence interval for \( \exp(\beta) \), MC MSE ratio is the ratio of Monte Carlo mean square error for the indicated estimator relative to that for the AIPW2 estimator, and MC pr(reject \( H_0 \)) is the proportion of times a two-sided, level-0.05 Wald-type test of \( H_0: \log(OR) = 0 \) based on the indicated estimator rejects \( H_0 \).

| Scenario | \( \hat{\beta}_{\text{ideal}} \) | \( \hat{\beta}_{\text{ideal,adj}} \) | \( \hat{\beta}_{\text{LOR}} \) | \( \hat{\beta}_{\text{AIPW1,full}} \) | \( \hat{\beta}_{\text{naive}} \) | \( \hat{\beta}_{90} \) | \( \hat{\beta}_{\text{IPW}} \) | \( \hat{\beta}_{\text{AIPW1}} \) | \( \hat{\beta}_{\text{AIPW2}} \) |
|----------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Scenario 1: 6 categories, \( \beta = \log(1.5) \) | 1.516 | 1.586 | 1.513 | 1.512 | 1.836 | 1.554 | 1.527 | 1.522 | 1.519 |
| MC mean | 1.498 | 1.569 | 1.499 | 1.497 | 1.786 | 1.487 | 1.492 | 1.490 | 1.498 |
| MC median | 0.224 | 0.240 | 0.208 | 0.208 | 0.426 | 0.419 | 0.302 | 0.289 | 0.253 |
| MC SD | 0.221 | 0.236 | 0.206 | 0.206 | 0.411 | 0.396 | 0.298 | 0.284 | 0.248 |
| Ave MC SE | 0.950 | 0.937 | 0.947 | 0.948 | 0.874 | 0.948 | 0.951 | 0.949 | 0.951 |
| MC Cov | 0.785 | 1.012 | 0.679 | 0.677 | 4.579 | 2.774 | 1.429 | 1.306 | 1.000 |
| MC MSE ratio | 0.792 | 0.861 | 0.844 | 0.845 | 0.739 | 0.357 | 0.543 | 0.580 | 0.696 |
| MC pr(reject \( H_0 \)) | 0.792 | 0.861 | 0.679 | 0.677 | 4.579 | 2.774 | 1.429 | 1.306 | 1.000 |
| Scenario 2: 6 categories, \( \beta = \log(1.0) \) | 1.010 | 1.008 | 1.007 | 1.007 | 1.200 | 1.031 | 1.015 | 1.012 | 1.008 |
| MC mean | 0.999 | 0.996 | 0.996 | 0.996 | 1.162 | 0.990 | 0.994 | 0.994 | 0.995 |
| MC median | 0.148 | 0.152 | 0.139 | 0.138 | 0.277 | 0.277 | 0.198 | 0.189 | 0.168 |
| MC SD | 0.147 | 0.150 | 0.137 | 0.136 | 0.267 | 0.262 | 0.195 | 0.186 | 0.163 |
| Ave MC SE | 0.950 | 0.948 | 0.948 | 0.948 | 0.884 | 0.948 | 0.949 | 0.948 | 0.947 |
| MC Cov | 0.780 | 0.815 | 0.681 | 0.670 | 4.104 | 2.737 | 1.394 | 1.269 | 1.000 |
| MC MSE ratio | 0.050 | 0.052 | 0.052 | 0.052 | 0.116 | 0.052 | 0.051 | 0.052 | 0.053 |
| MC pr(reject \( H_0 \)) | 0.050 | 0.052 | 0.052 | 0.052 | 0.116 | 0.052 | 0.051 | 0.052 | 0.053 |
| Scenario 3: 10 categories, \( \beta = \log(1.5) \) | 1.520 | 1.592 | 1.520 | 1.517 | 1.851 | 1.553 | 1.537 | 1.535 | 1.529 |
| MC mean | 1.502 | 1.574 | 1.508 | 1.505 | 1.802 | 1.505 | 1.509 | 1.507 | 1.506 |
| MC median | 0.219 | 0.234 | 0.210 | 0.202 | 0.415 | 0.398 | 0.318 | 0.307 | 0.252 |
| MC SD | 0.220 | 0.233 | 0.209 | 0.202 | 0.413 | 0.391 | 0.317 | 0.304 | 0.246 |
| Ave MC SE | 0.953 | 0.937 | 0.952 | 0.952 | 0.872 | 0.950 | 0.951 | 0.953 | 0.948 |
| MC Cov | 0.751 | 0.982 | 0.689 | 0.640 | 4.592 | 2.512 | 1.589 | 1.479 | 1.000 |
| MC MSE ratio | 0.805 | 0.876 | 0.849 | 0.861 | 0.760 | 0.365 | 0.513 | 0.545 | 0.719 |
| MC pr(reject \( H_0 \)) | 0.805 | 0.876 | 0.849 | 0.861 | 0.760 | 0.365 | 0.513 | 0.545 | 0.719 |
| Scenario 4: 10 categories, \( \beta = \log(1.0) \) | 1.012 | 1.012 | 1.012 | 1.011 | 1.206 | 1.031 | 1.023 | 1.021 | 1.015 |
| MC mean | 1.002 | 1.002 | 1.003 | 1.002 | 1.179 | 0.997 | 1.005 | 1.001 | 1.000 |
| MC median | 0.145 | 0.149 | 0.144 | 0.135 | 0.268 | 0.265 | 0.210 | 0.203 | 0.168 |
| MC SD | 0.146 | 0.148 | 0.143 | 0.135 | 0.268 | 0.259 | 0.210 | 0.202 | 0.163 |
| Ave MC SE | 0.952 | 0.951 | 0.951 | 0.951 | 0.885 | 0.952 | 0.953 | 0.948 | 0.949 |
| MC Cov | 0.749 | 0.782 | 0.729 | 0.647 | 4.031 | 2.500 | 1.570 | 1.469 | 1.000 |
| MC MSE ratio | 0.749 | 0.782 | 0.729 | 0.647 | 4.031 | 2.500 | 1.570 | 1.469 | 1.000 |
| MC pr(reject \( H_0 \)) | 0.048 | 0.049 | 0.049 | 0.049 | 0.115 | 0.048 | 0.047 | 0.052 | 0.051 |
Table 3
Simulation results, \( n = 602 \), true proportional hazards model. Entries are as in Table 2.

| Scenario 5: 6 categories, “true” \( \beta = \log(1.48) \) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| \( \hat{\beta}_{\text{ideal}} \) | \( \hat{\beta}_{\text{ideal,adj}} \) | \( \hat{\beta}_{\text{LOR}} \) | \( \hat{\beta}_{\text{AIPW1,full}} \) | \( \hat{\beta}_{\text{naive}} \) | \( \hat{\beta}_{90} \) | \( \hat{\beta}_{\text{IPW}} \) | \( \hat{\beta}_{\text{AIPW1}} \) | \( \hat{\beta}_{\text{AIPW2}} \) |
| MC mean | 1.496 | 1.497 | 1.505 | 1.516 | 1.898 | 1.538 | 1.531 | 1.531 | 1.528 |
| MC median | 1.478 | 1.481 | 1.486 | 1.499 | 1.842 | 1.491 | 1.498 | 1.498 | 1.499 |
| MC SD | 0.219 | 0.220 | 0.223 | 0.224 | 0.438 | 0.407 | 0.309 | 0.310 | 0.275 |
| Ave MC SE | 0.218 | 0.219 | 0.222 | 0.223 | 0.425 | 0.391 | 0.300 | 0.299 | 0.265 |
| MC Cov | 0.953 | 0.953 | 0.951 | 0.953 | 0.831 | 0.951 | 0.948 | 0.948 | 0.946 |
| MC MSE ratio | 0.620 | 0.626 | 0.648 | 0.663 | 4.708 | 2.178 | 1.261 | 1.265 | 1.000 |
| MC pr(reject \( H_0 \)) | 0.768 | 0.769 | 0.770 | 0.788 | 0.786 | 0.345 | 0.548 | 0.546 | 0.647 |
Table 4
Simulation results, n = 602, Scenario 6. Entries are as in Table 2 of the main paper.

|                  | $\hat{\beta}_{\text{ideal}}$ | $\hat{\beta}_{\text{ideal,adj}}$ | $\hat{\beta}_{\text{LOR}}$ | $\hat{\beta}_{\text{AIPW1,full}}$ | $\hat{\beta}_{\text{naive}}$ | $\hat{\beta}_{90}$ | $\hat{\beta}_{\text{IPW}}$ | $\hat{\beta}_{\text{AIPW1}}$ | $\hat{\beta}_{\text{AIPW2}}$ |
|------------------|-------------------------------|-----------------------------------|----------------------------|----------------------------------|------------------------------|-----------------|------------------|------------------|------------------|
| Scenario 6: 6 categories, “true” $\beta = \log(1.49)$ |                               |                                   |                             |                                  |                             |                 |                  |                  |                  |
| MC mean          | 1.504                         | 1.569                             | 1.501                       | 1.519                            | 1.556                        | 1.539            | 1.535            | 1.533            | 1.528            |
| MC median        | 1.487                         | 1.550                             | 1.487                       | 1.503                            | 1.518                        | 1.489            | 1.502            | 1.507            | 1.506            |
| MC SD            | 0.222                         | 0.238                             | 0.207                       | 0.210                            | 0.352                        | 0.407            | 0.298            | 0.285            | 0.245            |
| Ave MC SE        | 0.220                         | 0.234                             | 0.204                       | 0.207                            | 0.344                        | 0.393            | 0.291            | 0.277            | 0.238            |
| MC Cov           | 0.949                         | 0.941                             | 0.952                       | 0.949                            | 0.947                        | 0.951            | 0.945            | 0.946            | 0.943            |
| MC MSE ratio     | 0.805                         | 1.023                             | 0.700                       | 0.730                            | 2.087                        | 2.739            | 1.476            | 1.351            | 1.000            |
| MC pr(reject $H_0$) | 0.774                        | 0.839                             | 0.834                       | 0.858                            | 0.474                        | 0.347            | 0.571            | 0.616            | 0.749            |
Table 5
Simulation results, n = 903, true proportional odds model with K = 3. Entries are based on estimates of OR₁ = exp(β₁) and OR₂ = exp(β₂) using the indicated estimator. MC mean is the mean of 5000 Monte Carlo estimates; MC median is the median of 5000 Monte Carlo estimates; MC SD is the Monte Carlo standard deviation, Ave MC SE is the mean of Monte Carlo standard estimates, MC Cov is the Monte Carlo coverage of a nominal 95% Wald-type confidence interval for exp(βₐ), a = 1, 2, MC MSE ratio is the ratio of Monte Carlo mean square error for the indicated estimator relative to that for the AIPW² estimator, and MC pr(reject H₀) is the proportion of times a two-sided, level-0.05 Wald-type test of H₀: log(OR) = 0 based on the indicated estimator rejects H₀.

| Scenario 1: 6 categories, β₁ = log(1.5), β₂ = log(1.2) | β₁,IPW | β₁,AIPW₁ | β₁,AIPW₂ | β₂,IPW | β₂,AIPW₁ | β₂,AIPW₂ |
|--------------------------------------------------------|---------|---------|---------|---------|---------|---------|
| MC mean                                                | 1.529   | 1.528   | 1.524   | 1.221   | 1.221   | 1.216   |
| MC median                                              | 1.500   | 1.499   | 1.507   | 1.198   | 1.202   | 1.198   |
| MC SD                                                  | 0.304   | 0.291   | 0.254   | 0.243   | 0.233   | 0.207   |
| Ave MC SE                                              | 0.298   | 0.285   | 0.249   | 0.239   | 0.228   | 0.199   |
| MC Cov                                                 | 0.949   | 0.948   | 0.948   | 0.951   | 0.947   | 0.941   |
| MC MSE ratio                                            | 1.430   | 1.312   | 1.000   | 1.385   | 1.275   | 1.000   |
| MC pr(reject H₀)                                       | 0.550   | 0.593   | 0.700   | 0.156   | 0.165   | 0.207   |

| Scenario 2: 6 categories, β₁ = β₂ = log(1.0)           | β₁,IPW | β₁,AIPW₁ | β₁,AIPW₂ | β₂,IPW | β₂,AIPW₁ | β₂,AIPW₂ |
|--------------------------------------------------------|---------|---------|---------|---------|---------|---------|
| MC mean                                                | 1.016   | 1.016   | 1.011   | 1.015   | 1.015   | 1.011   |
| MC median                                              | 0.997   | 0.999   | 0.997   | 0.997   | 0.998   | 0.998   |
| MC SD                                                  | 0.199   | 0.190   | 0.167   | 0.202   | 0.193   | 0.172   |
| Ave MC SE                                              | 0.195   | 0.187   | 0.163   | 0.198   | 0.189   | 0.165   |
| MC Cov                                                 | 0.949   | 0.948   | 0.946   | 0.951   | 0.950   | 0.941   |
| MC MSE ratio                                            | 1.426   | 1.303   | 1.000   | 1.372   | 1.262   | 1.000   |
| MC pr(reject H₀)                                       | 0.051   | 0.052   | 0.054   | 0.049   | 0.050   | 0.059   |