ESCAPING THE TRAP: REPLACING THE TRAPEZOIDAL RULE TO BETTER IMPUTE CENSORED COVARIATES WITH THEIR CONDITIONAL MEANS

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ABSTRACT

Clinical trials to test experimental treatments for Huntington’s disease are expensive, so it is prudent to enroll subjects whose symptoms may be most impacted by the treatment during follow-up. However, modeling how symptoms progress to identify such subjects is problematic since time to diagnosis, a key covariate, can be censored. Imputation is an appealing strategy where censored covariates are replaced with their conditional means, the calculation of which requires estimating and integrating over its conditional survival function from the censored value to infinity. To flexibly estimate the survival function, existing approaches use the semiparametric Cox model with Breslow’s estimator. Then, for integration, the trapezoidal rule is used, but the trapezoidal rule is not designed for indefinite integrals and leads to bias. We propose a conditional mean calculation that properly handles the indefinite integral with adaptive quadrature. Yet, even with adaptive quadrature, the integrand (the survival function) is undefined beyond the observed data, so we explore methods to extend it. In extensive simulation studies, we show that replacing the trapezoidal rule with adaptive quadrature corrects the bias seen with existing methods. We further illustrate how imputing with corrected conditional means can help prioritize patients for a new Huntington’s disease trial.

Keywords Adaptive quadrature · Breslow’s estimator · Conditional mean imputation · Huntington’s disease · Time to diagnosis

1 Introduction

1.1 Modeling the Progression of Huntington’s Disease

Prospective studies are common for genetically inherited diseases because at-risk subjects can be identified through genetic testing and their symptom development can be followed over time. Such studies are especially powerful for Huntington’s disease, a genetically inherited neurodegenerative disease caused by unstable cytosine-adenine-guanine (CAG) repeats in the HTT gene [The Huntington’s Disease Collaborative Research Group, 1993]. Huntington’s disease is fully penetrant, so anyone with ≥ 36 CAG repeats is not just at risk of but sadly guaranteed to develop the disease. One such prospective study is the Neurobiological Predictors of Huntington’s Disease (PREDICT-HD) [Paulsen et al., 2008].

Modeling the progression of Huntington’s disease using data from prospective studies like PREDICT-HD is appealing, for example, as we investigate experimental treatments designed to slow or delay symptoms. Models of how impairment (i.e., in daily, motor, and cognitive function) progresses relative to the time of clinical diagnosis can help identify subjects to recruit into new clinical trials. Huntington’s disease symptoms are most detectable in the few years immediately before and after a diagnosis, so subjects in this window of time would be ideal to test a new therapy in a clinical trial.
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Unfortunately, Huntington’s disease progresses slowly, with functional, motor, and cognitive decline spanning decades, so prospective studies often end before all at-risk subjects have met the criteria for diagnosis. (A diagnosis is made when motor abnormalities are unequivocal signs of Huntington’s disease [Huntington Study Group, 1996].) Therefore, the slow-moving nature of the disease leaves the key variable “time to diagnosis” right-censored among subjects who have yet to be diagnosed (i.e., their motor abnormalities will merit a diagnosis sometime after their last study visit, but exactly when is unknown). Thus, we face a pressing statistical challenge when investigating Huntington’s disease progression: how to model the association between a fully observed outcome (impairment) and a right-censored covariate (time to diagnosis).

1.2 Imputing a Censored Covariate

Inspired by missing data techniques, one appealing strategy is conditional mean imputation, where we replace all right-censored times to diagnosis with their conditional means [Atem et al., 2017, 2019a,b]. This conditional mean imputation ensures that the imputed time to diagnosis is realistic (i.e., after the last study visit) and adjusts for other variables that may influence time to diagnosis (e.g., CAG repeat length). The conditional mean for a right-censored value is the expected time to diagnosis given that it must happen after the censored value (the last study visit) and additional covariates. In theory, this expected time to diagnosis can be anywhere from the last study visit to infinity, so computing it involves an integral over this range.

Existing approaches to conditional mean imputation use the trapezoidal rule to compute this integral [Atem et al., 2017, 2019a,b]. Specifically, they define partitions based on the observed covariate values and their corresponding survival functions. However, the trapezoidal rule is intended for definite integrals (meaning those with finite lower and upper bounds), not indefinite integrals, which are needed to compute conditional means. Existing methods rely on the data to define their upper bound, ending the final partition at the largest observed covariate value. Thus, for the trapezoidal rule to hold in this indefinite integral case, the largest observed covariate value in the data must represent the variable’s true maximum (which, in theory, could be infinity); otherwise, data beyond that value will be “cut off.” Since the survival function of the censored covariate is nonnegative and decreases monotonically, this “cut-off” leads the trapezoidal rule to underestimate the integral and miscalculate the conditional means.

For example, if the last time to diagnosis in PREDICT-HD was 10 years from study entry, the trapezoidal rule used by existing approaches will assume that all unobserved times to diagnosis should be observed within 10 years of study entry, and the possibility of longer disease-free survival is ignored. Clinically, we know this is likely not the case and that diagnosis could occur at any time point between the last study visit and time of death, both of which are unique to each subject. Therefore, existing methods that use the trapezoidal rule are likely to impute censored covariates with incorrect conditional means, leading to invalid (i.e., biased) statistical inference. To avoid this situation, we propose several improvements to conditional mean imputation for a censored covariate.

1.3 Numerical Integration of Indefinite Integrals

Many methods may come to mind that handle integrals with infinite bounds, such as Gauss–Hermite quadrature. In fact, there are many attractive methods for numerical integration already implemented in existing software that can handle indefinite bounds, for example, the `integrate` function in R, which uses adaptive quadrature [R Core Team, 2019]. However, even with these methods, we can only integrate over values of the covariate where the integrand is defined.

As we will discuss in Section 2.2, calculating the conditional mean involves integrating over the conditional survival function (the integrand) of the censored covariate up to infinity. Typically, this function relies on a step function (in this case, Breslow’s estimator), which is only defined up to the largest uncensored covariate value. Importantly, this step function leaves the integrand undefined beyond the observed covariate values and up to infinity, so more accurate quadrature alone will not improve the estimation of the conditional means. (We note that this is “typical” because nonparametric or semiparametric estimators are often chosen because of their distribution-free robustness but they rely on step functions; a parametric survival function would already be defined up to infinity.)

To truly improve the calculation, we need the integrand to be defined up to the infinite bound in the conditional mean formula. Specifically, before we can adopt an improved integration approach (in our case, adaptive quadrature), we need a way to extrapolate from Breslow’s estimator beyond the largest uncensored value. Drawing from the more traditional survival analysis literature (e.g., Klein and Moeschberger [2003]), we evaluate multiple methods to perform this extrapolation and provide a thorough comparison of their performance in Section 3.3.
1.4 Overview

We propose an improved conditional mean calculation to impute censored covariates in statistical models: one that replaces the trapezoidal rule with adaptive quadrature with an infinite upper bound. Since Breslow’s estimator is not well defined for larger values than those in the data, we explore various methods to extend it for use with quadrature. We quantify the bias introduced by the trapezoidal rule and show that replacing it with adaptive quadrature as described does an excellent job of correcting for that bias. In addition to our extensive simulation studies, we illustrate how imputing with biased conditional means can impact clinical decision-making and clinical trial recruitment. The rest of the paper is organized as follows: we describe the proposed methods in Section 2, we evaluate the performance of the proposed methods against existing ones through extensive simulations in Section 3, we apply both approaches to the analysis of Huntington’s disease data in the PREDICT-HD study in Section 4, and we discuss our findings in Section 5.

2 Methods

2.1 Model and Data

Consider an outcome \( Y \) and covariates \((X, Z)\), which are assumed to be related through a regression model parameterized by \( \theta \) and denoted by \( P_\theta(Y|X, Z) \). For example, if \( Y, X, \) and \( Z \) follow a linear regression model, we would have that

\[
P_\theta(Y|X, Z) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp \left\{ -\frac{(Y - \alpha - \beta X - \gamma^T Z)^2}{2\sigma^2} \right\},
\]

where \( \theta = (\alpha, \beta, \gamma^T, \sigma^2)^T \). Our primary interest is in statistical inference of \( \theta \).

Unfortunately, estimating \( \theta \) is difficult because the covariate \( X \) is right-censored. Rather than observe \( X \) directly, we observe the covariate \( W = \min(X, C) \) and corresponding “event” indicators \( \Delta = I(X \leq C) \), where \( C \) is a random censoring value. (Having \( C \) random rather than fixed means that \( C \) changes for every subject. In the Huntington’s disease example, \( C \) is the subject-specific length of follow-up from first to last study visit.) Thus, observations for a sample of \( n \) subjects are captured as \((Y_i, \Delta_i, W_i, Z_i)\) \((i = 1, \ldots, n)\).

If we were to ignore the covariate censoring, we could “plug in” the observed values \( W \) and fit the model \( P_\theta(Y|W, Z) \) instead of \( P_\theta(Y|X, Z) \). However, this “naive” model will lead to biased parameter estimates for \( \theta \) and inflated variability [Austin and Hoch, 2004]. A straightforward alternative is the complete case analysis, which subsets to only the observations with uncensored covariates. However, excluding censored observations would be inefficient and could also lead to biased inference unless the censoring is independent of all other variables (a strong assumption) [Lipsitz et al., 2004]. Therefore, more advanced methods are needed to obtain efficient, unbiased statistical inference when \( X \) is censored.

2.2 Conditional Mean Imputation

In missing data settings, imputation is a popular approach to obtain valid statistical inference without sacrificing the power of the full sample. Imputation is also a promising method to handle censored covariates, with one simple change [Aten et al., 2017]. Whenever \( X_i \) is right-censored, rather than impute any value for it, we impute a value that is larger than \( W_i \) because, by the definition of right-censoring, the true unobserved \( X \) must be larger than \( W_i \). This partial information (i.e., that \( X > W_i \)) is captured through a conditional mean imputation approach [Little, 1992, Richardson and Ciampi, 2003].

In conditional mean imputation, we replace any right-censored covariates \( W_i \) with their corresponding conditional means

\[
E(X|X > W_i, Z_i) = W_i + \int_{W_i}^{\infty} \frac{S(x|Z_i)dx}{S(W_i|Z_i)},
\]

where \( S(t|z) \) is the conditional survival function for \( X \) given \( Z \), defined as \( P(X \geq t|Z = z) \). To our knowledge, this form of \( E(X|X > W_i, Z_i) \) was first introduced by Atem et al. [2017], and recently a thorough derivation was set forth by Lotspeich et al. [2022]. Importantly, deriving Equation (1) relies on the assumption of noninformative censoring, such that the censoring values \( C \) and true covariates \( X \) are assumed to be conditionally independent given the other fully observed covariates \( Z \).

Remark. We use the \( i \) subscript for \( W_i \) and \( Z_i \) in Equation (1) because these are observed values of random variables \( W \) and \( Z \), respectively, whereas \( X \) (no subscript) is still random.
Now, conditional mean imputation proceeds in two stages. First, we calculate the conditional means for all censored covariates, which requires estimating $S(t \mid z)$ (Section 2.3) and approximating the integral over it (Sections 2.4–2.5). Then, we replace (i.e., impute) the censored covariates with these conditional means and fit the outcome model for $Y$ given (imputed) $X$ and $Z$ using the “usual” methods, for example, ordinary least squares, to obtain the conditional mean imputation estimators $\bar{\theta}$.

### 2.3 Estimating the Survival Function

In the simplest case when there are no additional covariates $Z$, we can instead estimate the simplified conditional means $E(X \mid X > W_i)$ using the marginal survival function $S(t)$ for $X$ using the Kaplan–Meier estimator, which imposes no restrictive assumptions [Kaplan and Meier, 1958]. However, in our Huntington’s disease example and others, we have additional covariates $Z$ (e.g., CAG repeat length) that are known to influence the survival function. Therefore, to robustly estimate $S(t \mid Z)$ in Equation (1) without assuming a distribution for $X$ given $Z$ (and in doing so, bypassing some potential misspecification), existing approaches use semiparametric models [Atem et al., 2017, 2019a,b]. Specifically, existing approaches use a Cox proportional hazards model, from which the survival function can be calculated as $S(t \mid z) = S_0(t)^{\exp(\lambda^T z)}$ with $\lambda$ the log hazard ratios and $S_0(t)$ the baseline survival function of $X$ (i.e., at $Z = 0$).

This semiparametric model for $S(t \mid Z)$ requires estimating two key parts: (i) the log hazard ratios $\lambda$ and (ii) the baseline survival function $S_0(t)$. The log hazard ratios are easily estimated from existing software, like the `survival` package [Therneau and Grambsch, 2000], and a common way to estimate $S_0(t)$ is with Breslow’s estimator [Breslow, 1972]:

$$\hat{S}(t) = \exp \left[ - \sum_{i=1}^{n} I(W_i \leq t) \left\{ \frac{\Delta_i}{\sum_{j=1}^{n} I(W_j \leq W_i) \exp \left( \hat{X}^T Z_j \right) } \right\} \right].$$

After estimating $\lambda$ and $S_0(t)$, we will construct $S(t \mid z) = \hat{S}_0(t)^{\exp(\hat{X}^T z)}$ and use this estimated survival function to compute $E(X \mid X > W_i, Z_i)$ from Equation (1). Alas, computing this conditional mean still requires integrating over $S(t \mid z)$ from $t = W_i$ to $\infty$.

### 2.4 The Problem with Using the Trapezoidal Rule to Calculate Conditional Means

Existing approaches use the trapezoidal rule to estimate this integral and compute the conditional means. That is, they estimate the integral $\int_{W_i}^{\infty} \hat{S}_0(x)^{\exp(\hat{X}^T z)} \, dx$ with

$$\frac{1}{2} \sum_{j=1}^{n-1} I(W_j \geq W_i) \left\{ \hat{S}_0(W_{j+1})^{\exp(\hat{X}^T Z_i)} + \hat{S}_0(W_j)^{\exp(\hat{X}^T Z_i)} \right\} \left( W_{j+1} - W_j \right),$$

where $W_1 < \cdots < W_{(n)}$ denotes $n$ distinct, ordered values of $W$ from the data. Going forward, let the conditional mean following the trapezoidal rule be $\hat{E}(X \mid X > W_i, Z_i) =$

$$W_i + \frac{1}{2} \left( \sum_{j=1}^{n-1} I(W_j \geq W_i) \left\{ \hat{S}_0(W_{j+1})^{\exp(\hat{X}^T Z_i)} + \hat{S}_0(W_j)^{\exp(\hat{X}^T Z_i)} \right\} \left( W_{j+1} - W_j \right) \right).$$

This formula for the conditional mean is prominent in the current literature around imputing randomly right-censored covariates [Atem et al., 2017, 2019a,b, Lotspeich et al., 2022].

Notice that the “trapezoids” in Expression (3) are defined between the observed covariate values $W_j \geq W_i$ and their survival functions given the $j$th subject’s covariates, $\hat{S}(W_j \mid Z_i) = \hat{S}_0(W_j)^{\exp(\hat{X}^T Z_i)}$. Since some $W_j$ will be censored, computing $\hat{E}(X \mid X > W_i, Z_i)$ requires evaluating Breslow’s estimator $\hat{S}_0(\cdot)$ between and beyond the uncensored data on which it is defined. Between uncensored values, $\hat{S}_0(\cdot)$ should be carried forward (interpolated) from the last uncensored value. Beyond the largest uncensored value, $\hat{S}_0(\cdot)$ is not well defined; we consider multiple methods to extrapolate from it in Section 2.5.

**Remark.** Instead of using Breslow’s estimator as defined, the existing approaches (e.g., Atem et al. [2019a]) interpolate with the mean baseline survival from the uncensored values immediately below and above a censored $W_j$. Here, we will adopt carry forward interpolation between uncensored values because of its computational simplicity and because
it follows from the original formula in Breslow [1972], although we show in Section 3.3 that either mean or carry forward interpolation seems to work well.

Critically, we recognize that this use of the trapezoidal rule in Expression (3) estimates the wrong integral, approximating \( \int_{W_{(n)}}^{W(n)} \hat{S}_0(x)^\exp(\hat{X}^Tz_i)\,dx \) rather than \( \int_{W_{(n)}}^{W(n)} \hat{S}_0(x)^{\exp(\hat{X}^Tz_i)}\,dx \). The validity of this approximation, and with it the quality of the conditional means, hinges on how well the maximum of the observed covariate \( W_1(n) \) represents the true maximum of the covariate \( X \). If \( W_1(n) \) is far below the true upper bound of \( X \), then approximating with \( \int_{W_{(n)}}^{W(n)} \hat{S}_0(x)^{\exp(\hat{X}^Tz_i)}\,dx \) will underestimate the integral by “cutting off” the tail of the survival function. We conclude that using the trapezoidal rule to calculate conditional means is only appropriate when \( \hat{S}_0(W_1(n)) \approx 0 \), because in this case the survival function is entirely captured by \( W_1(n) < \cdots < W_{(n)} \). Therefore, we set out to propose a more general approach to correctly calculate conditional means even when \( \hat{S}_0(W_1(n)) > 0 \).

### 2.5 Replacing the Trapezoidal Rule with Adaptive Quadrature

We sought an improved calculation to capture the entirety of the indefinite integral in the conditional means by extending beyond \( W_1(n) \) to better approximate the infinite upper bound. Conveniently, the \texttt{integrate} function in R implements “adaptive quadrature of functions ... over a finite or infinite interval” [Piessens et al., 1983; R Core Team, 2019]. This function is included in the basic R functions and does not require installing any additional packages, making it an accessible and sustainable software choice for our approach. Telling the \texttt{integrate} function that we want an infinite upper bound is simple enough. In fact, as a user, it is no different than supplying the function with a finite one.

Still, adopting software that can integrate up to infinity does us no good if the integrand, i.e., the survival function of the censored covariate, is not defined as such; this is a problem not just for the \texttt{integrate} function in R but for all quadrature software. Before using adaptive quadrature with an infinite upper bound, we have to “extend” (i.e., extrapolate from) Breslow’s estimator beyond the largest uncensored value \( \bar{X} = \max(W_1, \ldots, W_n) \). This way, we will give the \texttt{integrate} function something to integrate over on its way up to infinity and better calculate the conditional means, as desired.

#### 2.5.1 Extending Breslow’s estimator beyond the largest uncensored value

We sought a method to extend Breslow’s estimator beyond the largest uncensored covariate value \( \bar{X} \), i.e., to extrapolate from \( \hat{S}_0(t) \) to cover values of \( t \) up toward infinity. Extrapolating from step functions is a challenge commonly discussed with censored outcomes, since other popular estimators, like Kaplan–Meier, are not well defined for values of \( t \) larger than the observed data, either. We discuss four potential methods to extend Breslow’s estimator.

- **Carry forward**: Carry forward Breslow’s estimator from \( \hat{S}_0(t) = \hat{S}_0(\bar{X}) \) for all \( t > \bar{X} \), this asserts that all censored covariates would have had \( \bar{X} = \infty \).
- **Immediate drop-off**: Do not extrapolate from Breslow’s estimator at all. Assuming that \( \hat{S}_0(t) = 0 \) at all \( t > \bar{X} \) is equivalent to assuming that the true values \( X \) for all censored covariates would have fallen just beyond their observed values \( W \).
- **Exponential extension**: “Tie in” an exponential survival function where Breslow’s estimator leaves off and assume that \( \hat{S}_0(t) = \exp \left( \left[ t \log \left( \hat{S}_0(\bar{X}) \right) \right] / \bar{X} \right) \) for \( t > \bar{X} \).
- **Weibull extension**: For added flexibility, “tie in” a Weibull survival function instead of an exponential and assume that \( \hat{S}_0(t) = \exp \left\{ -\hat{\nu} t^{\hat{\nu}} \right\} \), where the shape and scale parameters \( \hat{\nu} \) and \( \hat{\nu} \), respectively, are found using constrained maximum likelihood estimation [Moeschberger and Klein, 1985].

While these methods are well established for censored outcomes, to our knowledge this is the first time extrapolation from the survival functions of censored covariates has been considered. Without them, improving the conditional mean calculation from a step survival function like Breslow’s estimator would be impossible; no matter how well we can integrate, the integrand must be defined across the entire range, which requires extrapolation.

Either carry forward or immediate drop-off would be a valid modification if modeling the survival function were our end goal, since they are known to converge to the true survival functions in large samples [Klein and Moeschberger, 2003]. However, neither is a good choice when our ultimate objective is to integrate over the survival function. Carry forward makes the integral up to infinity diverge. Immediate drop-off forces the integral to cut off at \( \bar{X} \); therefore, we expect it to offer little improvement over the trapezoidal rule, even with adaptive quadrature. Fortunately, theoretical justification exists for both parametric extensions, so we explored them in extensive simulations before making recommendations.
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(Section 3.2). Derivations for the parametric extensions can be found in Web Appendix A, along with an illustration of these four extrapolation methods (Supplemental Figure S1).

Remark. Calculating the conditional means with the trapezoidal rule still involves evaluating Breslow’s estimator for values beyond \( \hat{X} \) (i.e., extrapolation). However, instead of extrapolating, the existing approaches (e.g., Atem et al. [2019a]) treat the largest observed covariate value \( W_{(n)} \) as uncensored regardless of \( \Delta_{(n)} \), so that \( \hat{S}_0(W_{(n)}) = 0 \), a recommendation from Datta [2005] and equivalent to Efron’s immediate drop-off approach [Efron, 1967]. We know that immediate drop-off can “cut off” the tail of the survival function. However, when used with the trapezoidal rule, this impact of immediate drop-off may be subtle, since the tail would have been cut off regardless of the extrapolation method.

3 Simulation Studies

We first show that even when the survival function is the truth, conditional mean imputation using the trapezoidal rule leads to biased estimates of the model parameters \( \theta \) relating \( Y \) to \( X \) and \( Z \) (Section 3.2). We then demonstrate the impact of imputing with the two conditional means when there is uncertainty around the survival function. (In practice, we would need to estimate the survival function, so this setting is more realistic than the first.) Before we can use adaptive quadrature with an infinite upper bound (hereafter called “adaptive quadrature”) on the estimated survival function, we must decide how to extend Breslow’s estimator beyond the observed data. We choose the Weibull extension from the methods introduced in Section 2.5.1, which we show offers low bias and high efficiency even when \( X \) given \( Z \) is not truly Weibull (Section 3.2). Lastly, we highlight the improved performance for statistical inference (i.e., substantially reduced bias and some heightened efficiency) of conditional mean imputation using adaptive quadrature rather than the trapezoidal rule in a real-world scenario with an estimated survival function (Section 3.4).

3.1 Data Generation and Metrics for Comparison

Our simulation settings are based on those of Atem et al. [2017], who, to the best of our knowledge were the first to propose conditional mean imputation for a randomly right-censored covariate. We simulated data for samples of \( n = 100, 500, \) or \( 2000 \) subjects in the following way. First, a binary covariate \( Z \) was generated from a Bernoulli distribution with \( P(Z = 1) = 0.5 \). Next, \( X \) was generated from a Weibull distribution with shape 0.75 and scale 0.25, leading to proportional hazards in \( X \) given \( Z \). In the spirit of reproducibility, we note that \( X \) was generated in R using the \( \text{rweibull} \) function with these shape and scale parameters [R Core Team, 2019]. Based on \( X \) and \( Z \), a continuous outcome was generated as \( Y = 1 + 0.5X + 0.25Z + \epsilon \), where \( \epsilon \) was a standard normal random variable.

We explored light, moderate, and heavy censoring in the covariate \( X \), induced by generating \( C \) from an exponential distribution with rates 0.5, 2.9, and 20, respectively. On average, these specifications led to around 12% “light,” 41% “moderate,” and 78% “heavy” censoring. Notice that \( C \) was generated independently of all other variables, which more than satisfies our assumption of noninformative censoring. Finally, the observed covariates and event indicators were constructed as \( W = \min(X, C) \) and \( \Delta = I(X \leq C) \), respectively.

Given that we have a continuous outcome \( Y \), the analysis model \( P_\theta(Y \mid X, Z) \) was a normal linear regression. We considered two imputation approaches to estimate \( \hat{\theta} \): one calculated the conditional means using adaptive quadrature and the other calculated them using the trapezoidal rule instead. To assess these methods’ validity, we report the empirical bias and standard errors for \( \hat{\theta} = (\hat{\alpha}, \hat{\beta}, \hat{\gamma}) \). Under moderate and heavy censoring, the trapezoidal rule leads to sizable bias; however, both approaches are valid under light censoring. Therefore, under light censoring, we are interested in which method offers the best statistical precision. We gauge statistical precision by the relative efficiency, which is calculated as the empirical efficiency (i.e., the inverse of the empirical variance) of the imputation approaches divided by that of the full cohort analysis where all \( n \) observations had uncensored \( X \). The closer the relative efficiency is to one, the more efficiency is being recovered through imputation. Unless otherwise stated, all summary metrics (bias, standard errors, and relative efficiency) are based on 1000 replications.

3.2 Using the Gold Standard: Conditional Mean Imputation with the True Survival Function

Using the true survival function allows us to isolate the improvements to conditional mean imputation due to replacing the trapezoidal rule with adaptive quadrature. This “gold standard” imputation approach removes the uncertainty around the survival function, since it is assumed, rather than estimated. Also, there is no need for extrapolation, because the Weibull survival function is already defined for \( X \) out to infinity. Following Section 3.1, \( X \) given \( Z \) was generated from a Weibull distribution with survival function \( S(t \mid z) = \exp \left\{ - (t/0.25)^{0.75} \right\} \). Instead of estimating the survival function, we first considered imputing censored \( X \) with its conditional mean based on this true \( S(t \mid z) \).
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Table 1: Simulation results for Weibull \( X \) from the full cohort and imputation approaches using the true survival function and adaptive quadrature versus the trapezoidal rule. (SE: empirical standard error; RE: empirical relative efficiency to full cohort.)

| Censoring | \( n \) | Full Cohort | Adaptive Quadrature | Trapezoidal Rule |
|-----------|--------|-------------|---------------------|------------------|
|           | \( \hat{\alpha} \) | Bias | SE | Bias | SE | RE | Bias | SE | RE |
| Light     | 100    | -0.001 | 0.161 | 0.000 | 0.167 | 0.924 | -0.003 | 0.168 | 0.915 |
|           | 500    | 0.001  | 0.071 | 0.002 | 0.074 | 0.928 | -0.003 | 0.074 | 0.921 |
|           | 2000   | 0.001  | 0.036 | 0.003 | 0.037 | 0.941 | 0.002  | 0.037 | 0.938 |
| Moderate  | 100    | -0.001 | 0.161 | -0.003 | 0.181 | 0.791 | -0.015 | 0.187 | 0.736 |
|           | 500    | 0.001  | 0.071 | -0.002 | 0.080 | 0.782 | -0.009 | 0.082 | 0.754 |
|           | 2000   | 0.001  | 0.036 | 0.003 | 0.040 | 0.796 | -0.002 | 0.040 | 0.776 |
| Heavy     | 100    | -0.001 | 0.161 | -0.010 | 0.246 | 0.428 | -0.033 | 0.272 | 0.350 |
|           | 500    | 0.001  | 0.071 | -0.002 | 0.107 | 0.440 | -0.017 | 0.114 | 0.388 |
|           | 2000   | 0.001  | 0.036 | -0.001 | 0.055 | 0.428 | -0.012 | 0.058 | 0.385 |

\( \hat{\beta} \): Coefficient on Censored \( X \)

| Censoring | \( n \) | Full Cohort | Adaptive Quadrature | Trapezoidal Rule |
|-----------|--------|-------------|---------------------|------------------|
|           | \( \hat{\beta} \) | Bias | SE | Bias | SE | RE | Bias | SE | RE |
| Light     | 100    | -0.001 | 0.275 | -0.020 | 0.291 | 0.896 | 0.001  | 0.306 | 0.808 |
|           | 500    | 0.001  | 0.116 | 0.007 | 0.123 | 0.887 | 0.001  | 0.126 | 0.847 |
|           | 2000   | 0.002  | 0.057 | -0.004 | 0.063 | 0.818 | 0.000  | 0.063 | 0.805 |
| Moderate  | 100    | -0.001 | 0.275 | -0.010 | 0.370 | 0.554 | 0.118  | 0.484 | 0.324 |
|           | 500    | 0.001  | 0.116 | 0.007 | 0.162 | 0.508 | 0.073  | 0.185 | 0.392 |
|           | 2000   | 0.002  | 0.057 | -0.004 | 0.081 | 0.490 | 0.034  | 0.089 | 0.406 |
| Heavy     | 100    | -0.001 | 0.275 | 0.025  | 0.675 | 0.166 | 0.906  | 1.870 | 0.022 |
|           | 500    | 0.001  | 0.116 | 0.008 | 0.283 | 0.168 | 0.579  | 0.623 | 0.035 |
|           | 2000   | 0.002  | 0.057 | 0.003  | 0.151 | 0.142 | 0.425  | 0.289 | 0.039 |

\( \hat{\gamma} \): Coefficient on Uncensored \( Z \)

As seen in Table 1, the bias in estimating \( \hat{\beta} \) (the coefficient on censored \( X \)) using conditional mean imputation with the trapezoidal rule was alarming: as high as 181% and 24% under heavy and moderate censoring, respectively. Meanwhile, conditional mean imputation using adaptive quadrature instead led to virtually unbiased estimates everywhere, with ≤ 5% bias for all sample sizes and censoring rates. Also, even under light censoring – when the bias with the trapezoidal rule was reasonable – imputing with conditional means calculated using adaptive quadrature could lead to more efficient inference (e.g., relative efficiency = 0.90 vs. 0.81 with \( n = 100 \)), though in some cases (e.g., \( n \geq 1000 \)), not by much.

For either imputation approach, the relative efficiency to the full cohort analysis for \( \hat{\beta} \) decreased as censoring increased. This result is to be expected, since we are imputing more, and incurring more uncertainty, when more covariates are censored.

Finally, inference about the other coefficients \( \hat{\alpha} \) and \( \hat{\gamma} \) was comparable between the two imputation approaches. Namely, both approaches were unbiased (< 3%), and while some efficiency was lost in estimating the intercept relative to the full cohort analysis (relative efficiency ≥ 0.35 for \( \hat{\alpha} \)), the efficiency for the coefficient on uncensored \( Z \) was nearly equal (relative efficiency ≥ 0.92 for \( \hat{\gamma} \)).
Recall that both imputation approaches use the same true survival function; they differ only in how they approximate the integral over it (i.e., with the trapezoidal rule or adaptive quadrature). The impact of this difference between integral approximations is evident. Replacing the trapezoidal rule with adaptive quadrature led to huge improvements in bias and some notable gains in efficiency, too. Clearly, something needed to be done to better calculate the conditional means; in the current work, we propose this “something.”

3.3 Extending the Estimated Survival Function: How to Extrapolate from Breslow’s Estimator

To extend Breslow’s estimator, we considered three of the extrapolation methods for $\hat{S}_0(t)$ introduced in Section 2.5.1: (i) immediate drop-off, (ii) exponential extension, and (iii) Weibull extension. (We did not consider carry forward extrapolation, since it caused the integral to diverge.) To compare them, we focus on estimating $\hat{\beta}$, the coefficient on censored covariate $X$, because it will be most impacted by censoring. Extrapolating $\hat{S}_0(t)$ beyond $X$ with the Weibull extension offered the lowest bias and best efficiency for $\hat{\beta}$ in conditional mean imputation with adaptive quadrature (Supplemental Figure S2). These improvements were evident in all settings, but were most pronounced under heavy censoring. We note that the exponential extension offered similar efficiency to the Weibull extension but could be slightly more biased, particularly under heavy censoring and in small samples; still, it offered lower bias and better efficiency than the immediate drop-off method.

Thus, in these data, the “winning method” used the Weibull extension to extrapolate from Breslow’s estimator beyond the largest uncensored value and improve conditional mean imputation. However, it is important to note that $X$ was truly generated from a Weibull distribution. Therefore, to offer more general recommendations, we also considered a censored covariate $X$ that was instead generated from a log-normal distribution with mean $= 0$ and variance $= 0.25$ (on the log scale). For light, moderate, and heavy censoring in log-normal $X$, we generated $C$ from an exponential distribution with rates $= 0.2, 0.4$, and $1.67$, respectively. These specifications for $C$ led to $20\%$, $35\%$, and $79\%$ light, moderate, and heavy censoring, respectively, on average, in the covariate $X$.

With log-normal $X$, the bias when using conditional mean imputation with adaptive quadrature was very low and relatively unchanged by the three different extrapolation methods (Supplemental Figure S3). Therefore, any of the methods appeared similarly appropriate for these log-normal data, although immediate drop-off could still be the most biased, particularly in small samples and under heavy censoring. We also compared approaches that used mean versus carry forward interpolation between uncensored values for Breslow’s estimator (Remark 2.4) and found that they performed the same in terms of bias and efficiency (Supplemental Figure S4).

There were only minor differences between the different extrapolation methods when using conditional mean imputation with the trapezoidal rule (Supplemental Figure S5). This result was expected, since the trapezoidal rule “cuts off” any $X$ after the observed data (see Remark 2.5.1). Therefore, the only differences between the extrapolation methods with the trapezoidal rule were from extrapolating for censored values that were larger than the last uncensored $X$, but were smaller or equal to the last observed $W_{(n)}$.

Now, armed with the Weibull extension, shown herein to offer unbiased and efficient inference, we can extend Breslow’s estimator up toward infinity. We now proceed with comparing our proposed conditional mean imputation approach that uses adaptive quadrature to the existing approach using the trapezoidal rule in a variety of real-world scenarios.

3.4 Constructing a More Realistic Setting: Conditional Mean Imputation with the Estimated Survival Function

Having selected the Weibull extension method for extrapolation, we compare statistical inference from the imputation approaches based on the adaptive quadrature and trapezoidal rule conditional mean calculations. Unlike Section 3.2, here $S(t \mid z)$ was treated as unknown and instead had to be estimated; this simulation setting goes beyond the gold standard and is constructed to be more realistic in terms of what we see in practice.

After estimating the survival function, the trapezoidal rule led to an even larger bias in estimating $\hat{\beta}$ ($X$’s coefficient) with conditional mean imputation for Weibull $X$ than was seen with the gold standard (Table 2). Under moderate and heavy censoring, the trapezoidal rule led to as much as $23\%$ and $183\%$ bias in $\hat{\beta}$, respectively. Meanwhile, imputation using adaptive quadrature offered no more than $10\%$ and $27\%$ bias under moderate and heavy censoring, respectively. While larger than we would like, this residual bias seemed to stem from the estimated survival function; recall that we saw $\leq 5\%$ bias across these same settings when assuming the true survival function instead (Table 1). With minor exceptions (e.g., in the largest samples), adaptive quadrature continued to have efficiency gains over the trapezoidal rule even when estimating $S(t \mid z)$.
Replacing the trapezoidal rule to better impute censored covariates

### Table 2: Simulation results for Weibull $X$ from the full cohort and imputation approaches using the estimated survival function and adaptive quadrature versus the trapezoidal rule. (SE: empirical standard error; RE: empirical relative efficiency to full cohort.)

| Censoring | $n$  | Full Cohort | Adaptive Quadrature | Trapezoidal Rule |
|-----------|------|-------------|---------------------|------------------|
|           |      | Bias        | SE                  | Bias  | SE  | RE |
| Light     | 100  | -0.001      | 0.161               | 0.003 | 0.172 | 0.872 | -0.005 | 0.171 | 0.882 |
|           | 500  | 0.001       | 0.071               | 0.003 | 0.072 | 0.983 | -0.006 | 0.074 | 0.911 |
|           | 2000 | -0.001      | 0.036               | 0.003 | 0.037 | 0.949 | -0.002 | 0.036 | 0.965 |
| Moderate  | 100  | -0.001      | 0.161               | -0.006 | 0.187 | 0.736 | -0.013 | 0.187 | 0.739 |
|           | 500  | 0.001       | 0.071               | 0.000 | 0.077 | 0.853 | -0.012 | 0.084 | 0.714 |
|           | 2000 | -0.001      | 0.036               | 0.003 | 0.040 | 0.783 | -0.005 | 0.041 | 0.771 |
| Heavy     | 100  | -0.001      | 0.161               | 0.009 | 0.266 | 0.365 | -0.027 | 0.271 | 0.350 |
|           | 500  | 0.001       | 0.071               | 0.002 | 0.111 | 0.405 | -0.013 | 0.114 | 0.385 |
|           | 2000 | -0.001      | 0.036               | 0.002 | 0.055 | 0.427 | -0.008 | 0.057 | 0.396 |

| $\hat{\alpha}$: Intercept |
|---------------------------|
| Light                     |
| 100  | -0.001 | 0.275 | -0.011 | 0.312 | 0.778 | 0.018 | 0.317 | 0.756 |
| 500  | 0.001  | 0.116 | -0.012 | 0.125 | 0.857 | 0.012 | 0.129 | 0.805 |
| 2000 | 0.002  | 0.057 | -0.008 | 0.064 | 0.782 | 0.005 | 0.063 | 0.806 |
| Moderate                   |
| 100  | -0.001 | 0.275 | 0.051 | 0.447 | 0.380 | 0.115 | 0.476 | 0.335 |
| 500  | 0.001  | 0.116 | 0.017 | 0.179 | 0.416 | 0.073 | 0.199 | 0.338 |
| 2000 | 0.002  | 0.057 | -0.003 | 0.096 | 0.348 | 0.037 | 0.096 | 0.352 |
| Heavy                      |
| 100  | -0.001 | 0.275 | -0.136 | 0.744 | 0.047 | 0.913 | 1.900 | 0.007 |
| 500  | 0.001  | 0.116 | 0.004 | 0.403 | 0.031 | 0.572 | 0.647 | 0.012 |
| 2000 | 0.002  | 0.057 | 0.082 | 0.229 | 0.024 | 0.423 | 0.298 | 0.014 |

| $\hat{\beta}$: Coefficient on Censored $X$ |
|------------------------------------------|
| Light                                    |
| 100  | 0.005  | 0.208 | -0.003 | 0.206 | 1.017 | 0.001 | 0.201 | 1.063 |
| 500  | -0.002 | 0.090 | -0.002 | 0.090 | 0.989 | 0.004 | 0.089 | 1.017 |
| 2000 | 0.001  | 0.045 | -0.002 | 0.045 | 1.014 | 0.003 | 0.045 | 0.995 |
| Moderate                                 |
| 100  | 0.005  | 0.208 | -0.003 | 0.210 | 0.977 | 0.002 | 0.202 | 1.051 |
| 500  | -0.002 | 0.090 | -0.001 | 0.091 | 0.978 | 0.004 | 0.090 | 1.002 |
| 2000 | 0.001  | 0.045 | -0.002 | 0.045 | 0.996 | 0.003 | 0.045 | 0.986 |
| Heavy                                    |
| 100  | 0.005  | 0.208 | -0.001 | 0.285 | 0.318 | -0.001 | 0.205 | 0.611 |
| 500  | -0.002 | 0.090 | 0.003 | 0.100 | 0.500 | -0.001 | 0.092 | 0.601 |
| 2000 | 0.001  | 0.045 | 0.000 | 0.049 | 0.537 | 0.001 | 0.045 | 0.623 |

| $\hat{\gamma}$: Coefficient on Uncensored Z |

9
Interestingly, unlike the Weibull $X$ case, estimating the survival function for log-normal $X$ led to similar bias when using adaptive quadrature or the trapezoidal rule (Supplemental Table S1). We were initially surprised, as we expected the trapezoidal rule to continue to produce more biased estimates; upon further investigation, we discovered that this was due to the symmetry of the log-normal distribution. With this symmetry, the tail of the survival function $S(t|z)$ was well approximated regardless of whether we used adaptive quadrature or the trapezoidal rule. In contrast, the skewness of the Weibull distribution became a problem for the trapezoidal rule as we increased the rate parameter for $C$ to induce heavier censoring in $X$. Specifically, under heavy censoring, we saw smaller values of $W_{(n)}$ (Supplemental Figure S6), and since the survival function was unchanged between censoring settings, decreasing $W_{(n)}$ increased $S(W_{(n)}|z)$. Thus, this finding actually echoes our intuition from Section 2.4: under heavy censoring, $S(W_{(n)}|z) > 0$ and the trapezoidal rule encounters bias because the integral approximation “cuts off” all values of $X > W_{(n)}$.

We already demonstrated the severe bias attributable to calculating conditional means with the trapezoidal rule with the “gold standard” imputation approach based on the true survival function (Section 3.2). Herein, we constructed a more realistic simulation setting where the survival function had to be estimated before calculating conditional means. The improvements to conditional mean imputation persisted with the estimated survival function, with our adoption of adaptive quadrature offering much lower bias and some efficiency gains. Now, we investigate the progression of Huntington’s disease symptoms relative to time of diagnosis, despite the key covariate — time of diagnosis — being censored.

## 4 Application to Huntington’s Disease Data

### 4.1 Designing Clinical Trials to Test Experimental Treatments for Huntington’s Disease

Damage due to Huntington’s disease is irreversible, so slowing symptom progression is often the objective of experimental treatments. Clinical trials are critical to the success of potential treatments, but they are expensive, leading to several practical constraints in their design and implementation. Most notably, the number of subjects recruited and their follow-up time can be financially constrained, leaving clinical trials to strive for efficiency, both statistical and logistical, on a budget. Thus, when investigating experimental treatments for Huntington’s disease, clinical trials seek to recruit subjects for whom the treatment could have the greatest potential impact during follow-up [Paulsen et al., 2019].

Recruiting from an existing Huntington’s disease study can be a powerful first step, since more information is available than when recruiting “from scratch.” For example, we could measure symptom change leading up to the subject’s consideration for the trial. Having some information about symptom change is important, since the impact of the experimental treatment in slowing symptom progression would be more measurable for subjects whose symptoms are steeply progressing. Still, an existing study can only tell us how a subject’s symptoms have been changing thus far, while what we really want to know is how their symptoms are going to change during the trial.

While future symptom progression is not measurable, fortunately there are promising ways to estimate it. Specifically, we can model symptom change using data from PREDICT-HD. With this model, we can then estimate subjects’ symptom progression after recruitment to identify high priority subjects for a new clinical trial (i.e., those with the largest expected declines) based only on the information available at recruitment.

Time to diagnosis has been shown to be highly predictive of symptom severity, with the steepest change in symptoms seen in the years immediately before and after diagnosis (e.g., Long et al. [2014]). Thus, time to diagnosis is an important covariate in our symptom progression model, but in a study like PREDICT-HD, where not everyone has been diagnosed, it is a right-censored covariate that must first be dealt with.

In the sections that follow, we discuss the details of modeling the progression of Huntington’s disease symptoms in a prospective study of diagnosed and undiagnosed subjects using data from PREDICT-HD (Section 4.2). Then, we walk through imputing censored times to diagnosis for undiagnosed subjects (Section 4.3). Finally, we discuss our strategy to recruit subjects for a new clinical trial based on these models (Section 4.4).

### 4.2 Modeling the Progression of Huntington’s Disease Symptoms

One way to gauge symptom severity is the composite Unified Huntington Disease Rating Scale (cUHDRS), which collectively measures functional, motor, and cognitive impairments. As Huntington’s disease progresses toward diagnosis, impairment worsens and the cUHDRS is designed to decrease as it does. Following from Schobel et al. [2017],

\[
c_{UHDRS} = \frac{TFC - 10.4}{1.9} - \frac{TMS - 29.7}{14.9} + \frac{SDMT - 28.4}{11.3} + \frac{SWR - 66.1}{20.1} + 10,
\]
where TFC is total functional capacity, TMS is total motor score, SDMT is the Symbol Digit Modality Test, and SWR is the Stroop Word Reading Test. The component scores measure symptom severity in different areas of life: (i) TFC assesses the subject’s capacity to perform “everyday tasks” (e.g., chores or self-care), (ii) TMS assesses the degree of motor impairment (e.g., chorea or balance), and (iii) SDMT and (iv) SWR both assess cognitive impairment.

We captured Huntington’s disease symptom progression over the course of several follow-up visits by modeling the adjusted association between the cUHDRS at the first and last visits (cUHDRS₀ and cUHDRS₁, respectively), controlling for other known covariates. Included in these covariates were (i) proximity to diagnosis, defined as \( \text{TME}_0 \) from the last visit to diagnosis, and (ii) baseline information about age, \( \text{CAG} \) repeat length, and their interaction (denoted by \( \text{AGE}_0 \), \( \text{CAG}_0 \), and \( \text{AGE}_0 \times \text{CAG}_0 \), respectively). In addition, we included an interaction between cUHDRS₀ and \( \text{TME}_0 \) because if a subject is farther from diagnosis, then their cUHDRS is not expected to be changing much, while if the subject is closer to diagnosis, it is expected to be changing noticeably. Thus, the symptom progression model of clinical interest was captured with normal linear regression as:

\[
E_\theta(c\text{UHDRS}_1 | \text{TME}_1, c\text{UHDRS}_0, \text{AGE}_0, \text{CAG}_0) = \alpha + \beta \text{TME}_1 + \gamma_0 c\text{UHDRS}_0 + \gamma_1 \text{TME}_1 \times c\text{UHDRS}_0 + \gamma_2 \text{AGE}_0 + \gamma_3 \text{CAG}_0 + \gamma_4 \text{AGE}_0 \times \text{CAG}_0.
\]

(4)

Note that the subscripts 0 and 1 delineate variables measured at study entry and those measured at or relative to the last visit, respectively. For interpretability, covariates were rescaled so that the intercept was the expected cUHDRS of the hypothetical “healthiest” group of subjects (i.e., the youngest with the fewest qualifying mutations and the highest cUHDRS at the first visit), if they were to be clinically diagnosed at their last visit. Specifically, \( \text{AGE}_0 \), \( \text{CAG}_0 \), and cUHDRS₀ were centered at 18, 36, and 23.8, respectively, to achieve this. The remaining covariate, \( \text{TME}_1 \), was right-censored and is defined in Section 4.3.

To be included in our analysis, subjects needed to have (i) a \( \text{CAG} \) repeat length \( \geq 36 \) on the \( \text{HTT} \) gene, (ii) not yet been clinically diagnosed with Huntington’s disease at study entry, (iii) undergone all necessary testing to calculate the cUHDRS at the first and last visits, and (iv) returned for at least one follow-up visit. Patterns of missing data among the 34 subjects excluded for reason (iii) can be found in Supplemental Figure S7. These criteria left a sample of \( n = 970 \) at-risk subjects, 238 (25%) of whom were clinically diagnosed with Huntington’s disease before their last visit, leaving 75% with a censored covariate \( \text{TME}_1 \). Since we employed conditional mean imputation, a single imputation approach (described in Section 4.3), to replace censored times to diagnosis, we used the robust sandwich estimator from the sandwich package for inference [Zeileis, 2004].

### 4.3 Imputing Censored Times to diagnosis

Calculating time to diagnosis was done in the following way. First, \( \text{DATE} \) of diagnosis was taken as the first visit from study entry to diagnosis was randomly right-censored but could be imputed with \( E(\text{TME}_0 | \text{TME}_0 > \text{FOLLOW}_\text{UP}_1, \text{AGE}_0, \text{CAG}_0) \), its conditional mean, where \( \text{FOLLOW}_\text{UP}_1 \) was the length of follow-up before the last visit. Imputation began by modeling the conditional survival function for \( \text{TME}_0 \) given other fully observed covariates from study entry. First, we fit the Cox proportional hazards model,

\[
h_\lambda(\text{TME}_0 | \text{AGE}_0, \text{CAG}_0) = \lambda_0(\text{TME}_0) \exp(\lambda_1 \text{AGE}_0 + \lambda_2 \text{AGE}_0 \times \text{CAG}_0),
\]

and tested for proportional hazards using the survival package [Therneau and Grambsch, 2000]. (There was no evidence that the assumption was violated, with both \( p \)-values > 0.1.) The covariates \( \text{AGE}_0 \) and \( \text{AGE}_0 \times \text{CAG}_0 \), were chosen to align with the CAP model proxy for time to diagnosis from Zhang et al. [2011]. Then, we calculated Breslow’s estimator \( \hat{S}(\text{TME}_0) \) based on the estimated log hazard ratios \( \hat{\lambda}_1 = -0.038 \) and \( \hat{\lambda}_2 = 0.022 \).

With this, we had an estimator \( \hat{S}(\text{TME}_0 | \text{AGE}_0, \text{CAG}_0) \) for values of \( \text{TME}_0 \) up to \( \overline{X} = 11.422 \), the longest observed time from study entry to diagnosis in PREDICT-HD. Following from our empirical findings in Section 3.3, we used the Weibull extension to extrapolate the survival estimator beyond the largest censored value, where \( \hat{S}(t = 11.422 | \text{AGE}_0 = 34.13, \text{CAG}_0 = 4) = 0.532 \). While we cannot guarantee that these data follow a Weibull distribution, the added flexibility of this extension over the exponential was appealing. Also, unlike our simulations, the context of \( \text{TME}_0 \) could be used to refine the upper bound of the integral in Equation (1). Specifically, \( \text{TME}_0 \) from study entry to clinical Huntington’s disease diagnosis could not be infinite for the simple reason that humans are not immortal. Instead, we assumed \( \text{TME}_0 \) of diagnosis would be no longer than 60 years from study entry. Additional details can be found in the Web Appendix A.3.
Now, having imputed the censored covariates, we prepared to fit the models. Because symptoms were expected to worsen near diagnosis, time to diagnosis (in years) was a key covariate in our models. Since cUHDRS from the last visit was our outcome, we defined time to diagnosis from the last visit, too. For uncensored subjects, TIME1 was computed by subtracting their last visit date from their DATE of diagnosis. For censored subjects, TIME1 was computed by subtracting their last visit date from the imputed DATE of diagnosis instead, where DATE was found by adding their conditional mean to their first visit date.

4.4 Strategic Recruitment for a Clinical Trial

Like the densities of time to diagnosis (Supplemental Figures S8–S9), the two imputation approaches led to different models, each with its own clinical implications. While the individual coefficients and inference varied between the models (Supplemental Table S2), we focused on the practical adoption to guide recruitment into a new clinical trial.

Suppose we were recruiting at-risk subjects from their last regular study visit and that the clinical trial was expected to last for 2 years. Our recruitment strategy proceeds in two steps: (i) computing the subject-specific expected change in cUHDRS between recruitment and the end of the clinical trial 2 years later and (ii) prioritizing subjects with the steepest expected drops in cUHDRS during that time. We first start by estimating one subject’s symptom progression during the trial and discussing their resulting recruitment priority (Section 4.4.1). Then, we outline our large-scale recruitment strategy (Section 4.4.2).

4.4.1 How to Estimate Symptom Progression and Prioritize an At-Risk Subject for Recruitment

Consider a randomly selected subject whose cUHDRS was already seen to decline from cUHDRS0 = 15.9 to cUHDRS1 = 13.3 between their first to last visits in PREDICT-HD, a pre-trial change of \( \Delta_1(cUHDRS) = -2.6 \). In planning a clinical trial for the next 2 years, the subject’s symptom change during the trial, rather than before, was of interest but unobservable at recruitment. Fortunately, estimating the subject’s change in cUHDRS during the trial can be a powerful alternative. Specifically, we can predict cUHDRS 2 years post recruitment, denoted cUHDRS2, using the symptom progression models and then calculate expected change in symptoms during the clinical trial from it as \( \Delta_2(cUHDRS) = cUHDRS2 - cUHDRS1 \). Thus, \( \Delta_2(cUHDRS) < 0 \) indicates symptoms expected to worsen.

For each subject, we can plug their covariates along with the estimated model parameters \( \hat{\theta} \) into Equation (4) to estimate their cUHDRS at the end of the trial, denoted by cUHDRS2. However, we wanted to predict end-of-trial cUHDRS from recruitment cUHDRS (and covariates), whereas the models were fit to predict last visit from first visit. Thus, baseline covariates AGE0 and CAG0 were unchanged, but we replaced (i) time from last visit to diagnosis (TIME1) with time from end of trial to diagnosis (TIME2) and (ii) cUHDRS at first visit (cUHDRS0) with cUHDRS at recruitment (cUHDRS1). Ultimately, cUHDRS2 can be estimated from either model as \( E_{\hat{\theta}}(cUHDRS2|TIME2, cUHDRS2, AGE0, CAG0) \). As a bonus, cUHDRS2 can be used to construct a complete trajectory of the subject’s symptom severity (Supplemental Figure S10), where \( \Delta_2(cUHDRS) \) summarizes the latter part of this trajectory.

For the example subject, the model imputed using adaptive quadrature predicted their cUHDRS at the end of the trial to be cUHDRS2 = 10.8, leading to an estimated change of \( \Delta_2(cUHDRS) = -2.5 \) during the trial. Based on this, the subject had the 43rd largest estimated decrease in cUHDRS among censored subjects, making them high priority for recruitment. In contrast, the model imputed using the trapezoidal rule predicted cUHDRS2 = 11.8 for a smaller change of \( \Delta_2(cUHDRS) = -1.5 \) during the trial (ranking 201st and giving this subject low priority for recruitment).

Because we saw in the simulation studies (Section 3) that the trapezoidal rule estimates can be biased, particularly under heavy censoring rates like the 75% in PREDICT-HD, we have more trust in the model based on adaptive quadrature and assume that its expected symptom change \( \Delta_2(cUHDRS) \) is closer to the true one. Therefore, if this subject were excluded from the trial based on the trapezoidal rule model, their spot may have gone to a non-ideal subject with smaller actual symptom change. Then, if the subject recruited in their place had little to no change in symptoms, it would be hard to discern whether this lack of change was due to the efficacy of the new treatment or simply the subject having little symptom change anyway. In general, misprioritizing trial candidates means that non-ideal subjects may take spots away from others who might have had more to gain.

4.4.2 How to Prioritize the Entire Study for Recruitment

We used the same process outlined above for everyone and then ordered the entire study by their estimated change in symptoms \( \hat{\Delta}_2(cUHDRS) \), starting from the biggest decline in function (i.e., largest decrease in cUHDRS). Then,
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we recruited the first 200 subjects based on $\hat{c}_{\text{UHDRS}}(\text{CAP})$, prioritizing subjects expected to have the worst symptom progression during the trial and with potentially the most to gain. We call this rank-based recruitment.

Although the PREDICT-HD study is over, we demonstrated our recruitment strategy with its data. Supplemental Figure S11 summarizes the recruitment statuses for the entire study. To introduce some realistic variability, we also created 1000 new datasets of 732 subjects each by resampling with replacement from the 732 censored subjects in PREDICT-HD; these resampled data mimicked the study but were not precisely those used to build the models. In each resampled dataset, we applied our rank-based recruitment strategy twice: once each with the models based on adaptive quadrature and the trapezoidal rule.

On average, the models agreed on 158 subjects to recruit and 490 to not recruit. For the other 42 subjects, the models disagreed: recruiting based on the trapezoidal rule “threw away” 42 spots in the trial on subjects that the adaptive quadrature model expected to have less change in symptoms, while excluding 42 subjects that the latter found to be better candidates to receive the new treatment. For a summary of the recruitment agreement between the two models across all of the resampled datasets, see Supplemental Figure S12.

In an all-knowing world, we would recruit subjects for a new clinical trial who would have the steepest change in their symptoms (i.e., most noticeably worsening impairment) without treatment. However, we are not psychics: we cannot know which subjects are going to have the steepest change in symptoms, so this is not a reasonable recruitment strategy. Recruiting subjects who are expected to have the steepest changes in symptoms is, though. With conditional mean imputation, we modeled the progression of Huntington’s disease symptoms despite censoring in time to diagnosis, and then used these models to guide recruitment for a hypothetical clinical trial. Using the trapezoidal rule for imputation recruited more than a fifth of the subjects into the trial despite their moderate (rather than high) symptom progression, leading to possible overoptimism about treatment efficacy and the exclusion of subjects who may have been more in need. In contrast, given its demonstrated accuracy in the simulations, using adaptive quadrature will give statisticians confidence in their model and clinicians confidence in who they recruited based on it.

5 Discussion

After demonstrating that the trapezoidal rule makes existing approaches miscalculate conditional means, leading to biased statistical inference, we propose an improved calculation using adaptive quadrature with an infinite upper bound instead. We adopt the integrate function, which implements adaptive quadrature in R and is available as part of the “base R” packages [R Core Team, 2019]. However, even though the integrate function can handle infinite upper bounds, we encountered an additional challenge since the integrand in the conditional means, $S(t|x)$, is only defined on the uncensored values. We provide an in-depth empirical investigation of how best to extend Breslow’s estimator beyond the observed data for indefinite integration, making recommendations to the reader based on a variety of real-world settings. Finally, we applied our proposed methods to model the progression of Huntington’s disease symptoms in the PREDICT-HD study relative to time of diagnosis, a censored covariate, and discussed using this model to recruit the most informative subjects for a new clinical trial.

In our simulations and real-world data analysis, we focused on linear regression modeling. However, the methods apply for any outcome model, such as logistic regression, that captures the associations between $Y$, censored $X$, and $Z$. This flexibility is one of the strengths of an imputation approach: once we have “filled in” the censored covariates with their conditional means, we can apply any of the usual modeling approaches.

Even with our improvements, there are limitations to conditional mean imputation. Namely, semiparametric imputation approaches like this one are sensitive to non-proportional hazards in $X$ given $Z$ because they rely on the Cox model to estimate the survival function. However, we could test for this and modify the imputation model (e.g., by incorporating time-varying coefficients) to accommodate non-proportionality [Hastie and Tibshirani, 1993]. Still, an entirely unspecified estimator, like the Kaplan–Meier, would be ideal, because it avoids distributional and proportional hazards assumptions.

Our proposed recruitment strategy takes a granular approach to targeting high priority subjects from existing studies. Other proposed strategies stratify a proxy for time to diagnosis and draw random samples from each stratum; for example, Paulsen et al. [2019] create “low” and “high” risk groups from the scaled CAP score (calculated as $\text{AGE} \times (\text{CAG} - 33.66)$ as in Zhang et al. [2011]), where the high risk group is made up of subjects with $\text{CAP} > 390.4$ who are believed to be nearest to diagnosis. One potential drawback of stratified sampling strategies like this is that information from the continuous CAP variable is lost when categories are created, overlooking the variability across subjects within each category. In other words, once subjects are placed into categories, there is no way for clinicians to gauge the relative priority of subjects within a risk group; this means that a subject with a CAP of 666.4 (the largest in the study) has the same chance of being recruited as someone with a CAP of 390.5 (barely large enough to be high risk). In ranking
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subjects from smallest to largest expected symptom change rather than categorizing, our strategy empowers clinicians to directly recruit the highest priority subjects.

There are several interesting statistical directions for future work. The first would be to extend our framework to capture multiple censored covariates \((X_1, \ldots, X_p)\). Atem et al. [2019a] propose such an approach, but they use the trapezoidal rule to calculate the conditional means, so their formulas would need to be adapted in the ways discussed herein. Also, to our knowledge, imputation for randomly left-censored covariates has been thus far unaddressed and should be a relatively straightforward adaptation of the current work. The formula for the appropriate conditional means for this setting, \(E(X|X < W_i, Z_i)\), would need to be derived, and then adaptive quadrature could be used to calculate them. There is also a natural connection between our methods and nonparametric or semiparametric estimation of mean residual life that could be worth investigating since both seek to integrate over the survival function. Finally, an interesting clinical direction for future work might involve adopting our rank-based recruitment strategy for other measures of symptom progression (e.g., by ranking subjects on a proxy like CAP score).

Supplementary Materials

- **Additional appendices, tables, and figures:** The Web Appendices and Supplemental Figures and Tables referenced in Sections 2–4 can be found in the Supplementary Materials that follow this text.
- **R-package for conditional mean imputation:** R-package imputeCensRd containing code to perform the imputation methods described in the article can be found at [https://github.com/sarahlotspeich/imputeCensRd](https://github.com/sarahlotspeich/imputeCensRd).
- **R code for simulation studies:** R scripts to replicate the simulation studies from Section 3 can be found at [https://figshare.com/projects/Escaping_the_trap/147225](https://figshare.com/projects/Escaping_the_trap/147225).

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Web Appendix A  More About the Extrapolation Methods for Breslow’s Estimator

Web Appendix A.1 Derivation of the Exponential Extension

Assuming that among the baseline group (i.e., with \( \mathbf{Z} = 0 \)), \( X \) follows an exponential distribution with rate \( \rho \), we have \( S_0(t) = \exp \left\{ -\left( \frac{t}{\rho} \right) \right\} \). To connect to Breslow’s estimator, \( \hat{\rho} \) is constrained so that \( \exp \left\{ -\hat{\rho} \tilde{X} \right\} = \hat{S}_0(\tilde{X}) \). We can solve this constraint for \( \hat{\rho} = -\tilde{X} \log \left\{ \hat{S}_0(\tilde{X}) \right\} - 1 \) and extrapolate using \( \hat{S}_0(t) = \exp \left( \left[ t \log \left\{ \hat{S}_0(\tilde{X}) \right\} \right] / \tilde{X} \right) \) for \( t > \tilde{X} \). This is the exponential extension introduced in Section 2.5.1.

Web Appendix A.2 Derivation of the Weibull Extension

Assuming that among the baseline group (i.e., with \( \mathbf{Z} = 0 \)), \( X \) follows a Weibull distribution with shape and scale parameters \( \nu \) and \( \rho \), respectively, we have \( S_0(t) = \exp \left\{ -\rho t^{\nu} \right\} \). The parameters are once again constrained to ensure a clean transition from Breslow’s estimator to the extension, with \( \exp \left\{ -\hat{\rho} \tilde{X}^{\hat{\nu}} \right\} = \hat{S}_0(\tilde{X}) \). Unlike the exponential extension, there is not a closed form solution as in Web Appendix A.1. Herein, we adopt a constrained maximum likelihood approach to find \( \hat{\nu} \) and \( \hat{\rho} \).

The shape and scale parameters, \( \nu \) and \( \rho \), respectively, are constants that we can estimate directly through maximum likelihood estimation. Using the probability density function and survival function of the Weibull distribution, the usual (i.e., unconstrained) log-likelihood for the shape and scale parameters can be defined as

\[
l_n(\nu, \rho) = \sum_{i=1}^{n} \Delta_i \log \left\{ \lambda \nu W_i^{\nu-1} \exp \left\{ -\rho W_i^{\nu} \right\} \right\} + \sum_{i=1}^{n} (1 - \Delta_i) \log \left\{ \exp \left( -\rho W_i^{\nu} \right) \right\}
= -\rho \sum_{i=1}^{n} W_i^{\nu} + (\nu - 1) \sum_{i=1}^{n} \Delta_i \log \left( W_i \right) + n_1 \log \left( \rho \right) + n_1 \log \left( \nu \right),
\]

(S.1)

where \( n_1 \) is the number of uncensored observations (i.e., \( n_1 = \sum_{i=1}^{n} \Delta_i \)).

Recall that we want this Weibull curve to “tie into” Breslow’s estimator \( \hat{S}_0(t) \) at the largest uncensored value, \( \tilde{X} \). This constraint on the Weibull survival function can be expressed as \( \exp \left( -\rho \tilde{X}^{\nu} \right) = \hat{S}_0(\tilde{X}) \), and it further translates into the following relationship between the shape and scale parameters:

\[
\rho = -\log \left( \hat{S}_0(\tilde{X}) \right) / (\tilde{X}^{\nu}).
\]
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With Equation (S.2), we can modify Equation (S.1) to obtain the constrained log-likelihood in terms of just the shape parameter.

\[
\ell_n(\nu) = \left[ \log \left\{ \hat{S}_0(\bar{X}) \right\} / (\bar{X}^\nu) \right]\left[ \sum_{i=1}^{n} W_i^\nu + (\nu - 1) \sum_{i=1}^{n} \Delta_i \log (W_i) \right] + n_1 \log \left( \nu \right).
\]

(S.3)

Estimation of the maximum likelihood estimator (MLE) \( \hat{\nu} \) is done by finding the root of Equation (S.3) with a univariate Newton-type algorithm, as implemented in the \texttt{nlm} function in R [?]. Our initial guess for the shape parameter (which must be \( > 0 \)) is \( \hat{\nu}(0) = 1E^{-4} \), and the algorithm is restricted to positive values for \( \hat{\nu} \). Finally, \( \hat{\rho} \) is obtained by plugging \( \hat{\nu} \) at convergence into Equation (S.2), and with it we arrive at the parameters for the Weibull extension used to extrapolate from Breslow’s step function estimator of baseline survival, \( \hat{S}_0(t) \) for \( t > \bar{X} \) introduced in Section 2.5.1.

Web Appendix A.3 Finite Upper Limit for \( X \)

In the formulas used throughout this manuscript, we integrate from \( W_i \) to \( \infty \) in calculating the conditional means. This is the most general case, and it was appropriate in our simulation studies (Section 3) because \( X \) was generated from a Weibull distribution with a domain from 0 to \( \infty \). However, in some settings we have prior information about \( X \) that allows us to replace the infinite upper bound in the integral with some known constant, denoted by \( \omega \).

For example, in our PREDICT-HD example (Section 4), the censored covariate \( X \) was time from study entry to clinical Huntington’s disease diagnosis. Since this is an adult cohort, with all subjects having \( \texttt{AGE}_0 \geq 18 \) years old at study entry, we set the longest time from study entry to clinical diagnosis to be \( \omega = 60 \) years. We believe this is a conservative upper bound on \( \texttt{TIME}_1 \) that is in agreement with the recent overall life expectancy estimate in the United States of around 78 years [?]. There is no established life expectancy estimate for people who are at-risk for Huntington’s disease; we call 78 years a “conservative” upper bound, since it is probably higher than the life expectancy in our population. Choosing this finite limit is an important consideration. While we want to extract as much information from the data as we can, we also want to avoid imputing too far beyond the observed values of \( \texttt{TIME}_1 \) or beyond reasonable values based on the context, leading to a trade-off between setting \( \omega \) too low or high.

Now, our choice of finite \( \omega \) imposes an additional constraint on the Weibull extension: \( \exp (-\gamma \omega^\alpha) \approx 0 \), since \( S(\omega) \approx 0 \). Thus, we can find the corresponding values of \( \hat{\gamma} \) and \( \hat{\alpha} \) using the \texttt{uniroot} function in R [?], since \( \lambda \) can be treated as a function of \( \alpha \) as in Equation (S.2).
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Figure S1: Illustration of the four extrapolation methods for a step survival function $\hat{S}(t)$ in simulated data. The shaded area represents values of $t > \tilde{X}$ (the largest uncensored value), where extrapolation is needed.
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Web Appendix B  Additional Results from the Simulation Studies

Figure S2: With Weibull $X$, extrapolating Breslow’s estimator $\hat{S}_0(t)$ beyond the largest uncensored value $\bar{X}$ with any of the three extrapolation methods offered similar bias and efficiency for $\hat{\beta}$ in conditional mean imputation with adaptive quadrature. The dashed line denotes the true parameter value, $\beta = 0.5$. 
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Figure S3: With log-normal $X$, extrapolating Breslow’s estimator $\hat{S}_0(t)$ beyond the largest uncensored value $\tilde{X}$ with any of the three extrapolation methods offered similar bias and efficiency for $\hat{\beta}$ in conditional mean imputation with adaptive quadrature. The dashed line denotes the true parameter value, $\beta = 0.5$. 
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Figure S4: Interpolating Breslow’s estimator $\hat{S}_0(t)$ between uncensored values with either of the two interpolation methods offered similar bias and efficiency for $\hat{\beta}$ in conditional mean imputation with adaptive quadrature. The dashed line denotes the true parameter value, $\beta = 0.5$. 

Figure S4: Interpolating Breslow’s estimator $\hat{S}_0(t)$ between uncensored values with either of the two interpolation methods offered similar bias and efficiency for $\hat{\beta}$ in conditional mean imputation with adaptive quadrature. The dashed line denotes the true parameter value, $\beta = 0.5$. 

Figure S4: Interpolating Breslow’s estimator $\hat{S}_0(t)$ between uncensored values with either of the two interpolation methods offered similar bias and efficiency for $\hat{\beta}$ in conditional mean imputation with adaptive quadrature. The dashed line denotes the true parameter value, $\beta = 0.5$.
Replacing the trapezoidal rule to better impute censored covariates

Figure S5: Extrapolating Breslow’s estimator \( \hat{S}_0(t) \) beyond the largest uncensored value \( \bar{X} \) with any of the three extrapolation methods offered similar bias and efficiency for \( \hat{\beta} \) in conditional mean imputation with the trapezoidal rule. The dashed line denotes the true parameter value, \( \beta = 0.5 \).
Replacing the trapezoidal rule to better impute censored covariates

In Table S1, Covariate $X$ was simulated from a log-normal distribution with mean $= 0$ and variance $= 0.25$ (on the log scale). The MLE for the Weibull extension converged in $\geq 99.8\%$ of replicates of imputation (just 8 of 12,000 total replicates did not converge); all other entries are based on 1000 replicates.

Table S1: Simulation results for log-normal $X$ from the full cohort and imputation approaches using the estimated survival function and adaptive quadrature versus the trapezoidal rule. (SE: empirical standard error; RE: empirical relative efficiency to full cohort.)

| Censoring | $n$ | Full Cohort | Adaptive Quadrature | Trapezoidal Rule |
|-----------|-----|-------------|---------------------|------------------|
|           |     | Bias  SE    | Bias  SE  RE       | Bias  SE  RE     |
| Light     | 100 | 0.005 0.242| 0.001 0.263 0.852 | -0.008 0.263 0.846 |
|           | 500 | 0.005 0.109| 0.003 0.115 0.899 | -0.003 0.115 0.900 |
|           | 2000| -0.001 0.052| 0.002 0.056 0.852 | 0.003 0.056 0.875 |
| Moderate  | 100 | 0.005 0.242| 0.009 0.281 0.744 | -0.008 0.283 0.732 |
|           | 500 | 0.005 0.109| 0.010 0.124 0.775 | -0.007 0.122 0.805 |
|           | 2000| -0.001 0.052| 0.004 0.060 0.755 | 0.000 0.062 0.705 |
| Heavy     | 100 | 0.005 0.242| -0.024 0.480 0.112| -0.060 0.496 0.105 |
|           | 500 | 0.005 0.109| -0.000 0.189 0.141| -0.027 0.195 0.132 |
|           | 2000| -0.001 0.052| 0.007 0.095 0.140 | -0.012 0.097 0.136 |

$\hat{\alpha}$: Intercept

$\hat{\beta}$: Coefficient on Censored $X$

$\hat{\gamma}$: Coefficient on Uncensored $Z$
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Figure S6: Due to the Weibull distribution’s skewness, higher censoring rates led to smaller values of $W(n)$, which led to worse performance (i.e., higher bias) when calculating the conditional mean with the trapezoidal rule. A and B are the empirical densities of $W(n)$ when $X$ was generated from a Weibull and a log-normal distribution, respectively, under light, moderate, or heavy censoring.
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Web Appendix C  Additional Results from the PREDICT-HD Analysis

Figure S7: Patterns of missing data in the outcome cUHDRS (composite Unified Huntington Disease Rating Scale) and its component variables total functional capacity (TFC), total motor score (TOTAL_MOTOR_SCORE), Symbol Digit Modality Test (SDMT), and Stroop Word Reading Test (STROOP_WORD) at study entry. This plot was created using the nanair package [?].

Empirical densities of observed and imputed TIME0 from study entry to clinical Huntington's disease diagnosis for the two imputation approaches exhibited some distinct differences (Figure S8). Using adaptive quadrature for imputation led to a smooth, unimodal density, with a peak not long after the largest uncensored value of ̄X = 11.422 years from study entry to diagnosis. Imputing using the trapezoidal rule instead led to a more volatile density that peaked earlier, at around 10 years to diagnosis. Interestingly, the trapezoidal rule led to a higher maximum of 45 years to diagnosis versus 29 with adaptive quadrature, but other quantiles were similar (e.g., within 4 years). We also noted differences between the densities of TIME1 from the last visit to clinical Huntington's disease diagnosis (Figure S9), with adaptive quadrature still leading to more support for values of TIME1 representing longer pre-diagnosis follow-up.
Replacing the trapezoidal rule to better impute censored covariates

Figure S8: Histograms of observed and imputed times from study entry to Huntington’s disease diagnosis in the PREDICT-HD study. The dashed line denotes the longest uncensored value observed in the data, \( \bar{X} = 11.4 \) years from study entry to diagnosis.

Figure S9: Histograms of observed and imputed times from last visit to Huntington’s disease diagnosis in the PREDICT-HD study. The dashed line denotes the time of diagnosis.
Replacing the trapezoidal rule to better impute censored covariates

Table S2: Huntington’s disease symptom progression models in PREDICT-HD fit using normal linear regression after imputing censored TIME\textsubscript{1} from last visit to diagnosis with conditional means. (95\% CI denotes the 95\% Wald-type confidence interval based on the sandwich standard errors.)

| Coefficient          | Adaptive Quadrature | Trapezoidal Rule |
|----------------------|---------------------|------------------|
|                      | Estimate            | 95\% CI          | Estimate            | 95\% CI          |
| Intercept            | 21.680              | (20.571, 22.790) | 23.298              | (22.349, 24.246) |
| TIME\textsubscript{1} | 0.084               | (−0.013, 0.181)  | 0.117               | (−0.032, 0.266)  |
| cUHDRS\textsubscript{0} | 1.048              | (0.941, 1.155)   | 0.961               | (0.861, 1.061)   |
| TIME\textsubscript{1} × cUHDRS\textsubscript{0} | −0.024            | (−0.036, −0.011) | −0.019              | (−0.036, −0.002) |
| AGE\textsubscript{0}  | −0.021              | (−0.046, 0.003)  | 0.012               | (−0.009, 0.032)  |
| CAG\textsubscript{0}  | −0.089              | (−0.166, −0.012) | −0.092              | (−0.160, −0.025) |
| AGE\textsubscript{0} × CAG\textsubscript{0} | 0.006             | (0.001, 0.011)   | −0.014              | (−0.018, −0.010) |
Figure S10: For each subject, we can estimate their cUHDRS at the end of the trial using the symptom progression models and then construct a complete trajectory of their symptom severity over study follow-up (i.e., the solid line from First Visit to Recruitment/Last Visit) and the 2-year clinical trial (i.e., the dashed line from Recruitment/Last Visit to Trial End).
Figure S11: Subjects were ranked by their estimated changes in symptoms based on the models, starting from the biggest decline in function (i.e., largest decrease in cUHDRS), and the first 200 subjects subsequently recruited into the hypothetical clinical trial. The shaded regions capture subjects who would have been recruited based on each model, with the overlapping area in the lower left capturing subjects who would have been recruited based on either model. Points represent the $n = 732$ censored subjects from PREDICT-HD.
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Figure S12: Statuses of $n = 732$ resampled subjects considered for recruitment into a hypothetical clinical trial based on Huntington’s disease symptom progression models using the two imputation approaches in PREDICT-HD. New datasets of $n = 732$ subjects were created by resampling from censored subjects in PREDICT-HD with replacement 1000 times.