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BIASED SAMPLING DESIGNS TO IMPROVE RESEARCH EFFICIENCY: FACTORS INFLUENCING PULMONARY FUNCTION OVER TIME IN CHILDREN WITH ASTHMA[1]

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Substudies of the Childhood Asthma Management Program [*Control. Clin. Trials* **20** (1999) 91–120; *N. Engl. J. Med.* **343** (2000) 1054–1063] seek to identify patient characteristics associated with asthma symptoms and lung function. To determine if genetic measures are associated with trajectories of lung function as measured by forced vital capacity (FVC), children in the primary cohort study retrospectively had candidate loci evaluated. Given participant burden and constraints on financial resources, it is often desirable to target a subsample for ascertainment of costly measures. Methods that can leverage the longitudinal outcome on the full cohort to selectively measure informative individuals have been promising, but have been restricted in their use to analysis of the targeted subsample. In this paper we detail two multiple imputation analysis strategies that exploit outcome and partially observed covariate data on the nonsampled subjects, and we characterize alternative design and analysis combinations that could be used for future studies of pulmonary function and other outcomes. Candidate predictor (e.g., IL10 cytokine polymorphisms) associations obtained from targeted sampling designs can be estimated with very high efficiency compared to standard designs. Further, even though multiple imputation can dramatically improve estimation efficiency for covariates available on all subjects (e.g., gender and baseline age), relatively modest efficiency gains were observed in parameters associated with predictors that are exclusive to the targeted sample. Our results suggest that future studies of longitudinal trajectories can be efficiently conducted by use of outcome-dependent designs and associated full cohort analysis.

1. Introduction. The Childhood Asthma Management Program [CAMP; CAMP Research Group (1999 and 2000)] was a randomized clinical trial that compared two anti-inflammatory medications and a placebo on lung growth over

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the course of 4 years in children with mild to moderate asthma. CAMP substudies have since examined the relationship between genetic factors and asthma phenotypes. Like other genetic data collected in CAMP, interleukin-10 (IL10) genotype data were obtained retrospectively by analysis of stored blood samples. IL10 is a type-2 T-helper cytokine with anti-inflammatory properties, and polymorphisms in the IL10 cytokine gene have been shown to be associated with asthma phenotypes in children [Lyon et al. (2004)]. However, as is often the case, ascertainment of expensive exposures can restrict sample size and therefore motivate thoughtful sampling strategies. Given that the outcome of interest was available on all subjects, we seek to determine whether the longitudinal response could or should be used to target a subset of select individuals for sampling of covariates. In particular, we explore both sampling designs and associated analysis options with the goal of providing recommendations for the efficient conduct of future retrospective studies.

We are specifically interested in the impact genetic variants have on both lung function and growth, and on the effect of medication (versus placebo) within subgroups defined by genetic variants of the IL10 gene. For nearly all children, forced vital capacity (FVC, a measure of lung function) was measured ten times over the course of 4 years, thereby providing rich detail on the primary response trajectory. Our scientific question can be addressed by appropriate longitudinal regression models with a focus on estimating the main effects of time since randomization, time-invariant randomized treatment assignment (Budesonide, Nedocromil, placebo), and their interactions with the presence or absence of at least one IL10 polymorphism. Valid IL10 and other data were available for 555 children who participated in CAMP. Even though all data were available for these children, we will illustrate the interplay between sampling strategies and analysis procedures by assuming study resources are limited and IL10 data can only be collected on approximately 250 children. The assumption of limited resources allows us to compare and contrast several sampling designs and estimation procedures in order to inform decisions when conducting similar substudies in the future.

In related work, Neuhaus, Scott and Wild (2002, 2006) discussed biased, outcome dependent sampling (ODS) designs with longitudinal response data and estimation from resulting data using a profile likelihood. In the longitudinal binary response setting, Schildcrout and Heagerty (2008, 2011) described stratified sampling designs based on the sum of the response series with an ascertainment corrected likelihood approach for analysis. Schildcrout and Rathouz (2010), Schildcrout et al. (2012) and Neuhaus et al. (2014) addressed auxiliary variable dependent sampling where the sampling variable is related but is not equal to the longitudinal response. In the univariate continuous response setting, Zhou et al. (2002, 2007) and Weaver and Zhou (2005) discussed ODS designs that combine simple random samples with a sample of subjects whose responses are more extreme. Further, several authors discussed unplanned outcome-dependent follow-up

for longitudinal continuous response data [e.g., Bůžková and Lumley (2009), Lin and Ying (2001), Lipsitz et al. (2002)].

In Schildcrout, Garbett and Heagerty (2013), we proposed biased epidemiological study designs for continuous longitudinal response data where sampling is based on strata defined by low-dimensional summaries of the response series. We proposed sampling based on the intercept, the slope, or both the intercept and slope of the subject-specific ordinary least squares (OLS) regressions of the response on a time-varying covariate (which may be time itself). We showed that sampling based on a variable related to a target predictor can lead to substantial efficiency gains relative to random sampling for the associated parameter. Such a result is well known to survey sampling methodologists [e.g., see Kish (1965), Korn and Graubard (2011)]. The estimation procedure discussed in Schildcrout, Garbett and Heagerty (2013) used a bias correcting, ascertainment corrected conditional likelihood that only includes subjects with fully observed exposure data (i.e., those who were sampled). Such an analysis can be referred to as a complete data (CD) analysis [Carroll et al. (2006), Lawless, Kalbfleisch and Wild (1999)]. In univariate response settings, such as the case-cohort design, other authors [e.g., Breslow et al. (2009a, 2009b), Marti and Chavance (2011)] have shown that utilizing the partial data on the unsampled subjects can add information and improve estimation efficiency.

With specific motivation from the CAMP study, the purpose of this manuscript is to detail the joint impact of sampling design and statistical analysis decisions toward efficient parameter estimation with longitudinal continuous response data. Longitudinal outcome-dependent sampling designs have only recently been proposed, and analysis options have not considered use of both sampled and unsampled subjects. Using the CAMP study for motivation and illustration, we focus on the following goals: (1) to evaluate circumstances under which multiple imputation (MI) increases efficiency appreciably over the bias-correcting complete data (CD) analysis under ODS designs, and (2) to evaluate the extent to which the ODS designs improve estimation efficiency when MI (rather than CD analysis) is the chosen analytical approach. We use a simulation study to explore relative efficiency across several sampling design and estimation procedure combinations. The CAMP study is an exemplar of a longitudinal randomized trial in which retrospective collection of additional explanatory data is conducted to in order to leverage the original cohort study and answer new scientific questions. The CAMP data provide an ideal context to inform efficient study design options for future ancillary studies of factors associated with longitudinal outcome trajectories.

Section 2 discusses the model of interest, briefly reviews the sampling strategy and estimation procedure discussed in Schildcrout, Garbett and Heagerty (2013), and proposes two multiple imputation analysis strategies that exploit the unsampled subjects' data. Section 3 examines the relative efficiency of design and analysis procedures in a number of plausible scenarios. Section 4 returns to the CAMP data to examine the impact of study designs on the FVC data, and Section 5 provides a discussion including directions for future research.

2. Methodological framework. We now introduce the mixed model, the class of ODS designs and associated CD analyses, and two multiple imputation (MI) extensions for conducting analyses.

2.1. *Linear mixed effects model for continuous longitudinal response data.* With N subjects in the original cohort, $\mathbf{Y}_i$, $i \in 1, 2, \ldots, N$, the n_i-vector of response values, $\mathbf{X}_i$, a $n_i \times p$ fixed effects design matrix, and $\mathbf{Z}_i$ the $n_i \times q$ design matrix for the random effects, we begin with the Laird and Ware (1982) linear mixed effects model given by

$$\mathbf{Y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\varepsilon}_i, \tag{2.1}$$

where $\boldsymbol{\beta}$ is a p-vector of fixed-effect coefficients, $\mathbf{b}_i \sim N(\mathbf{0}, \mathbf{D})$, and $\boldsymbol{\varepsilon}_i \sim N(0, \boldsymbol{\Sigma})$. A common design matrix for the random effects in the continuous data setting is $\mathbf{Z}_i = (\mathbf{1}, \mathbf{T}_i)$, where $\mathbf{T}_i$ is a time-varying covariate—perhaps time itself, $\mathbf{b}_i = (b_{0i}, b_{1i})$, and $\mathbf{D}_i$ is the 2×2 covariance matrix containing variance components (σ_0^2, σ_1^2) and correlation $\rho = \text{corr}(b_{0i}, b_{1i})$. Analysis based on a random sample of N_s subjects can be conducted by maximizing the log-likelihood

$$l(\boldsymbol{\theta}; \mathbf{Y}, \mathbf{X}) = \sum_{i=1}^{N_s} l_i(\boldsymbol{\theta}; \mathbf{Y}_i, \mathbf{X}_i) = \sum_{i=1}^{N_s} \log f(\mathbf{Y}_i|\mathbf{X}_i; \boldsymbol{\theta}), \tag{2.2}$$

where $\boldsymbol{\theta} = (\boldsymbol{\beta}, \sigma_0, \sigma_1, \rho)$ and $f(\cdot)$ is the multivariate normal density function.

2.2. *Coarsened summary sampling designs.* Study designs proposed in Schildcrout, Garbett and Heagerty (2013) propose subsampling from a larger cohort based on a user defined, low-dimensional summary of the outcome vector $\mathbf{Y}_i$ or, more accurately, on strata defined by the summary measure. Let $\mathbf{X}_{oi}$ be a covariate subset of $\mathbf{X}_i$ that is known prior to initiation of the substudy and let $\mathbf{Q}_i = g(\mathbf{Y}_i, \mathbf{X}_{oi})$ be any function of the response and observed covariates that summarizes important features of the response vectors. Three simple and useful summaries are the estimated intercept, slope, and the joint intercept and slope, based on the subject-specific OLS regression of $\mathbf{Y}_i$ on a time-varying covariate. For example, if $\mathbf{T}_i$ is the easily ascertained time-varying covariate, $\mathbf{X}_{ti} = (\mathbf{1}, \mathbf{T}_i) \subset \mathbf{X}_{oi}$, and $\mathbf{W}_{oi} = (\mathbf{X}_{ti}^t\mathbf{X}_{ti})^{-1}\mathbf{X}_{ti}^t$, then $\mathbf{Q}_i = \mathbf{W}_{oi}\mathbf{Y}_i$ is the estimated intercept and slope for the regression of $\mathbf{Y}_i$ on $\mathbf{T}_i$. We proposed stratified random sampling based on regions of $\mathbf{Q}_i$. Based on results from other literature [e.g., Zhou et al. (2002, 2007, 2011)], we oversampled the extremes of the $\mathbf{Q}_i$ distribution to realize substantial efficiency gains for target parameters. Let S_i equal 1 if subject i is sampled for exposure ascertainment and 0 if not. For region $R^k \in \{R^1, \ldots, R^K\}$, let $\pi(R^k) = \text{pr}(S_i = 1|\mathbf{Y}_i, \mathbf{X}_i) = \text{pr}(S_i = 1|\mathbf{q}_i \in R^k)$ be the probability of being sampled given $\mathbf{q}_i$, the observed value of $\mathbf{Q}_i$, is in region k. Importantly, $S_i \perp (\mathbf{Y}_i, \mathbf{X}_i)|\mathbf{q}_i$, that is, sampling depends upon the data $(\mathbf{Y}_i, \mathbf{X}_i)$ only through $\mathbf{q}_i$.

2.3. *An ascertainment corrected likelihood for coarsened summary sampling designs*. For inferences to the population represented by the original cohort—as opposed to the pseudo-population represented by the biased sample—Schildcrout, Garbett and Heagerty (2013) considered maximization of an ascertainment corrected likelihood (ACL). The ACL corrects for the design by conditioning the likelihood on inclusion into the ODS ($S_i = 1$). It is a "complete data" (CD) likelihood [Carroll et al. (2006), Lawless, Kalbfleisch and Wild (1999)] in that only subjects with complete exposure data contribute to the conditional likelihood, and therefore to the analysis. A key attraction of the CD approach is that valid inferences can be realized while only requiring a model for $\mathbf{Y}_i|\mathbf{X}_i$ without requiring a model for $\mathbf{X}_i$. Specifically, if $f(\mathbf{Y}_i|\mathbf{X}_i;\boldsymbol{\theta})$ is the density for subject i under simple random sampling from a population, the density for those who are included in the ODS is given by

$$
\begin{aligned}
&f(\mathbf{Y}_i|\mathbf{X}_i, S_i = 1;\boldsymbol{\theta}) \\
&\quad = \pi(\mathbf{q}_i) f(\mathbf{Y}_i|\mathbf{X}_i;\boldsymbol{\theta})\{\mathrm{pr}(S_i = 1|\mathbf{X}_i;\boldsymbol{\theta})\}^{-1} \\
&\quad = \pi(\mathbf{q}_i) f(\mathbf{Y}_i|\mathbf{X}_i;\boldsymbol{\theta})\left\{\sum_{k=1}^{K} \pi\big(R^k\big) \int_{R^k} f(\mathbf{q}_i|\mathbf{X}_i;\boldsymbol{\theta})\, d\mathbf{q}_i\right\}^{-1},
\end{aligned} \tag{2.3}
$$

where $\pi(\mathbf{q}_i)$ is subject i's sampling probability that is based on $\mathbf{q}_i$ [i.e., $\pi(\mathbf{q}_i) = \pi(R^k)$ if and only if $\mathbf{q}_i \in R^k$], $\pi(R^k)$ is the sampling probability for all values of $\mathbf{Q}_i$ in region R^k, and $\int_{R^k} f(\mathbf{q}_i|\mathbf{X}_i;\boldsymbol{\theta})\, d\mathbf{q}_i = \mathrm{pr}(\mathbf{q}_i \in R^k|\mathbf{X}_i;\boldsymbol{\theta})$. Because $\pi(\mathbf{q}_i)$ is parameter-free, being specified by the investigator, if a total of N_s subjects are selected into the ODS for exposure ascertainment, the ascertainment corrected log-likelihood, $l^C(\boldsymbol{\theta};\mathbf{Y},\mathbf{X})$, is given by

$$
l(\boldsymbol{\theta};\mathbf{Y},\mathbf{X}) - \sum_{i=1}^{N_s} \log\left\{\sum_{k=1}^{K} \pi\big(R^k\big) \int_{R^k} f(\mathbf{q}_i|\mathbf{X}_i;\boldsymbol{\theta})\, d\mathbf{q}_i\right\}. \tag{2.4}
$$

In the special case where $\mathbf{Q}_i = \mathbf{W}_{oi}\mathbf{Y}_i$ is a linear transformation of $\mathbf{Y}_i$, under the assumption $\mathbf{Y}_i|\mathbf{X}_i \sim N(\boldsymbol{\mu}_i, \mathbf{V}_i)$, then $\mathbf{Q}_i|\mathbf{X}_i \sim N(\boldsymbol{\mu}_{q,i}, \mathbf{V}_{q,i})$, where $\boldsymbol{\mu}_{q,i} = \mathbf{W}_{oi}\boldsymbol{\mu}_i$ and $\mathbf{V}_{q,i} = \mathbf{W}_{oi}\mathbf{V}_i\mathbf{W}_{oi}^t$. Thus, the ACL is a straightforward extension of the likelihood used for standard analyses, and details can be found in Schildcrout, Garbett and Heagerty (2013). We note that this log-likelihood is composed of two terms: the standard log-likelihood as in equation (2.2) and an additive ascertainment correction piece that accounts for the biased study design and is the probability of being sampled as a function of $\mathbf{X}_{oi}$. This is in contrast to inverse probability weighting or weighted likelihood approaches [e.g., Horvitz and Thompson (1952), Robins, Rotnitzky and Zhao (1994)] that multiply the log-likelihood by a function of the sampling probability to calculate an unbiased estimating equation.

2.4. *Multiple imputation*. Whereas the analysis procedures proposed in Schildcrout, Garbett and Heagerty (2013) were more efficient than random sampling, one can expect that there may be additional information in those subjects for whom the unmeasured, expensive exposure, X_{ei}, was not ascertained (i.e., those with $S_i = 0$). We therefore propose to multiply impute [Rubin (1976)] X_{ei} for all subjects in whom $S_i = 0$. Multiple imputation (MI) is expected to recover some of the information about the parameter associated with X_{ei} that is lost by not measuring X_{ei}, and it is expected to recover much more of the information in parameters associated with $\mathbf{X}_{oi}$ that is available but is not used in CD analyses. Multiple imputation is attractive because it can leverage existing methods and software without needing tailored programs. In the approaches described below, we generate imputation samples from the conditional exposure distribution in unsampled subjects $[X_{ei}|\mathbf{Y}_i, \mathbf{X}_{oi}, S_i = 0]$. Once the exposure model is constructed, we build M multiple imputation data sets, fit the target model to each one using standard maximum likelihood, and combine estimates across imputations to make inferences regarding model parameters. For any parameter θ in $\boldsymbol{\theta}$, we may estimate its value and variance with $\widehat{\theta} = M^{-1}\sum_{m=1}^{M}\widehat{\theta}^{(m)}$ and $\widehat{\mathrm{Var}}(\widehat{\theta}) = \overline{V} + (1 + M^{-1})B$, respectively, where $\overline{V} = M^{-1}\sum_{m=1}^{M}\widehat{\mathrm{Var}}(\widehat{\theta}^{(m)})$ and $B = (M-1)^{-1}\sum_{m=1}^{M}(\widehat{\theta}^{(m)} - \widehat{\theta})^2$. With adequate M, test statistics for parameters are well approximated by a standard Gaussian distribution; however, with small M, a t-distribution with $df = (M-1)[1 + M\overline{V}/\{(M+1)B\}]^2$ degrees of freedom is more appropriate [Little and Rubin (2002), Rubin (1976), Schafer and Graham (2002)]. In the settings we believe our designs could be most useful, X_{ei} is to be imputed in a relatively large percentage of subjects (i.e., well over 50 percent), and in such cases a larger number of imputation samples are required to use the normal approximation to the t-distribution.

We now describe two approaches to estimating the imputation model $[X_{ei}|\mathbf{y}_i, \mathbf{x}_{oi}, S_i = 0]$. The first is an extension of the CD analysis described in Section 2.3 and the second is a direct imputation approach that does not require estimation based on maximizing the ACL. Because the ODS sampling schemes we have described depend upon the data through a low-dimensional response summary and possibly observed covariates $\mathbf{X}_{oi}$,

$$\mathrm{pr}(x_{ei}|\mathbf{x}_{oi}, \mathbf{y}_i, S_i = 0) = \mathrm{pr}(x_{ei}|\mathbf{x}_{oi}, \mathbf{y}_i) = \mathrm{pr}(x_{ei}|\mathbf{x}_{oi}, \mathbf{y}_i, S_i = 1). \tag{2.5}$$

Thus, the design-based "missing data mechanism" is ignorable and generating X_{ei} for unsampled subjects can be based directly on model estimates derived from sampled data without consideration of the biased sample. Importantly, for the CAMP analysis, the missing exposure variable (X_{ei}) was binary and so for the present research, we only detail this special case explicitly; however, extensions to continuous and other exposure values are feasible.

2.4.1. *Imputation model construction*: *Combine response model and marginal exposure model*. The complete data plus multiple imputation analysis approach (CD+MI) combines the estimates from maximizing the ACL in Section 2.3 with an exposure model for $[X_{ei}|\mathbf{x}_{oi}, S_i = 1]$ to estimate $[X_{ei}|\mathbf{y}_i, \mathbf{x}_{oi}, S_i = 0]$. Specifically, we combine a CD estimate of $[\mathbf{Y}_i|\mathbf{x}_i, S_i = 1]$ with a covariate logistic regression for $[X_{ei}|\mathbf{x}_{oi}, S_i = 1]$ to identify the conditional exposure distribution $[X_{ei}|\mathbf{y}_i, \mathbf{x}_{oi}, S_i = 1]$ used for imputation among those with $S_i = 0$. Using equation (2.5) and Bayes' theorem,

$$\begin{aligned}(2.6)\qquad &\frac{\operatorname{pr}(X_{ei} = 1|\mathbf{x}_{oi}, \mathbf{y}_i, S_i = 0)}{\operatorname{pr}(X_{ei} = 0|\mathbf{x}_{oi}, \mathbf{y}_i, S_i = 0)} \\ &\quad = \frac{f(\mathbf{y}_i|X_{ei} = 1, \mathbf{x}_{oi}, S_i = 1)}{f(\mathbf{y}_i|X_{ei} = 0, \mathbf{x}_{oi}, S_i = 1)} \cdot \frac{\operatorname{pr}(X_{ei} = 1|\mathbf{x}_{oi}, S_i = 1)}{\operatorname{pr}(X_{ei} = 0|\mathbf{x}_{oi}, S_i = 1)}.\end{aligned}$$

Using the logistic regression model to obtain estimate $\widehat{\operatorname{pr}}(x_{ei}|\mathbf{x}_{oi}, S_i = 1)$ in the observed subjects' data, and then combining it with $\widehat{f}(\mathbf{y}_i|x_{ei}, \mathbf{x}_{oi}, S_i = 1)$ from the CD analysis, we are able to estimate and sample from $\widehat{\operatorname{pr}}(x_{ei}|\mathbf{x}_{oi}, \mathbf{y}_i, S_i = 0)$.

Note. We may write the exposure odds model itself as

$$\begin{aligned}(2.7)\qquad &\frac{\operatorname{pr}(X_{ei} = 1|\mathbf{x}_{oi}, S_i = 1)}{\operatorname{pr}(X_{ei} = 0|\mathbf{x}_{oi}, S_i = 1)} \\ &\quad = \frac{\operatorname{pr}(S_i = 1|X_{ei} = 1, \mathbf{x}_{oi})}{\operatorname{pr}(S_i = 1|X_{ei} = 0, \mathbf{x}_{oi})} \cdot \frac{\operatorname{pr}(X_{ei} = 1|\mathbf{x}_{oi})}{\operatorname{pr}(X_{ei} = 0|\mathbf{x}_{oi})}.\end{aligned}$$

The first term on the right side of the equation is a ratio of the ascertainment corrections for $X_{ei} = 1$ and $X_{ei} = 0$ that is shown in equation (2.3). We can therefore use the log of the ratio of ascertainment corrections as an offset in a logistic regression, marginal exposure model given by (2.7). In some cases, such an approach may be more natural or simple than modeling the marginal exposure model on the left side of equation (2.7) directly. This is due to the fact that the marginal exposure model, $\operatorname{pr}(X_{ei}|\mathbf{X}_{oi})$, may be simpler in the population as compared to the observed sample, $\operatorname{pr}(X_{ei}|\mathbf{X}_{oi}, S_i = 1)$. For example, in many realistic scenarios, one would expect that time-varying and time-invariant covariates are independent in the population. In the CAMP, time since randomization is expected to be independent of, say, genotype. However, for the biased sample, such time-varying covariates may be spuriously associated with genotype due to their impact on the probability of being sampled. If one wished to model the left-hand side of equation (2.7) directly, the functional forms of time-varying covariates must be carefully considered.

The steps for creating the imputation data sets used in the CD+MI approach are as follows:

(1) On sampled subjects, $S_i = 1$, maximize the ascertainment corrected log-likelihood shown in equation (2.4) to obtain estimates $\widehat{\boldsymbol{\theta}}$ and uncertainty $\widehat{\operatorname{Cov}}(\widehat{\boldsymbol{\theta}})$ associated with the response model.

(2) For $m = 1, \ldots, M$, draw $\boldsymbol{\theta}^{(m)}$ from the approximate posterior distribution for $\widehat{\boldsymbol{\theta}}$ given by the normalized likelihood function, and calculate
   (2a) $f(\mathbf{y}_i|X_{ei} = 1, \mathbf{x}_{oi}, S_i = 1; \boldsymbol{\theta}^{(m)})\{f(\mathbf{y}_i|X_{ei} = 0, \mathbf{x}_{oi}, S_i = 1; \boldsymbol{\theta}^{(m)})\}^{-1}$,
   (2b) $\log[\text{pr}(S_i = 1|X_{ei} = 1, \mathbf{x}_{oi}; \boldsymbol{\theta}^{(m)})\{\text{pr}(S_i = 1|X_{ei} = 0, \mathbf{x}_{oi}; \boldsymbol{\theta}^{(m)}\}^{-1}]$.
(3) On sampled subjects, using (2b) as an offset, fit a logistic regression of X_{ei} on $\mathbf{X}_{oi}$ to obtain parameter (call it $\boldsymbol{\alpha}$) and uncertainty estimates for the marginal exposure model shown in equation (2.7). Then, draw $\boldsymbol{\alpha}^{(m)}$ from a $N[\widehat{\boldsymbol{\alpha}}, \widehat{\text{Cov}}(\widehat{\boldsymbol{\alpha}})]$ and calculate
   (3a) $\text{pr}(X_{ei} = 1|\mathbf{x}_{oi}, S_i = 1; \boldsymbol{\alpha}^{(m)})\{\text{pr}(X_{ei} = 0|\mathbf{x}_{oi}, S_i = 1; \boldsymbol{\alpha}^{(m)})\}^{-1}$.
(4) For unsampled subjects, multiply the results of (2a) and (3a) to calculate the conditional exposure odds in equation (2.6) and then draw imputed values, $X_{ei}^{(m)}$.
(5) Conduct standard maximum likelihood analysis on the response model using the complete imputation data set.
(6) Repeat steps (2)–(5) M times and combine results in the standard manner.

To the extent that the assumptions of the response and marginal exposure models are correct, the foregoing CD+MI approach is expected to be valid and relatively efficient compared to the CD approach. It is worth noting that the imputation model for the CD+MI approach is a general location model that is discussed in, for example, Little and Schluchter (1985), Schafer (2010), and Little and Rubin (2002).

2.4.2. *Imputation model construction*: *Direct conditional exposure model*. Another approach to constructing the imputation model is relatively direct and could employ available MI software. In contrast to CD+MI, it decouples the imputation and the analysis models. We refer to it as direct multiple imputation (D-MI) and it is a special case of multiple imputation by chained equations [e.g., Raghunathan et al. (2001), White, Royston and Wood (2011)] which is implemented in software packages such as MICE [Van Buuren (2012)] in the R programming language [R Core Team (2013)]. We may ascertain and sample from $[X_{ei}|\mathbf{y}_i, \mathbf{x}_{oi}, S_i = 0]$ directly by noting that the conditional exposure odds model on the left-hand side of equation (2.6) can be constructed using logistic regression analysis with any functions of $\mathbf{y}_i$ and $\mathbf{x}_{oi}$ as independent variables. Since $X_{e,i} \perp S_i|(\mathbf{Y}_i, \mathbf{X}_{oi})$ by design, then if the Gaussian linear mixed model assumptions are satisfied, the induced conditional exposure log-odds from equation (2.6) can be written

$$
\begin{aligned}
&-\frac{1}{2}\{(\mathbf{Y}_i - \boldsymbol{\mu}_{1,i})^t \mathbf{V}_{1i}^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_{1,i}) - (\mathbf{Y}_i - \boldsymbol{\mu}_{0,i})^t \mathbf{V}_{0i}^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_{0,i})\} \\
&\quad - \frac{1}{2}\log\left\{\frac{|\mathbf{V}_{1,i}|}{|\mathbf{V}_{0,i}|}\right\} + \log\left\{\frac{\text{pr}(X_{ei} = 1|\mathbf{X}_{oi})}{\text{pr}(X_{ei} = 0|\mathbf{X}_{oi})}\right\},
\end{aligned} \tag{2.8}
$$

where $\boldsymbol{\mu}_{x,i} = E(\mathbf{Y}_i|X_{ei} = x, \mathbf{x}_{oi})$, $\mathbf{V}_{x,i} = \text{Var}(\mathbf{Y}_i|X_{ei} = x, \mathbf{x}_{oi}) = \mathbf{Z}_i \mathbf{D}_{xi} \mathbf{Z}_i + \sigma_e^2 \mathbf{I}$. If we assume homoscedasticity, then $\mathbf{V}_{1,i} = \mathbf{V}_{0,i} = \mathbf{V}_i$, and equation (2.8) simpli-

fies to

$$\underbrace{\mathbf{Y}_i^t \mathbf{V}_i^{-1}(\boldsymbol{\mu}_{1,i} - \boldsymbol{\mu}_{0,i})}_{\text{(a)}} - \frac{1}{2}\underbrace{(\boldsymbol{\mu}_{1,i}^t \mathbf{V}_i^{-1}\boldsymbol{\mu}_{1,i} - \boldsymbol{\mu}_{0,i}^t \mathbf{V}_i^{-1}\boldsymbol{\mu}_{0,i})}_{\text{(b)}} + \underbrace{\log\left\{\frac{\text{pr}(X_{ei}=1|\mathbf{X}_{oi})}{\text{pr}(X_{ei}=0|\mathbf{X}_{oi})}\right\}}_{\text{(c)}}. \tag{2.9}$$

In the Supplement A [Schildcrout et al. (2015)], we detail further simplifications with balanced and complete data that we examine in Section 3 and that are motivated by the CAMP analysis whose design was nearly balanced and complete. Briefly, with balanced and complete data, if $v_{i,jk}$ is the (j,k)th element of $\mathbf{V}_i^{-1}$ and $\omega_{ij}(t_{ij})$ is the x_{ei} effect at time t_{ij} (i.e., $\mu_{1,ij} - \mu_{0,ij}$), (a) equals $\sum_{j=1}^n \sum_{k=1}^n v_{i,jk} \cdot y_{ij} \cdot \omega_{ik}(t_{ik})$, (b) equals $\sum_{j=1}^n \sum_{k=1}^n v_{i,jk} \cdot \mu_{0,ij} \cdot \omega_{ik}(t_{ik}) + \sum_{j=1}^n \sum_{k=1}^n v_{i,jk} \cdot \omega_{ij}(t_{ij}) \cdot \omega_{ik}(t_{ik})$, and (c) contains terms involving $\mathbf{x}_{oi}$ useful for predicting X_{ei}. Our approach to imputation is then to directly model $[X_{ei}|\mathbf{X}_{oi}, \mathbf{Y}_i]$ with logistic regression and to follow standard multiple imputation methods. We note that the first two terms in equations (2.8) and (2.9), respectively, result in the functional form of quadratic and linear discriminant analysis [Fisher (1936)] that are used in many classification analyses.

3. Finite sampling operating characteristics. The key motivator in outcome dependent sampling schemes is to obtain nearly efficient inference at considerable cost savings by drawing and analyzing small to modest sample sizes. Indeed, the CAMP study could have realized considerable savings if it had only analyzed 250 genotypes, versus more than 500. As such, it is critical in application of these design strategies to quantify the degree to which theoretical results are realized in finite sample settings. Schildcrout, Garbett and Heagerty (2013) conducted such simulations, that are briefly summarized in the Introduction. We now examine the CD+MI and D-MI estimation procedures proposed in Section 2 to explore: (1) the scenarios under which MI does and does not improve estimation efficiency over a CD analysis; and (2) the extent to which the study design continues to improve efficiency if MI is the intended analytical strategy.

3.1. *Population model.* We conducted simulation studies under several study designs and population features motivated by the CAMP study and by studies with similarly-balanced longitudinal follow-up. Results presented here summarize 1000 replications per scenario. In each scenario, we generated a cohort of N subjects based on the model

$$Y_{ij} = \beta_0 + \beta_t t_{ij} + \beta_g g_i + \beta_{gt} g_i t_{ij} + \beta_c c_i + b_{0i} + b_{1i} t_{ij} + \varepsilon_{ij},$$

with $i \in \{1, 2, \ldots, N\}$ denoting subject, $j \in \{1, 2, \ldots, 10\}$ denoting observation within subject, t_{ij} an equally spaced, balanced time covariate ranging from -2 to 2, C_i a binary, time-invariant covariate with $\text{pr}(C_i = 1) = 0.5$, G_i an expensive, binary "group" or "genotype" variable with $\text{pr}(G_i = 1|C_i = c) = 0.4 + \delta_c c$, (b_{i0}, b_{i1}) the random intercept and slope, and ε_{ij} the measurement error. Across all scenarios, $(\beta_0, \beta_t, \beta_{gt}) = (5, 1.0, 0.75)$, the mean of the random effects and error distributions were 0, and the standard deviations of the random intercept, the random slope and the measurement error were $\sigma_0 = 5$, $\sigma_1 = 1.25$ and $\sigma_e = 5$, respectively. Additionally, $\rho = \text{corr}(b_{0i}, b_{1i}) = -0.25$.

We examined the relative efficiency of the designs and estimation procedures as a function of the following: the G_i effect size, $\beta_g \in \{-2.5, -4.0\}$, the strength of the $G_i \sim C_i$ relationship, $\delta_c \in \{0.15, 0.35, 0.55\}$, the sample size of the original cohort $N \in \{750, 2250\}$, and the impact of C_i being a proxy for G_i as opposed to being a confounder for the $G_i \sim \mathbf{Y}_i$ relationship. In the last scenario, $\beta_c = 0$ and C_i is used to impute G_i but is not included in the primary analysis model. In all other scenarios, $\beta_c = 1$ and C_i is included as an independent variable. Specifically, we examine five distinct scenarios uniquely identified by $(N, \beta_g, \delta_c, \beta_c)$. Scenarios studied are given by the following: (a) $(750, -2.5, 0.15, 1.0)$, (b) $(750, -4.0, 0.15, 1.0)$, (c) $(750, -2.5, 0.35, 1.0)$, (d) $(2250, -2.5, 0.15, 1.0)$, and (e) $(750, -2.5, 0.55, 0.0)$.

3.2. *Study designs*. The substudies we sought to examine were those that sampled, on average, 250 subjects for whom G_i should be ascertained, again motivated by the CAMP framework. For the random sampling (RS) design, we took a simple random sample of 250 subjects at each replication. For ODS designs based on the intercept (ods.i), slope (ods.s), and bivariate intercept and slope (ods.b), we calculated subject-specific intercepts and slopes based on the N separate OLS regressions of the response Y_{ij} on time t_{ij}, and sampled subject i with probability that depended upon the region in which $\mathbf{Q}_i$ was located. For ods.i and ods.s we split the distribution of the sampling variable $\mathbf{Q}_i$ into three regions defined by the 12th and 88th percentiles of the population distribution. We then sampled individuals with probability $\pi(\mathbf{q}_i) = \text{pr}(S_i = 1|\mathbf{Q}_i = \mathbf{q}_i)$ so that, on average, 90 subjects from each of the two outlying regions and 70 subjects from the central region were included in the outcome dependent sample. Similarly for the ods.b design, we sampled with probability so that 70 subjects were included from the central rectangular region that contained 76 percent of the population and 180 subjects were included from the outlying region containing 24 percent of the population. See Schildcrout, Garbett and Heagerty (2013) for a description and a figure describing these sampling schemes.

3.3. *Analyses*. After subsampling from the original cohort of N, we conducted the CD analysis by fitting the model with maximum ascertainment corrected likelihood under the ODS designs or with standard maximum likelihood

(ML) under the RS design. To conduct multiple imputation analyses, we estimated the multiple imputation model for G_i in unsampled subjects $\text{pr}(G_i|\mathbf{y}_i, c_i, S_i = 0)$ via approaches discussed in Sections 2.4.1 and 2.4.2. Specifically, the imputation model for CD+MI analyses was estimated by combining the CD analysis and the offsetted logistic regression analysis of g_i on c_i in sampled subjects. The imputation model for the D-MI approach was estimated with a regression model of G_i on predictors $\sum_j y_{ij}$, $\sum_j y_{ij} \cdot t_{ij}$ and C_i in sampled subjects. See the online supplementary materials [Schildcrout et al. (2015)] for an explanation of why these independent variables were used in the imputation model. The number M of imputation samples used was based on examination of the degrees of freedom that were calculated as described in Section 2.4 and with the intention of conducting sufficient imputation analyses so that the t-statistics associated with all parameter estimates were well approximated by normal distributions for all parameters. When $N = 750$, $M = 25$ was used; when $N = 2250$, $M = 35$.

3.4. *Results*. Because the models were properly specified, all estimation procedures were observed to be approximately valid with observed biases in parameter estimates less than 5% and observed biases in standard errors less than 10% (not shown).

Table 1 shows the efficiency of each design and analysis procedure combination relative to the RS design and standard CD maximum likelihood analysis. Relative efficiency is defined as the empirical variance under RS plus CD analyses divided by the empirical variance under each other design and estimation procedure. Note that the CD+MI and D-MI approaches perform similarly for nearly all parameter-by-scenario combinations. In scenario (a) we observe that for β_g and β_{gt} the impact of the study design far outweighs the impact of multiply imputing G_i. For example, using CD analyses to estimate β_{gt}, the ods.s design improves estimation efficiency by 87 percent over RS, but adding multiple imputation to the CD analysis by using the CD+MI approach improves efficiency only by an additional 7.4 percent ($2.01/1.87 = 1.074$). However, if interest is in estimates of β_c, which correspond to C_i, a covariate that is available in everyone, the impact of multiple imputation outweighs the study design. Notice that with both the CD+MI and D-MI approaches all designs have a relative efficiency for β_c of approximately 2.6–2.7 compared to random sampling with CD analyses. For estimates of β_0 and β_t, the study design and multiple imputation-based analyses independently contributed to optimal estimation efficiency.

Scenarios (b), (c), (d) and (e) provide some insight into how the results shown in scenario (a) depend upon population data features. We used these scenarios specifically to examine the extent to which MI adds to the optimal study design with CD analyses and we now focus our discussion exclusively on β_g and β_{gt}. Comparing results from scenario (b) to (a), we observed that the impact of MI is somewhat greater when the G_i effect size is larger. Whereas in scenario (b), when estimating β_g, CD+MI was 20 percent more efficient than CD for the optimal ods.i

TABLE 1

Relative efficiency: *Results show ratios of the empirical variance of the RS design with standard CD analyses to the empirical variance of all other study design and analysis procedures across* 1000 *replicates. The designs ods.i, ods.s and ods.b are ODS designs with sampling based on the intercept, slope, and both intercept and slope of subject-specific ordinary least squares regression of* Y_{ij} *on* t_{ij}. *For each parameter we show columns that correspond to CD, CD+MI and D-MI analyses, respectively. In scenario* (e) *we do not estimate* β_c, *as* C_i *is not included in the final model but is only used for* G_i *imputation*

	$N, \beta_g, \delta_c, \beta_c$	Design	β_0	β_t	β_g	β_{gt}	β_c
(a)	750, −2.5, 0.15, 1.0	RS	1.00, 1.88, 1.90	1.00, 1.68, 1.64	1.00, 1.02, 1.03	1.00, 1.13, 1.09	1.00, 2.66, 2.65
		ods.i	2.18, 2.63, 2.63	0.89, 1.37, 1.35	2.11, 2.20, 2.19	0.88, 0.94, 0.92	1.99, 2.64, 2.64
		ods.s	1.02, 1.89, 1.90	2.01, 2.32, 2.27	1.00, 1.00, 1.02	1.87, 2.01, 1.96	1.03, 2.61, 2.62
		ods.b	1.82, 2.42, 2.41	1.64, 1.97, 1.97	1.75, 1.79, 1.82	1.52, 1.59, 1.59	1.72, 2.67, 2.65
(b)	750, −4.0, 0.15, 1.0	RS	1.00, 1.90, 1.92	1.00, 1.65, 1.67	1.00, 1.20, 1.21	1.00, 1.14, 1.16	1.00, 2.65, 2.59
		ods.i	1.79, 2.17, 2.14	1.02, 1.61, 1.57	1.65, 1.99, 1.96	1.01, 1.07, 1.04	1.83, 2.27, 2.20
		ods.s	1.01, 1.85, 1.83	2.30, 2.71, 2.74	0.91, 1.06, 1.05	2.19, 2.35, 2.36	1.00, 2.49, 2.48
		ods.b	1.57, 2.13, 2.10	2.03, 2.44, 2.42	1.43, 1.57, 1.57	1.85, 1.98, 1.93	1.79, 2.53, 2.46
(c)	750, −2.5, 0.35, 1.0	RS	1.00, 1.90, 1.91	1.00, 1.61, 1.51	1.00, 1.05, 1.04	1.00, 1.23, 1.15	1.00, 2.26, 2.27
		ods.i	2.03, 2.62, 2.62	1.00, 1.56, 1.48	1.95, 2.09, 2.12	0.96, 1.15, 1.08	1.90, 2.37, 2.39
		ods.s	1.13, 2.06, 2.05	2.10, 2.53, 2.53	1.01, 1.06, 1.07	2.07, 2.33, 2.33	1.00, 2.28, 2.28
		ods.b	1.89, 2.51, 2.51	1.88, 2.28, 2.24	1.71, 1.81, 1.78	1.84, 2.02, 1.95	1.67, 2.45, 2.41
(d)	2250, −2.5, 0.15, 1.0	RS	1.00, 2.97, 3.01	1.00, 2.03, 2.00	1.00, 1.07, 1.07	1.00, 1.14, 1.11	1.00, 5.83, 5.79
		ods.i	2.06, 4.69, 4.67	0.99, 1.97, 1.89	1.76, 2.01, 2.01	0.95, 1.11, 1.07	1.89, 5.75, 5.74
		ods.s	0.98, 2.85, 2.89	2.12, 3.75, 3.70	0.92, 0.95, 0.97	2.05, 2.44, 2.39	0.86, 5.61, 5.52
		ods.b	1.65, 3.98, 4.07	1.83, 3.25, 3.21	1.52, 1.57, 1.60	1.81, 2.02, 1.98	1.53, 5.76, 5.50
(e)	750, −2.5, 0.55, 0.0	RS	1.00, 1.71, 1.60	1.00, 1.79, 1.59	1.00, 1.50, 1.37	1.00, 1.52, 1.32	
		ods.i	1.95, 2.33, 2.33	1.03, 1.64, 1.49	1.98, 2.29, 2.29	0.92, 1.39, 1.20	
		ods.s	1.04, 1.65, 1.58	1.99, 2.36, 2.33	0.99, 1.46, 1.36	2.03, 2.37, 2.33	
		ods.b	1.77, 2.16, 2.09	1.80, 2.21, 2.17	1.75, 2.06, 1.96	1.77, 2.17, 2.08	

design ($1.99/1.65 = 1.20$), in scenario (a) it was only 4 percent more efficient ($2.20/2.11 = 1.04$). As shown by comparing results from scenarios (c) and (d) to (a), we observe that MI appears to add modest additional precision to the optimal design when the $G_i \sim C_i$ relationship is stronger and when the original cohort size is larger. Finally, in scenario (e) we observed that when C_i is a proxy for G_i rather than a confounder and when the $G_i \sim C_i$ relationship is relatively strong with $\delta_c = 0.55$, adding MI to the optimal design led to larger efficiency gains for β_g and β_{gt}. For example, the relative efficiency of CD+MI relative to CD analyses for the optimal designs for β_g and β_{gt} were $2.29/1.98 = 1.16$ and $2.37/2.03 = 1.17$, respectively.

Multiple imputation resulted in substantial efficiency improvements over CD analysis for estimates of $(\beta_0, \beta_t, \beta_c)$, but had a far smaller impact on estimation efficiency for (β_g, β_{gt}). Figure 1 shows the relative efficiency for estimating the mean value at the end of the study period for those with $(G_i, C_i) = (1, 1)$, $\widehat{\mu}_{i,10} = E(Y_{ij}|G_i = 1, C_i = 1, t_{ij} = 2)$ under all scenarios. By combining parameter estimates to obtain the linear predictor estimate we observed that in all scenarios and for all study designs, CD+MI and D-MI analyses are substantially more efficient than CD analyses. That is, MI improved estimation efficiency dramati-

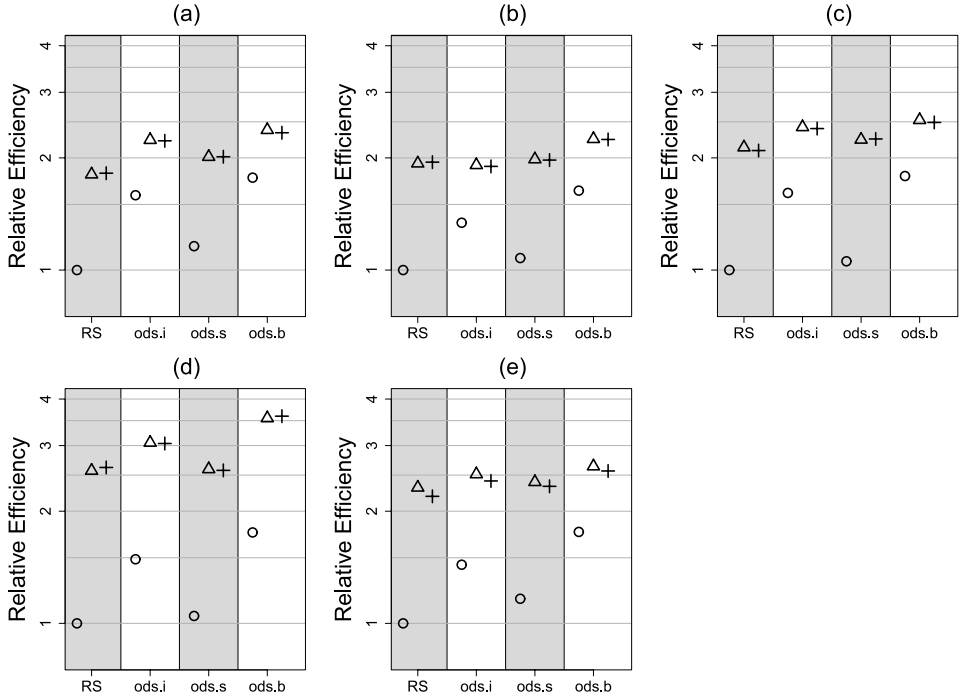

FIG. 1. *Relative efficiency for estimating the predicted value at the end of the study period* $\mu_{i,10} = E(Y_{i,10}|G_i = 1, C_i = 1, t_{ij} = 2)$ *for all design and analysis procedure combinations versus RS and standard CD analyses based on* 1000 *replications. Symbol* o *denotes CD analyses,* △ *denotes CD+MI analyses, and* + *denotes D-MI analyses. Parameter values* (a)–(e) *are given in Table* 1.

cally, and the study design itself had a more modest impact. However we also note that the ods.b design is the most efficient design in all scenarios for estimating the end-of-study mean value. Even though ods.b was not the optimal design for any single parameter (see Table 1), it is reasonably efficient for all parameters, which is beneficial if more than one parameter is of interest. In contrast, the ods.s and ods.i designs were efficient for individual parameters but were inefficient for other parameters.

4. CAMP data analysis. In this section we analyze the CAMP data using different subsampling designs both with and without imputation. Our goal is to empirically compare the research efficiency of candidate designs, and we have the complete data against which we can benchmark performance. Since our simulation study showed that CD+MI and D-MI approaches are similar, we focus our presentation on only one imputation approach (CD+MI). A total of 555 subjects had sufficient covariate and genotype data available, and we operate under the assumption that stored blood samples are available for all participants, although study resources only permit genotyping 250. Thus, approximately 250 genotypes are used at each of 30 replications of each study design. We report results based on the average estimates and (co)variances. Similar to the simulations, we consider four designs: random subsampling of 250 children (RS) and three ODS designs. To create the ODS designs, we first compute all estimated intercepts and slopes from subject-specific simple linear regressions of post-bronchodilator percent predicted FVC (FVC%) on time since randomization. Sampling was then based on the following: the estimated intercept (ods.i), the estimated slope (ods.s), or the estimated intercept and slope jointly (ods.b). In order to obtain 250 subjects, the cutoff points that define strata in the ods.i and ods.s designs are given by the 16th and 84th percentiles of the original cohort. We sampled with probability 1 subjects at or below the 16th percentile and at or above the 84th percentile, and with probability 0.19 all subjects falling in the central 68% region. For ods.b, we sampled with probability 0.19 all subjects who fell in the central 68% region of the joint intercept and slope distribution in the original cohort and with probability 1 all of those falling outside this region. Table 2 shows the characteristics of the CAMP cohort from which we subsampled for the ODS studies.

The primary scientific goals of the CAMP analysis are to examine the treatment effects within subgroups defined by the presence or absence of a variant allele (VA) on the fourth locus of the IL10 gene, and to examine the difference in lung growth between those with and without a VA. Three-way interactions (IL10 $\times$ medication $\times$ t_{ij}) were explored, however, we only report results from two-way interactions. Thus, the fitted model for this analysis was

$$E[y_{ij}|X_i] = \beta_0 + \beta_1 t_{ij} + \beta_2 \cdot bud_i + \beta_3 \cdot ned_i + \beta_4 \cdot \mathrm{IL10}_i + \beta_5 \cdot bud_i \cdot \mathrm{IL10}_i + \beta_6 \cdot ned_i \cdot \mathrm{IL10}_i + \beta_7 \cdot t_{ij} \cdot \mathrm{IL10}_i + \beta_C \cdot covariates_{ij}.$$

TABLE 2

Demographic and other characteristics of children participating in the CAMP with genotype and covariate data available. Continuous variables are summarized with the 10th, 50th and 90th percentiles, and categorical variables other than site are summarized with proportions

Variable	
Cohort size (N)	555
Albuquerque	41
Baltimore	71
Boston	72
Denver	64
San Diego	68
Seattle	80
Saint Louis	91
Toronto	68
Age at randomization (years)	6.23, 8.81, 11.71
Male gender	0.65
Black race	0.10
Other (noncaucasian) race	0.26
Randomized treatment	
Placebo	0.50
Budesonide	0.32
Nedocromil	0.17
IL10 variant allele	0.50
Observations per subject	9, 10, 10
Follow-up time (years)	3.85, 3.99, 4.1
Post-bronchodilator percent predicted	92, 105, 116

The covariates that represent the key biomedical questions include the following: the binary time invariant IL10 SNP (snp_i); time since randomization ($\mathbf{t}_i = \{t_{i1}, \ldots, t_{in_i}\}$); Budesonide ($bud_i$) and Nedocromil ($ned_i$) treatments (with placebo being the reference); and pairwise interactions between IL10 and the other variables. As described in Section 2.4, the imputation approaches required a model for the predictor of interest, $X_{ei} = snp_i$, in order to impute its value for subjects not selected for the subsample ($S_i = 0$). Therefore, the CD+MI analysis procedure required estimation of a marginal exposure distribution (i.e., $[X_{ei}|\mathbf{X}_{oi}, S_i = 1]$), and in that model, $race_i$, $site_i$, $gender_i$, bud_i and ned_i were used as independent variables ($\mathbf{X}_{oi}$) in an additive logistic regression model.

Table 3 shows CAMP regression summaries based on the original cohort analysis using all subjects ($N = 555$), and on eight combinations of subsampling designs with and without imputation, where only $N \approx 250$ children were included in a subsample. We provide the key summaries that specifically address the primary research questions, but interested readers may look to online supplementary materials [Schildcrout et al. (2015)] for all longitudinal model regression estimates and

TABLE 3

CAMP results: estimated summaries and standard error estimates (in parentheses) based on 30 replications of each study design. At each replication, twenty imputation samples were used for the CD+MI analyses. We do not include the standard errors for variance components with the CD+MI approach because the lme4 package [Bates and Maechler (2010)] does not provide them. Although site effects are not shown, they were included as fixed effects in regression analyses. The estimated mean row corresponds to the estimated, end-of-study mean value for the population of white, 12 year old girls, with VAs who were randomized to placebo treatment and who lived in Baltimore. The original cohort column displays results from the analysis of the full cohort of 555 participants

Variable	Original cohort	RS		ods.s		ods.i		ods.b	
		CD	CD+MI	CD	CD+MI	CD	CD+MI	CD	CD+MI
Primary summaries									
Budesomide (vs placebo) at all times									
No VAs	−2.11 (1.16)	−1.57 (1.73)	−2.09 (1.46)	−3.65 (1.73)	−2.92 (1.45)	−2.39 (1.41)	−2.73 (1.29)	−2.65 (1.56)	−2.68 (1.34)
With VAs	3.29 (1.24)	3.08 (1.86)	3.08 (1.52)	4.12 (1.92)	4.18 (1.54)	3.99 (1.55)	3.95 (1.38)	3.51 (1.67)	3.69 (1.38)
Difference	5.40 (1.70)	4.65 (2.54)	5.17 (2.43)	7.78 (2.57)	7.10 (2.42)	6.39 (2.10)	6.68 (2.03)	6.16 (2.34)	6.37 (2.10)
Nedocrimil (vs placebo) at all times									
No VAs	−0.77 (1.17)	−0.62 (1.73)	−0.56 (1.46)	−2.96 (1.73)	−1.59 (1.46)	−1.11 (1.41)	−0.56 (1.24)	−2.16 (1.51)	−0.96 (1.31)
With VAs	0.69 (1.10)	0.73 (1.63)	0.54 (1.39)	0.42 (1.63)	1.45 (1.36)	0.31 (1.31)	0.64 (1.21)	−0.02 (1.36)	0.92 (1.20)
Difference	1.46 (1.61)	1.35 (2.39)	1.10 (2.36)	3.38 (2.41)	3.04 (2.33)	1.42 (1.94)	1.20 (1.87)	2.14 (2.08)	1.88 (1.95)
Time trend (per year) irrespective of treatment									
No VAs	0.14 (0.16)	0.11 (0.23)	0.09 (0.19)	0.14 (0.17)	0.10 (0.16)	−0.04 (0.22)	0.09 (0.18)	0.19 (0.18)	0.13 (0.17)
With VAs	−0.25 (0.15)	−0.19 (0.23)	−0.19 (0.19)	−0.19 (0.17)	−0.21 (0.16)	−0.38 (0.22)	−0.21 (0.18)	−0.25 (0.18)	−0.24 (0.16)
Difference	−0.39 (0.22)	−0.30 (0.33)	−0.27 (0.31)	−0.33 (0.24)	−0.31 (0.24)	−0.35 (0.31)	−0.30 (0.29)	−0.44 (0.26)	−0.37 (0.25)
IL10 (VA vs no VA) in the placebo arm at baseline and year 4									
$t_{ij=0}$	−1.65 (1.15)	−1.67 (1.70)	−1.78 (1.69)	−2.20 (1.65)	−2.13 (1.67)	−1.72 (1.30)	−1.90 (1.32)	−1.29 (1.46)	−1.50 (1.39)
$t_{ij=4}$	−3.2 (1.17)	−2.87 (1.73)	−2.88 (1.71)	−3.51 (1.68)	−3.35 (1.68)	−3.11 (1.5)	−3.12 (1.52)	−3.05 (1.52)	−2.98 (1.48)
Estimated mean	106.33 (1.51)	106.86 (2.32)	106.47 (1.64)	107.95 (2.20)	106.23 (1.62)	106.69 (1.99)	106.42 (1.63)	106.79 (1.97)	106.47 (1.59)

TABLE 3
(*Continued*)

Variable	Original cohort	RS		ods.s		ods.i		ods.b	
		CD	CD+MI	CD	CD+MI	CD	CD+MI	CD	CD+MI
				Other mean model parameters					
Male (vs female)	−1.14 (0.72)	−1.47 (1.08)	−1.22 (0.73)	−1.47 (1.07)	−1.13 (0.72)	−0.71 (0.86)	−1.16 (0.72)	−1.19 (0.90)	−1.21 (0.72)
Black (vs white)	0.51 (1.21)	0.52 (1.87)	0.53 (1.25)	1.22 (1.85)	0.76 (1.23)	1.19 (1.56)	0.47 (1.24)	1.88 (1.50)	0.67 (1.23)
Other (vs white)	−0.81 (0.98)	−0.95 (1.44)	−0.74 (0.99)	−1.31 (1.44)	−0.59 (1.00)	−0.01 (1.15)	−0.71 (0.99)	−0.32 (1.20)	−0.61 (0.99)
Age ($t_{ij} = 0$)	−0.21 (0.17)	−0.23 (0.26)	−0.22 (0.17)	−0.40 (0.26)	−0.23 (0.17)	−0.50 (0.21)	−0.22 (0.17)	−0.39 (0.22)	−0.22 (0.17)
				Variance components					
$\log(\sigma_0)$	2.19	2.18 (0.05)	2.19	2.16 (0.05)	2.18	2.18 (0.04)	2.18	2.18 (0.04)	2.18
$\log(\sigma_1)$	0.84	0.85 (0.06)	0.84	0.84 (0.05)	0.84	0.83 (0.05)	0.84	0.84 (0.05)	0.84
$\frac{\log(1+\rho)}{\log(1-\rho)}$	−1.70	−1.13 (0.15)	−1.70	−1.06 (0.12)	−1.70	−1.11 (0.12)	−1.70	−1.08 (0.12)	−1.69
$\log(\sigma_e)$	1.55	1.54 (0.02)	1.55	1.60 (0.02)	1.55	1.60 (0.02)	1.55	1.62 (0.02)	1.55

interactions used to generate the summaries. Specifically, we focus on medication effects and time trends within subgroups defined by presence or absence of an IL10 variant, the difference in expected FVC between those with and without an IL10 variant at baseline ($t_{ij} = 0$) and at the end of the study ($t_{ij} = 4$) for subjects on placebo treatment, and the end-of-study predicted mean value.

In the original cohort analysis we observed the following associations that were statistically significant at the $\alpha = 0.05$ level: (1) for subjects with an IL10 variant, the expected FVC% was estimated to be 3.29 (1.24) units higher across all times in those randomized to Budesomide compared to placebo; (2) the effect of Budesomide compared to placebo was 5.40 (1.70) units higher in those with an IL10 variant than in those without an IL10 variant; and (3) at the end of the study ($t_{ij} = 4$), those with an IL10 variant were estimated to have FVC% values that were 3.20 (1.17) units lower than those without an IL10 variant. Our interest is in the impact of subsampling design choices, so a natural option to consider is a simple random sample. However, although the random sampling design produced point estimates that were similar to results from the original cohort, none of the full cohort-based associations would be considered statistically significant using the RS design. In contrast, all ODS designs detected the three significant effects seen in the original cohort, demonstrating the potential efficiency gains though use of biased sampling in a resource-limited environment.

Furthermore, for all designs the use of imputation (CD+MI analysis) improved estimation efficiency of key parameters. For example, when sampling using ods.b, the standard error for the Budesomide versus placebo contrast was 1.67 under the CD analysis, 1.38 under the CD+MI analysis and 1.24 for the original cohort analysis. Such efficiency gains due to MI were also observed in all coefficient estimates for the other baseline covariates measured on all subjects (e.g., age, race and gender). In contrast, and consistent with simulations, CD + MI did not produce appreciably smaller estimates of uncertainty than CD analyses for parameters that capture (retrospectively ascertained) IL10 effects and interactions. For example, under the ods.b design, the standard error estimate for the IL10 VA association with FVC% in the placebo arm at $t_{ij} = 4$ was 1.52 and 1.48 with CD and CD + MI analyses, respectively. Similarly, the standard error estimate for the difference in the time trends between those with and without the IL10 VA was 0.26 and 0.25 with CD and CD + MI analyses, respectively.

Finally, for many parameters, the combination of subsampling and the use of imputation was able to recover a large fraction of the information present in the original cohort but with less than half the cost in terms of number of subjects for whom covariates would be ascertained. For example, all estimators produced quite similar estimates of the predicted mean value at the end of the study, ranging from 106.33 to 107.95, and the ods.b plus CD+MI combination estimated the standard error to be 1.59, only slightly higher than the 1.51 estimated from the original cohort. In summary, the CAMP analysis illustrates that targeted subsampling is typically more efficient than simple random sampling, and that using all available

data is also beneficial and can be easily accomplished through imputation of data for those subjects not selected in a given subsample. We recommend that future ancillary studies of existing longitudinal cohorts consider the benefits of directed sampling coupled with efficient analysis.

5. Discussion. The CAMP longitudinal clinical trial was conducted in an era when genotyping was more expensive than today. Owing to ongoing interest in treatment heterogeneity, it is of interest to examine whether treatment effectiveness varies across genotype. Because this would be a secondary aim of most trials, it makes sense economically to conduct the trial, obtain response trajectories and test for overall treatment effectiveness first. Depending on what is learned through those primary investigations, investigators—or their colleagues—may then wish to move ahead with other exposure assessments to examine exposure effects or treatment-by-exposure interactions. Such data could be used for confirmatory analyses or, more likely, for pilot or preliminary data in an exploratory model. In these kinds of settings, especially, cost effectiveness is critical, and can make the difference between a study being viable or not.

To address such problems, in this manuscript we discussed novel statistical approaches to the combination both of ODS designs and of efficient analyses for longitudinal continuous response data. We observed that MI-based approaches can improve efficiency dramatically over CD analyses for parameters corresponding to estimation targets involving covariates that were not imputed (e.g., demographics and the estimated mean value in CAMP). Efficiency improvements were more modest for the coefficients of imputed covariates (e.g., the VA by time interaction under the *ods.s* design in CAMP), although such results can be influenced by data features (e.g., effect size in simulation). Importantly, we also observed that, even when MI is a default analytical choice, ODS designs can still improve efficiency dramatically in targets associated (directly or indirectly through interactions) with the retrospectively ascertained covariate.

Because this manuscript discusses what we believe are new study designs, we were not able to analyze data directly from such a study. Such studies have yet to be conducted. Instead, to describe the characteristics of the designs and estimators, we replicated simulated substudies from CAMP. While this may not appear to be ideal at first, it allowed us to explore alternative CAMP substudy designs and did not lock us in to a single design.

The two MI strategies, CD-MI and D-MI, approach parameter estimation in somewhat different ways, even in the context of the overall MI framework. Specifically, both approaches require careful consideration of two model specifications. Whereas the outcome model $[\mathbf{Y}_i|X_{ei}, \mathbf{X}_{oi}]$ is common to both strategies, CD+MI requires the direct specification of a marginal exposure model $[X_{ei}|\mathbf{X}_{oi}]$ and D-MI requires the direct specification of the fully conditional exposure model $[X_{ei}|\mathbf{X}_{oi}, \mathbf{Y}_i]$. We believe that each approach has an important advantage. In a

relative way, CD+MI may be considered advantageous because the marginal exposure model is likely to be relatively simple as compared to the conditional exposure model, and so the focus of analysis with CD+MI is on the outcome model. The conditional exposure model that is directly specified with D-MI is likely to involve additional consideration of the functional form of a time-varying (response) variable toward prediction of a time-fixed exposure variable. In contrast, the D-MI may be considered more flexible because the outcome and imputation models are decoupled. As compared to CD+MI, it could potentially be more robust to misspecification of the outcome model.

Finally, a rigorous evaluation of competing approaches (e.g., inverse probability weighting) is next in this line of research. A key reason we have not pursued that here is that we are primarily interested in situations wherein a full likelihood approach for both estimation and inference is of interest. The IPW approaches step out of that paradigm, instead relying on sandwich-type variance estimators, making the comparison among the methods more complex. Other areas of future research that specifically pertain to the imputation approaches involve extensions of the exposure variable to continuous, ordinal and time-varying data. We also intend to explore imbalanced time-varying covariates, unequal cluster sizes, general patterns of missing data/dropout, mean model misspecification and imputation model misspecification.

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SUPPLEMENTARY MATERIAL

Supplement A: D-MI Derivation for the model used in simulation (DOI: 10.1214/15-AOAS826SUPPA; .pdf). Derivation of the D-MI imputation model used in simulations (in Section 2.4.2).

Supplement B: CAMP Results: Parameter and uncertainty estimates (DOI: 10.1214/15-AOAS826SUPPB; .pdf). Results from the CAMP analysis that were used to derive the summaries in Table 3.

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