Use of Historical Individual Patient Data in Analysis of Clinical Trials

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Abstract

Historical data from previous clinical trials, observational studies and health records may be utilized in analysis of clinical trials data to strengthen inference. Under the Bayesian framework incorporation of information obtained from any source other than the current data is facilitated through construction of an informative prior. The existing methodology for defining an informative prior based on historical data relies on measuring similarity to the current data at the study level that can result in discarding useful individual patient data (IPD). This paper proposes a family of priors that utilize IPD to empower statistical inference. IPD-based priors can be obtained as a weighted likelihood of the historical data where each individual’s weight is a function of their similarity to the current study population. We demonstrate that the proposed prior construction approach can considerably improve estimation accuracy and precision in compare with existing methods.

Keywords: Historical controls; Informative prior; Similarity measure; Synthetic controls.

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1 Introduction

The use of historical data to strengthen statistical inference appears in various settings and applications. A few examples are analysis of clinical trials data where information is available from observational studies, meta-analysis, and analysis of social survey results with information borrowed from other sources such as the census (Golchi, 2017). The focus of the present paper is informed analysis of clinical trials using external data sources. However, the proposed methodology can be well adapted to other settings.

Use of historical data or data from any external source other than the concurrent study has become essential in many clinical trials. Common scenarios include trials where required sample sizes are infeasible to collect. Sample size restriction can be either due to scarcity of the eligible population (rare diseases) or small effect sizes that are clinically meaningful but require larger than feasible study sizes to achieve statistical significance. Another interesting family of studies consists of trials where a control cohort is completely or partially absent for ethical or practical reasons. Single arm phase I or II trials have become popular in oncology and drug development; the analysis of these trials require effective and robust statistical methodology in utilizing past studies.

Under the Bayesian framework, information from any source other than the study data are incorporated via the prior distribution. A variety of approaches have been proposed in the literature for construction of informative priors based on historical data. One of the most popular methods is referred to as power priors. Introduced formally by Chen & Ibrahim (2000), power priors are based on a weighted log-likelihood of the historical data. The role of the weight (or power) is to control the level of contribution of past studies to inference.
Various methods have been proposed for specification of the power(s). For a comprehensive review of theory and application of power priors see Ibrahim et al. (2015).

Another popular method for taking advantage of historical and external data is via a hierarchical modeling approach that treats the parameters of the concurrent and historical studies as random effects with a common mean and variance. This approach and its variations are referred to by various terms including commensurate priors, dynamic borrowing and meta-analytic predictive priors. Examples of work on this family of priors include Hobbs et al. (2012); Schmidli et al. (2014); Rover & Friede (2019); Lewis et al. (2019) and Weber et al. (2019) that introduces an R package implementing it. In addition, Chen & Ibrahim (2006) study the relationship between power priors and priors based on hierarchical modeling. Finally, Hong et al. (2018) consider power and commensurate priors for synthesizing aggregate and IPD in a network meta-analysis (NMA) framework. However, information borrowing is decided at the study level rather than at the individual level.

While both above mentioned methods are powerful tools, they have a common shortcoming. The amount of information incorporated into the prior from external data sources depends on the overall legitimacy of the study as a source of information. Under the power prior approach, for example, each study is given a power based on its similarity to the concurrent study. Commensurate priors are even less forgiving of heterogeneity of historical studies since the amount of information borrowed is determined by the variability among the studies. As a result, less information is used from all of the studies even if some of them strongly resemble the concurrent data. In other words, the gap in the literature on prior construction from historical data is in utilizing individual patient data (IPD).

Consider, for example, the hypothetical scenario presented in Figure 1. The study pop-
ulation of the concurrent study $S_c$ is the target population. Among the three available historical studies, the first one $S_1$ is assumed to have the same study population as the concurrent study and is, therefore, fully exchangeable with the concurrent study. The second study $S_2$ is a sample of a hypothetical population, B, that has a negligible overlap with the target population. This means that there may be individuals in $S_2$ whose characteristics match the target population but the majority of individuals do not belong to the target population. The hypothetical population, A, on the other hand, contains the target population — for example is defined based on a wider age range of patients. Therefore, $S_3$ is expected to have a significant overlap with the concurrent study but there are individual patient data under $S_3$ that should not be included in the inference.

Currently, no method of prior construction exists that allows the researcher to use a portion of historical IPD. Under the existing approaches, a measure of similarity or target population membership is explicitly (power priors) or implicitly (commensurate priors) estimated at the study level rather than the individual level. This results in loss of potentially useful information in cases where the study populations have some but not complete overlap.

In this paper we propose an approach for construction of informative priors from historical data that aims at using individual patient data. We generalize the power prior framework such that every individual within the historical studies is assigned a distinct power (or weight). The powers are specified with respect to a distance measure to the target population. Assuming that the concurrent trial sample is the closest proxy for the target population, this distance measure is estimated according to the similarity of individuals to the concurrent study sample. The data-prior conflict is dealt with via eliminating historical IPD that fall outside a credible set defined based on the distribution of the similarity measures within the
The remainder of the paper is organized as follows: A motivating example is presented in Section 2. The proposed methodology is described in Section 3. Section 4 follows with a simulation study where the proposed method is compared to existing prior construction methods. The proposed approach is applied to the motivating example in Section 5 and finally a discussion follows in Section 6.

2 Motivating Example

As a motivating example consider four trials in second line non-small cell lung cancer (NSCLC) with sufficiently similar patient population and the common primary outcome of overall survival: INTEREST (Douillard et al., 2010), ZODIAC (Herbst et al., 2010), PROCLAIM (Senan et al., 2016) and Study 57 (Natale et al., 2011). All trials were conducted for participants who had previously been treated for NSCLC. The IPD data for these studies was acquired from Project Data Sphere (http://www.projectdatasphere.com), an open-source repository of individual-level patient data from oncology trials. A brief summary of key trial characteristics for the included trials is provided in Table 1.

Patients within INTEREST, ZODIAC and Study 57 were predominantly stage IV, however PROCLAIM exclusively recruited stage III patients (of which 52% were stage IIIB). This is reflected in the control group median survival time which was between 8-10 months for all trials except for PROCLAIM that demonstrated a median survival time of 25 months (Figure 2a).

Other differences between studies included exposure to prior therapy. Whilst all included
patients had previously received at least one previous chemotherapy regimen, the proportion of patients who had received two or more varied between 0 (PROCLAIM, ZODIAC) to 35% (Study 57). Similarly, radiotherapy varied significantly, with PROCLAIM being the only trial which permitted (concurrent) chemoradiotherapy. Other patient characteristics were largely well balanced between groups, with an average age of 60 ± 1 years, and a majority of patients (54-75%) having adenocarcinoma histology.

Consider the hypothetical scenario that ZODIAC is the “concurrent” trial and we are interested in using data from the other three clinical trials to enrich the control arm with the hope of improving inference and achieving more power. Given the brief description of the four trials provided above, PROCLAIM is substantially different than the three other trials and should not be used to inform the inference. Suppose, however, that the above-mentioned differences were not reported and/or were not visible from data visualization. Figure 2b shows Bayesian point estimates (posterior mean) and 95% credible intervals for the hazard ratio in ZODIAC obtained with no prior (NP), using the full control data from the other three trials with the same weight as the concurrent data (FH), using power priors (PP) and commensurate priors (CP) and the proposed approach (TIW) that is described in the next section. It is clear that blindly using any available data can mislead the analysis: FH results in credible intervals including 1 while analysis of ZODIAC data alone yields significance in favour of the treatment. PP and CP result in almost identical results as NP since historical study heterogeneity results in minimal amount of borrowing from past data under these methods. TIW however results in smaller HR estimates with higher precision as a result of using individual patient data that closely resemble the ZODIAC study population.
3 Methodology

While the focus of the present work is on using historical controls for analysis of clinical trials, the proposed method can be generally applied to Bayesian inference. In fact, the distinction between the control and treatment arm data in clinical trials is not necessary to the approach and would only complicate the notation. Therefore, in the following, the methodology is explained in a general inference framework.

Consider a (concurrent) study that is designed to estimate a set of parameters, $\theta$, based on sample data $S_c = (S_{1,c}, \ldots, S_{N_c,c})$ where $S_{n,c}$ indicates all the available data on subject $n$ in the concurrent study and $N_c$ is the concurrent study sample size. Suppose that $H$ historical studies are available whose data may be used to improve the inference. The data of each historical study $h = 1, \ldots, H$ are denoted by $S_h = (S_{1,h}, \ldots, S_{N_h,h})$ where $N_h$ denotes the sample size of each historical study data. The likelihood is denoted by

$$\pi(S_c | \theta) = \prod_{n=1}^{N_c} \pi(S_{n,c} | \theta).$$

Bayesian inference may be performed using only the concurrent study data via the posterior distribution of the parameters given the concurrent study data,

$$\pi_{NP}(\theta | S_c) \propto \pi_0(\theta)\pi(S_c | \theta),$$

where $\pi_0(\theta)$ is a non-informative prior distribution.

At the other end of the spectrum of using historical data the following informative prior assigns equal weight to the past and present data,
\[ \pi_{FH}(\theta) \propto \pi_0(\theta) \prod_{h=1}^{H} \pi(S_h \mid \theta) = \pi_0(\theta) \prod_{h=1}^{H} \prod_{n=1}^{N_h} \pi(S_{n,h} \mid \theta). \]

This approach can significantly mislead the inference since past studies are commonly different than the concurrent study in various aspects and conclusions drawn from past data most often cannot be immediately generalized to the target population. In addition, the prior can overpower the likelihood in cases of prior-data conflict.

As an alternative, we propose the following individually weighted prior

\[ \pi_{IW}(\theta) \propto \pi_0(\theta) \prod_{h=1}^{H} \prod_{n=1}^{N_h} \pi(S_{n,h} \mid \theta)^{\omega_{n,h}}. \tag{1} \]

where the weights \( \omega_{n,h} \) are specified such that subjects who are considered “eligible” under the concurrent study population will receive a larger weight.

While \( \pi_{IW}(\theta) \) moderates the amount of information contained in the prior, there is still risk of overpowering the likelihood. A large number of conflicted data with small weights can result in sufficient information to bias the inference. Therefore we propose to use only the portion of the IPD with corresponding weights above a specific threshold,

\[ \pi_{TIW}(\theta) \propto \pi_0(\theta) \prod_{h=1}^{H} \prod_{n=1}^{N_h} \pi(S_{n,h} \mid \theta)^{\omega_{n,h}1(\omega_{n,h} > \rho)}. \tag{2} \]

The main challenge is to define the power \( \omega_{n,h} \) such that they meaningfully represent eligibility under the target population. Stuart et al. (2001) used propensity scores to measure generalizability of clinical trial results. However, propensity scores do not capture complex data structure including non-linearity. In the following we address this issue and provide an intuitive approach for specifying the truncation threshold, \( \rho \).
3.1 Specification of the weights

We propose two methods for specifying the individual weights in the likelihood according to the types of available data. The first method is based on the distance of each individual to the target population that is estimated by the Mahalanobis distance of the individual to the concurrent study distribution. The Mahalanobis distance is a simple and reliable dissimilarity measure as long as all the variables are continuous and their joint distribution can be characterized by a mean vector and a covariance matrix. The second method is to specify the weights as the posterior predictive probability of each historical patient data given the present data. This posterior predictive probability is computed based on a model that captures important features of the data but is not necessarily the same as the analysis model. We refer to it as the similarity model.

3.1.1 Mahalanobis distance

The powers $\omega_{n,h}$ should be specified such that subjects who better fit the target population receive larger weights. Considering the concurrent study as the most representative sample of the target population, the weight of every patient in historical studies is specified as a function of their Mahalanobis distance to the concurrent study sample. The Mahalanobis distance is defined based on the joint distribution of all the common variable among studies, i.e., response and covariates, characterized by a mean vector and a covariance matrix. The only underlying assumption is that all variables are continuous.

Let $S_{n,h}$ denote the vector of all (continuous) variables including covariates and response for patient $n$ in historical study $h$. The distance of patient $n, h$ to the target population is estimated as
\[ d_{n,h} = \sqrt{(S_{n,h} - \mu)^T \Sigma^{-1} (S_{n,h} - \mu)}, \]

where \( \mu \) and \( \Sigma \) are the sample mean vector and covariance matrix of the concurrent study.

The weights are then obtained as follows

\[ \omega_{n,h} = 1 - G(d_{n,h}), \]

where \( G \) maps \( d \) monotonically onto \((0, 1)\),

\[ G(d_{n,h}) = \frac{d_{n,h} - \max_n d_{n,h}}{\max_n d_{n,h} - \min_n d_{n,h}}. \]

Note that the minimum and maximum of the Mahalanobis distances used in the mapping are taken across all calculated distances for all the available data including those of the concurrent study.

With this definition using the information of subjects whose weights are larger than a given threshold \( \omega_0 \) is equivalent to selecting the subjects whose distance to the target population is within a certain threshold,

\[ \omega_{n,h} > \omega_0 \iff d_{n,h} < G^{-1}(1 - \omega_0) \overset{\Delta}{=} \delta_0, \]

where \( \delta_0 \) can be specified as a quantile of the distribution of the Mahalanobis distances within the concurrent study. For example if \( \delta_0 \) is the 95% quantile of the distance distributions, any historical individual patient data that demonstrates characteristics that fall outside the centre 95% of the concurrent study data distribution is discarded from the prior.
3.1.2 Similarity model

The Mahalanobis distance is not appropriate as a dissimilarity measure when discrete variables are present. Generalizations of the Mahalanobis distance have been proposed in the literature for mixed discrete and continuous variables (Barhen & Daudin, 1995; Bedrick et al., 2000; de Leon & Carrière, 2005). The generalized distances are based on models over the joint distribution of variables, namely modeling nominal variables according to a multinomial distribution and assuming multivariate Gaussian distributions for the continuous variables under each level (or level combination) of the nominal variables.

Similarly, we propose a model-based approach for cases with a mix of discrete and continuous variables. However, instead of defining a distance measure that needs to be converted into a similarity measure, we use the posterior predictive probability of the historical data given the concurrent data as the similarity measure. Note that the model which the predictive probability is based upon is not necessarily the same as the analysis model in that all the variables (including covariates) are assumed to follow a probability distribution. The reason is that joint modelling of all the existing variables is crucial for calculating a similarity measure that reflects patient/study differences while in most clinical trial data analysis covariates are treated as fixed. Moreover, the similarity model does not have to provide the best fit to the data and therefore can be simpler than the analysis model. For example, one could model all continuous variables as Gaussian random variables for measuring similarity despite presence of non-Gaussian features in the data.

Consider the joint similarity model of a set of variables represented by $\mathcal{S}$ is denoted by

$$\pi(\mathcal{S} | \psi), \quad (3)$$
where \( \psi \) is the vector of model parameters. Note that \( \psi \) is generally not identical to \( \theta \) since, as mentioned above, the similarity model is not the same as the analysis model. However, \( \psi \) and \( \theta \) may have common components.

The weight \( \omega_{n,h} \) is then obtained as the posterior predictive density of patient \( n \) in study \( h \) given the concurrent study data,

\[
\pi(S_{n,h} | S_c) = \int \pi(S_{n,h} | \psi) \pi(\psi | S_c) d\psi,
\]

which is estimated by Monte Carlo. Given a sample \( \{\psi_n\}_{n=1}^N \) from \( \pi(\psi | S_c) \) by fitting (3) to \( S_c \) we have,

\[
\hat{\pi}(S_{n,h} | S_c) = \frac{1}{N} \sum_{n=1}^{N} \pi(S_{n,h} | \psi_n).
\]

The weights are then obtained by mapping this posterior predictive probability estimate onto \((0, 1)\),

\[
\hat{\omega}_{n,h} = G(\hat{\pi}(S_{n,h} | S_c)).
\]

Similar to what was explained for the Mahalanobis distance method, the truncation threshold is obtained as a quantile of the weights in the concurrent study.

### 4 Simulation study

In this section we make comparisons between the proposed IPD-weighted prior and the existing approaches for borrowing historical information that were discussed in Section 1. At each iteration of the simulation, data for a concurrent clinical trial and four historical studies are generated from a Gaussian likelihood,
\[ \mathbf{y}_c \sim \mathcal{N}(\beta \mathbf{x}_c + \theta \mathbf{z}, \sigma^2) , \]

where \( \mathbf{y}_c \) is the vector of responses for the concurrent trial that is of size, \( N_c = 1000 \); \( \mathbf{x}_c \) is a continuous covariate vector of size \( N_c \); \( \beta \) denotes the covariate effect; \( z \) is the vector of arm allocation indicators that is generated from a Bernoulli(0.5) distribution where \( z_n = 1 \) shows that subject \( n \) is assigned to the treatment arm and \( z_n = 0 \) represents control arm assignment; and \( \theta \) is the parameter of interest that represents the treatment effect and its value for the simulations is fixed at \( \theta = 2 \).

Data for the control arms of historical studies are generated as follows:

\[ \mathbf{y}_h \sim \mathcal{N}(\delta_h + \beta \mathbf{x}_h, \sigma^2) , \quad h = 1, \ldots, 4 , \]

where \( \mathbf{y}_h \) are vectors of size \( N_h = 500 \), \( \delta_h \) are the study effects that are fixed at \( \delta = (0, 0, 1, -0.5) \) for the four studies meaning that the control data from the first two historical studies are exchangeable with the concurrent trial control arm while there are unmeasured variables or unreported differences between the last two historical studies and the concurrent trial that shift the mean responses.

The observation error follows a normal distribution with variance 0.01 across all studies.

The covariates for the concurrent and historical studies are generated in the following manner to represent overlapping structure of the study populations,

\[ \mathbf{x}_c, \mathbf{x}_2 \sim \mathcal{N}(10, 1); \quad \mathbf{x}_3 \sim \mathcal{N}(15, 1) \quad \mathbf{x}_1, \mathbf{x}_4 \sim \frac{1}{3} \mathcal{N}(15, 1) + \frac{2}{3} \mathcal{N}(10, 1). \]

Bayesian analysis is then performed using priors that are constructed by the proposed method and the other existing methods. More specifically, the following model is fit to each data set simulated using the above procedure,
\[
\pi(\theta, \beta_0, \beta, \sigma^2 \mid y) \propto \pi_0(\theta, \beta_0, \beta, \sigma^2) \prod_{h=1}^{H} \prod_{n=1}^{N_h} \phi(y_{n,h} \mid \beta_0 + \beta x_{n,h}, \sigma^2)^{\omega_{n,h}} \\
\prod_{n=1}^{N_c} \phi(y_n \mid \beta_0 + \beta x_n + \theta z_n, \sigma^2),
\]

where \( \pi_0(\theta, \beta_0, \beta, \sigma^2) \) is an independent non-informative prior and \( \phi(\cdot \mid a, b^2) \) denotes the Gaussian probability density function with mean \( a \) and variance \( b^2 \). The weights \( \omega_{n,h} \) are given for each of the competing methods for prior construction as follows,

**No prior:** The historical controls are not used in analysis of the concurrent trial, i.e., \( \omega_{n,h} = 0, \quad \forall n, h; \)

**Full history prior:** The historical controls are fully combined with the concurrent study controls, i.e., \( \omega_{n,h} = 1, \quad \forall n, h; \)

**Power prior:** Each historical study is assigned a weight according to the similarity to the concurrent trial

\[
\omega_{n,h} = \omega_h = \frac{1}{N_h} \sum_{n=1}^{N_h} (1 - G(d_{n,h})) \quad h = 1, \ldots, H.
\]

**Truncated power prior:** Similar to power priors but the weights are truncated such that only the historical studies that are similar enough to the concurrent study are used;

\[
\omega_h = \begin{cases} 
\frac{1}{N_h} \sum_{n=1}^{N_h} (1 - G(d_{n,h})) & \text{if } \frac{1}{N_h} \sum_{n=1}^{N_h} (1 - G(d_{n,h})) > \rho \\
0 & \text{if } \frac{1}{N_h} \sum_{n=1}^{N_h} (1 - G(d_{n,h})) < \rho,
\end{cases}
\]

where

\[
\rho = Q_{0.95}(1 - G(d_{n,c})).
\]

**Individually weighted prior:** Using historical controls with each individual weighted, i.e., \( \omega_{n,h} = 1 - G(d_{n,h}) \) for \( n = 1, \ldots, N_h, \ h = 1, \ldots, H. \)
**Truncated individually weighted prior:** Similar to the individually weighted approach but including individuals from the historical study who have a sufficiently high posterior predictive probability of being included in the concurrent study;

\[
\omega_h = \begin{cases} 
1 - G(d_{n,h}) & \text{if } 1 - G(d_{n,h}) > \rho \\
0 & \text{if } 1 - G(d_{n,h}) < \rho.
\end{cases}
\]

Note that using the Mahalanobis distance and the posterior predictive probability for the weights \(\omega_{n,h}\) are equivalent for this simulated example since \(y\) and \(x\) can be modelled by the Gaussian distribution.

**Commensurate prior:** The commensurate prior is the only prior that cannot be described by the general model in (7),

\[
\pi_{CP}(\theta, \delta_s, \beta, \sigma^2, \mu_\delta, \tau^2 | y_c, y_h) \propto \pi_0(\mu_\delta, \tau^2, \theta, \beta, \sigma^2) \prod_{s=1}^{5} \phi(\delta_s | \mu_\delta, \tau^2) \prod_{h=1}^{4} \prod_{n=1}^{N_h} \phi(y_{n,h} | \delta_{h+1} + \beta x_{n,h}, \sigma^2)^{\omega_{n,h}} \prod_{h=1}^{N_c} \prod_{n=1}^{N} \phi(y_n | \delta_1 + \beta x_n + \theta z_n, \sigma^2),
\]

where \(\mu_\delta\) and \(\tau^2\) are the common mean and variance of the study random effects. The variance \(\tau^2\) is the key parameter that controls the amount of information borrowed according to the study heterogeneity. Note that the commensurate prior is in fact the “correct” model as it captures the data generative mechanism.

The methods are compared in terms of the root mean squared error,

\[
\text{RMSE} = \frac{1}{K} \sum_{m=1}^{K} (\theta_k - \theta_T)^2,
\]
where $\theta_k$ is the $k$th draw of the posterior and $K = 2000$ is the number of draws. The distribution of the RMSE over the simulation iterations are plotted in Figure 3.

It is not surprising that using the full historical controls with equal weights as the concurrent trial control data (FH), or weighted either individually (IW) or at the study level (PP) result in the highest RMSE among the compared methods (Figure 3a). Any contribution from the non-exchangeable portion of the historical data can result in estimation bias (Figure 3b). It is, however, interesting that the commensurate prior (CP) results in almost as large RMSE as FH, IW and PP. When looking at bias and estimation variance, it becomes clear that CP yields unbiased estimates, however, the estimation variance is the highest due to the hierarchical modelling structure that translates the heterogeneity in historical data into estimation variance. The truncated power prior (TPP) and the truncated individually weighted (TIW) prior result in smallest estimation errors. TIW results in slightly lower RMSE as it takes advantage of more individual patient data and therefore yields more precise estimates. The improvement by TIW over TPP is expected to be more visible when more studies with partially overlapping populations with the target population are available.

5 Analysis of the NSCLC data

In this section the proposed methodology is applied to the data introduced in Section 2. ZODIAC is considered as the concurrent trial and the other three studies are used to enrich the control arm. As mentioned earlier, one of the three historical trials (PROCLAIM) showed significantly different patient and survival characteristics. Dron et al. (2019) showcase analysis of these studies using the commensurate prior approach with different levels of
borrowing arising from including/excluding PROCLAIM among the historical studies. Given the clear differences in eligibility criteria and control arm definition, this trial should be excluded from the set of historical studies. However, we keep this study among the historical studies to demonstrate that the proposed method can be used to automatically exclude ineligible historical data.

Since the data includes a number of discrete covariates such as sex and race, for specification of the weights in the individually weighted prior, we use the proposed model-based approach. In the following, we introduce the similarity model as well as the model used for Bayesian analysis of the ZODIAC trial.

In this historical controls approach the similarity model is used only to model the control arm data. The outcome is time of death for observed events and the time of lost to follow-up for patients with censored data. Available covariates among all four studies include age (treated as continuous), sex (dichotomous) and race with four categories that was reconstructed as three dummy variables. Denoting the outcome of patient $n$ in the control arm by $y_{n}^{ctrl}$, the censoring variable by $\nu_{n}^{ctrl}$ and vector of covariates by $x_{n}^{ctrl}$, the similarity model is defined as follows,

$$y_{n}^{ctrl} \sim N(\mu_{n}^{y}, \sigma_{y}^{2}), \quad \nu_{n}^{ctrl} \sim \text{Bernoulli}(p_{\nu}),$$

$$x_{1,n}^{ctrl} \sim N(\mu_{x}, \sigma_{x}^{2}), \quad x_{2:4,n}^{ctrl} \sim \text{Bernoulli}(p_{x})$$

where $x_{1,n}^{ctrl}$ is the first component of $x_{n}^{ctrl}$, i.e. age and $x_{2:4,n}^{ctrl}$ is the vector of dichotomous covariates, i.e., sex and race categories; and

$$\mu_{n}^{y} = \beta^{T} x_{n}^{ctrl} + \nu_{n}^{ctrl} \eta_{1} + (1 - \nu_{n}^{ctrl}) \eta_{2}.$$
All the continuous parameters and hyper-parameters (i.e., $\beta, \eta_1, \eta_2, \mu_x$) are assigned vague normal priors with mean zero and variance $10^6$; probability parameters, $p_\nu$ and the vector $p_x$ are assigned uniform priors; and the variance parameters, $\sigma_y^2$ and $\sigma_x^2$ are assigned half-Cauchy (truncated to exclude negative numbers) distributions with mean zero and variance $10^6$ as prior. The similarity model is fit to the IPD control data from the concurrent study (ZODIAC) that is denoted by $(y_c^{\text{ctrl}}, X_c^{\text{ctrl}}, \nu_c^{\text{ctrl}})$. The weight for each individual within the control arms of the historical studies is calculated using (6),

$$\hat{\omega}_{n,h} = \pi(y_{n,h}^{\text{ctrl}}, x_{n,h}^{\text{ctrl}}, \nu_{n,h}^{\text{ctrl}} | y_c^{\text{ctrl}}, X_c^{\text{ctrl}}, \nu_c^{\text{ctrl}}).$$

The analysis model is defined as a Bayesian hierarchical model with the proportional hazards assumption that is used to analyse the survival data (control and intervention arms) of the concurrent study. More specifically the likelihood is given by

$$\pi(y | \alpha, \lambda_n) = \prod_{n=1}^{N_C} f(y_n | \alpha, \lambda_n)^{\nu_n} S(y_n | \alpha, \lambda_n)^{(1-\nu_n)},$$

where $y$ is the vectors of responses, $f(y_n | \alpha, \lambda_n)$ is a Weibull probability density function with shape parameter $\alpha$ and scale parameter $\lambda_n$, $S(y_n | \alpha, \lambda)$ is the Weibull survival function, and $\nu_n = 0$ indicates that patient $n$ is right-censored. The regression model is embedded within the scale parameter,

$$\lambda_n = \delta + x_n\beta + a_n\theta,$$

where $a_n = 1$ indicates treatment assignment. The parameter of interest is $\theta$ which represents the treatment effect. The hazard ratio is given as,

$$HR = \exp(\theta).$$

The IPD-based prior is defined as follows,
\[ \pi_{TW}(\alpha, \beta, \delta, \theta) = \pi_0(\alpha, \beta, \delta, \theta) \prod_{h=1}^{H} \prod_{n=1}^{N_h} \left[ f(y_{n,h} | \alpha, \beta, \delta)^{\nu_{n,h}} S(y_{n,h} | \alpha, \beta, \delta)^{(1-\nu_{n,h})} \right] \hat{\omega}_{n,h}(1-a_{n,h}), \]

where \( \pi_0(\alpha, \beta, \delta, \theta) \) is an independent uninformative prior. Specifically, \( \delta, \beta \) and \( \theta \) are assigned normal distributions centered at zero with variance \( 10^6 \) and \( \alpha \), is assigned the same normal distribution truncated at zero since \( \alpha > 0 \). The power \( (1 - a_n) \) indicates that only control arm historical data are incorporated into the prior. Note that the informative prior does not contain information about \( \theta \) since it only uses historical data from the control arm.

The posterior kernel is then given as the product of the prior and the likelihood,

\[ \pi(\alpha, \beta, \delta, \theta | y) \propto \pi_{TW}(\alpha, \beta, \delta, \theta) \pi(\nu_{n,h} | \alpha, \lambda_n(\beta, \delta, \theta)). \]

Samples are drawn from the above posterior distribution using Markov chain Monte Carlo.

The data of the ZODIAC trial are analysed using the proportional hazards Weibull model with and without an informative prior that is constructed using the proposed approach based on the other three trials. Figure 4 shows a summary of results obtained from the two methods. Specifically, figure 4a shows the Kaplan-Meier curves for the data from ZODIAC trial, figure 4b shows the estimated survival curves for the control and treatment arms obtained with no prior (top panel) and the individually weighted prior (bottom panel). A larger gap between the survival curves in the bottom panel is the result of incorporating additional control information included from the historical data. With respect to the effect estimates this translates into an estimated hazard ratio that is 25\% smaller with narrower credible intervals (figure 4c).

Considering the between study differences and specially the fact that PROCLAIM stands out among the three historical trials as one that should not be used to inform inference, it is interesting to see what percentage of individual patient data from each historical trial
is incorporated into the prior. Figure 5 shows the distribution of raw powers for the four studies. The vertical line shows the truncation point which is specified as the 5% quantile of the power distribution for ZODIAC, i.e., 95% of individuals within the control arm of ZODIAC trial have powers greater than this threshold. Note that all individuals within ZODIAC will be included in the analysis model with power one. For the other three trials, Study57 contributes most to the prior with 97% of powers above the cut-off value, followed by INTEREST with 82% of IPD contributing to the prior with their corresponding weights and last is PROCLAIM with only 34% of powers greater than the threshold. In fact, the majority of posterior predictive probabilities are zero for PROCLAIM representing the non-exchangeability of this study with the concurrent study.

6 Discussion

In this article we have proposed methodology for incorporating individual patient data from past studies to the analysis of clinical trial data with the goal of improving statistical inference. The proposed family of priors can be considered a generalization of power priors where instead of assigning a power to study each individual within the historical studies receives a power. The weight or power assigned to each individual is a function of their similarity to the concurrent study population. The similarity is measured through a set of available variables including covariates and outcome(s) that are shared among the past and present studies. The Mahalanobis distance for continuous data and a general model-based approach that suits any data type are recommended for specification of the weights.

The general weight specification approach relies on a similarity model that is intended
to capture important data structure including correlations among variables. We emphasize that the similarity model is not necessarily identical to the analysis model. It can be more complex in that it assigns probability distributions to covariates that may be considered fixed under the analysis model. But it can be simpler in that approximate Gaussian distributions may be used even when data are not entirely Gaussian.

In our simulation studies we did not observe any significant difference in the results from using a similarity model that is exactly the data generating model versus one that assumes an approximate Gaussian distribution for all continuous variables. However, as non-Gaussian features become more dominant in the data, a similarity model that captures these features can result in more appropriate information borrowing.

An essential component of the proposed prior construction approach is a cut-off value for the powers and discarding individual patient data whose powers fall below this cut-off value. The truncation is introduced to avoid prior-data conflict. The intuitive explanation is that any individual data from the historical studies that fall outside a pre-specified credible set of the concurrent study distribution should not be used to inform inference.

A question that remains open is how to select the variables to be included in the similarity model. This is not a serious issue in the NSCLC application included in the present work since the covariates consist of a small number of demographic variables that can be reasonably used to define the study population. However, in cases where there are a large number of shared covariates among studies it is important to select a subset of variables that meaningfully characterize the target population.
Data and Code

The IPD under the control arm for the four NSCLC trials was obtained from Project Data Sphere (http://www.projectdatasphere.com), an open-source repository of individual-level patient data from oncology trials. No IPD was available under the intervention arms of either trials. Therefore, we recovered IPD for the intervention arm of ZODIAC by digitizing the Kaplan-Meier curves provided in the publication.

All the Bayesian computation, i.e., posterior sampling, was performed in RStan. The Stan models together with the R script that can be used to reproduce the results of the paper are provided at https://github.com/sgolchi/IPD_prior.

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|                                | INTEREST | ZODIAC | PROCLAIM | Study 57 |
|--------------------------------|----------|--------|----------|----------|
| Control group median overall survival (months) | 8 | 10 | 25 | 7.8 |
| Stage III, (%)                  | 38 | 15 | 100 | 17 |
| Stage IV, (%)                   | 53 | 85 | 0 | 83 |
| Average age (years)             | 60.5 | 59 | 59 | 61 |
| Adenocarcinoma histology (%)    | 54 | 60 | 75 | 60 |
| Two or more prior chemotherapy regimens (%) | 16 | 0 | 0 | 35 |
| Radiotherapy sequence, dose (control arm) | None | None | 60-66Gy, Concurrent | None |

**Table 1:** Summary of key trial characteristics for the four NSCLC trials

**Figure 1:** Hypothetical example representing partially overlapping study populations.
Figure 2: (a) Overall survival distribution for the four NSCLC trials (b) Bayesian 95% credible intervals for the hazard ratio for ZODIAC obtained by no prior (NP), truncated individually weighted prior (TIW), commensurate prior (CP), power prior (PP) and full historical data (FH).

Figure 3: Simulation results: (a) RMSE, (b) bias, and (c) length of 95% credible intervals for the seven methods: full history prior (FH), individually weighted prior (IW), power prior (PP), commensurate prior (CP), no prior (NP), truncated power prior (TPP) and truncated individually weighted prior (TIW).
Figure 4: Analysis of ZODIAC trial data (a) Kaplan-Meier curves (b) Survival curves obtained from the Weibull model with no historical data (top panel) and the individually weighted historical data prior (bottom panel) (c) Bayesian point estimates (posterior mean) and 95% credible intervals for the hazard ration resulted from the no-prior and TIW-priors.
Figure 5: Raw power distribution for the four NSCLC trials.