RESEARCH ARTICLE

A novel approach to bivariate meta-analysis of binary outcomes and its application in the context of surrogate endpoints

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Abstract

Bivariate meta-analysis provides a useful framework for combining information across related studies and has been widely utilised to combine evidence from clinical studies in order to evaluate treatment efficacy. Bivariate meta-analysis has also been used to investigate surrogacy patterns between treatment effects on the surrogate and the final outcome. Surrogate endpoints play an important role in drug development when they can be used to measure treatment effect early compared to the final clinical outcome and to predict clinical benefit or harm. The standard bivariate meta-analytic approach models the observed treatment effects on the surrogate and final outcomes jointly, at both the within-study and between-studies levels, using a bivariate normal distribution. For binomial data a normal approximation can be used on log odds ratio scale, however, this method may lead to biased results when the proportions of events are close to one or zero, affecting the validation of surrogate endpoints. In this paper, two Bayesian meta-analytic approaches are introduced which allow for modelling the within-study variability using binomial data directly. The first uses independent binomial likelihoods to model the within-study variability avoiding to approximate the observed treatment effects, however, ignores the within-study association. The second, models the summarised events in each arm jointly using a bivariate copula with binomial marginals. This allows the model to take into account the within-study association through the copula dependence parameter. We applied the methods to an illustrative example in chronic myeloid leukemia to investigate the surrogate relationship between complete cytogenetic response (CCyR) and event-free-survival (EFS).

KEYWORDS:

bivariate meta-analysis, binary outcomes, copula modelling, surrogate endpoints

1 | INTRODUCTION

Bivariate meta-analytic methods provide a natural framework for synthesising evidence obtained from two outcomes. As discussed by Riley et al., many clinical outcomes are correlated with each other, and correlation at the individual level will lead to correlation between treatment effects at the study level. A bivariate random effects meta-analysis model (BRMA) can be used to perform bivariate meta-analysis of correlated and normally distributed treatment effects on two outcomes. This method
models treatment effects on both outcomes jointly with a bivariate normal distribution. When this approach is applied to binomial data the proportions of events in each arm across outcomes are are transformed to obtain treatment effects on log odds ratio scale which are assumed to be approximately normally distributed. A very popular form of the bivariate normal meta-analytic method has been described by Houwelingen et al. This approach can be easily implemented in the Bayesian framework and used to obtain pooled effects on both outcomes whilst taking into account of the correlation between them, as well as, to assess the study level association between the true treatment effects between the first and the second outcome. However, when modelling binomial data on log OR scale, the assumption of normality may not be reasonable. Hamza et al. showed that the normal approximation, used for binomial data in univariate meta-analysis leads to biased results, especially when the proportions of events are very close to zero or one and the variance is large.

In this paper, we investigate modelling bivariate binomial data in a meta-analytic framework in the context of surrogate endpoint evaluation. Bivariate meta-analysis of treatment effects on a surrogate and a final outcome allows for the study level validation of a surrogate endpoint. Surrogate endpoints are becoming increasingly popular nowadays as they play a very important role in drug development process. New advances in science have led to discovering of promising therapies which often are targeted to specific patient populations, for example defined by a genetic biomarker. This resulted in modern clinical trials carried out in smaller samples of population, whilst the increased effectiveness of these therapies led to reduced number of events (such as deaths in cancer patients). Consequently measurement of treatment effect on overall survival (OS) requires very long follow up time, otherwise its estimate is obtained with large uncertainty. Therefore, surrogate endpoints allowing the measurement of treatment effect with higher precision at earlier follow up time compared to the final clinical outcome have been investigated to accelerate the availability of these treatments to the patients.

A standard way to validate the study level surrogacy is to perform a form of bivariate meta-analysis, such as BRMA, to model jointly correlated and normally distributed treatment effects on surrogate and final outcomes and monitor the between-studies correlation parameter. However as explained above, this approach may be problematic for binary outcomes. We proposed two random effect meta-analytic methods for the evaluation of study level surrogate relationships of the treatment effects on binomial outcomes, using exact likelihood approach based on the binomial distribution when modelling within-study variability. The first approach uses the exact independent binomial likelihoods across outcomes to model the within-study variability, however it ignores potential within-study associations. In a previous work, Riley et al. highlighted the importance of taking into account the within-study correlation when BRMA model is used. To take into account the within-study association, we have developed another method which models the summarised events on each outcome jointly using a bivariate copula with binomial marginal distributions. This model takes into account the within-study association between the summarised events on the surrogate and the final outcome through the copula dependence parameter. This makes the copula model a more appropriate approach as the events on the surrogate endpoint and the final outcome are obtained from the same patients and therefore, they are correlated. Copulas have been previously used to model individual level surrogacy patterns modelling dependencies between, for example, time to event surrogate and final outcomes in individual patient data (IPD) based methods. IPD, however, are often not available, and only study level surrogacy can be validated using summary data. Thus robust methods for the synthesis of aggregate data for surrogate endpoint evaluation are very important.

We investigate the impact of assumptions made when modelling the within-study variability on the results of the between-studies parameters on two binomial outcomes (surrogate and final) and in particular when the proportions of events (such as responses to treatment or deaths) are close to zero or one. We carry out this investigation in a simulation study as well as by applying the methods (the standard BRMA model using log OR scale and the two proposed models) to an illustrative example in chronic myeloid leukemia (CML). CML is a myeloproliferative neoplasm of hematopoietic stem cells associated with a characteristic chromosomal translocation called the Philadelphia chromosome. The main characteristic of CML is that it is regarded as a slow progressive disease. Before the molecular pathogenesis of the disease was well understood, the median survival was 6 years, with a predicted 5-year overall survival (OS) of 47.2%. However, the introduction of tyrosine kinase inhibitor (TKI) therapies have led to dramatically improved patients outcomes with high rates of complete cytogenetic response (CCYR) at 12 months and very few events at 2-year OS and event-free survival (EFS). By applying the proposed methods we aim to assess the whether CCYR at 12 months can be considered as a valid surrogate endpoint for event free survival (EFS) at 24months.

We describe all methods in detail in Section 2. Section 3 presents the simulation study and its results. In Section 4 we discuss the application of the methods to the illustrative example. The paper concludes with a discussion in Section 5.
2 | METHODS

2.1 Bivariate random effects meta-analysis (BRMA)

The BRMA model for correlated and normally distributed treatment effects on two outcomes \(Y_{1i}, Y_{2i}\) was firstly introduced by McIntosh \cite{16} and since then many extensions have been proposed. It is usually presented in the form described by van Houwelingen et al \cite{3} and Riley et al \cite{17}.

\[
\begin{align*}
(Y_{1i}, Y_{2i}) & \sim N\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \begin{pmatrix} \sigma^2_{1i} & \sigma_{1i} \sigma_{2i} \\ \sigma_{1i} \sigma_{2i} & \sigma^2_{2i} \end{pmatrix} \right)  \\
(\delta_{1i}, \delta_{2i}) & \sim N\left(\begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \begin{pmatrix} \tau^2_1 & \tau_1 \tau_2 \\ \tau_1 \tau_2 & \tau^2_2 \end{pmatrix} \right)
\end{align*}
\]  

(1) (2)

In this model, the treatment effects on the first and the second outcome \(Y_{1i}, Y_{2i}\), which can be log odds ratios, are assumed to estimate the correlated true treatment effects \(\delta_{1i}\) and \(\delta_{2i}\) with corresponding within-study variances \(\sigma^2_{1i}\) and \(\sigma^2_{2i}\) of the estimates and the within-study correlation \(\rho_{ui}\) between them. In this hierarchical framework, these true study-level effects follow a bivariate normal distribution with means \((d_1, d_2)\) corresponding to the two outcomes between-studies variances \(\tau^2_1\) and \(\tau^2_2\) and a between-studies correlation \(\rho_b\). In the context of surrogate endpoints the between-studies correlation \(\rho_b\) is the main parameter of interest and it is used to assess the study level association between the treatment effect on the surrogate endpoint and the effect on the final outcome. Equation (1) represents the within-study model and (2) is the between-studies model.

The elements of the within-study covariance matrix, \(\sigma^2_{1i}\), \(\sigma^2_{2i}\) and \(\rho_{ui}\) are assumed to be known. Whilst the estimates of the variances are easily obtained by taking the square of the standard error for each outcome, the estimates of the within-study correlations between the two outcomes are more difficult to obtain as they would not be reported in the original articles. When IPD are available, the correlation can be obtained by bootstrapping \cite{17} (see details in the section A.1 of the supplementary material) or alternatively by fitting a regression model for the two outcomes with correlated errors \cite{17}. Other methods of estimating the within-study correlations have been discussed elsewhere and are summarized in Bujkiewicz et al. \cite{9}

Implementing the model in the Bayesian framework the unknown parameters \(\tau^2_1\), \(\tau^2_2\), \(d_1\), \(d_2\) and \(\rho_b\) have to be estimated and therefore, prior distributions should be specified on them. For instance, the following prior distributions can be placed on the these parameters: \(\beta_{1,2} \sim N(0, 10^2)\), \(\tau_{1,2} \sim U(0, 2)\), to implement the natural constrain of \(-1 \leq \rho_b \leq 1\) we used the Fisher’s \(z\) transformation as, \(\rho_b = tanh(z)\), \(z \sim N(0, 1)\).

When this model is applied to binomial data (summarised events), they are transformed to obtain treatment effects on the log OR scale: \(Y_{1i} = \log(\frac{r_{1Bi}}{N_{B1-i}}) - \log(\frac{r_{1A1}}{N_{A1-i}})\), \(Y_{2i} = \log(\frac{r_{2Bi}}{N_{B1-i}}) - \log(\frac{r_{2A1}}{N_{A1-i}})\) with corresponding the variances: \(\sigma^2_{1i} = \frac{1}{r_{1Bi} + \frac{1}{N_{B1-i}} + \frac{1}{N_{A1-i}}}\) and \(\sigma^2_{2i} = \frac{1}{r_{2Bi} + \frac{1}{N_{B1-i}} + \frac{1}{N_{A1-i}}}\). Where \(r_{1A1}, r_{2A1}, r_{1B1}, r_{2B1}\) are the number of events in the control arm \(A\) and treatment arm \(B\) on both outcomes in study \(i\) whereas, \(N_{A1}\) and \(N_{B1}\) are the arm sizes in study \(i\). A modelling issue occurs when there are no events in either of the treatment arms as the log odds ratios \((Y_{1i}, Y_{2i})\) and their variances cannot be defined. A very simple way to tackle this problem is to apply a correction, for instances, by adding 0.5. However, in some situations the effect of adding 0.5 may lead to biased results \cite{17,18}. Furthermore, when the proportions of events are close to zero or one the assumption of normality of log ORs is unreasonable and can lead to biased results \cite{17}.

2.2 Bivariate random effect meta-analysis with independent Binomials (BRMA-IB)

In this section, we introduce a bivariate meta-analytic model with independent binomial likelihoods for the first and the second outcomes at the within-study level. This is very similar to a standard model for meta-analysis of diagnostic test accuracy studies (where true positive and true negative observations are not correlated within a study as they are obtained from different patients). We assume that the number of events \(r_{1A1}, r_{2A1}\), in the control arm \(A\) and \(r_{1B1}, r_{2B1}\) in the experimental arm \(B\), on the two outcomes (the surrogate and the final outcome respectively) follow independent Binomial distributions with the corresponding true probabilities of events \(p_{1A1}, p_{2A1}, p_{1B1}\) and \(p_{2B1}\):

\[
r_{1A1} \sim Bin(p_{1A1}, N_{A1}), \quad r_{2A1} \sim Bin(p_{2A1}, N_{A1}), \quad r_{1B1} \sim Bin(p_{1B1}, N_{B1}), \quad r_{2B1} \sim Bin(p_{2B1}, N_{B1})
\]  

(3)

At the between-studies level \cite{3}, the true probabilities of events are transformed using a link function \(g(\cdot)\) (e.g. logit). \(\mu_{ij}\) are study specific baseline effects (i.e. the log-odds for the control group \(A\) and outcome \(j = 1, 2\) in study \(i\)) while, \(\delta_{ij}\) are the study
specific true treatment effects on the log OR scale for outcome \( j = 1, 2 \) in study \( i \).

\[
\begin{align*}
g(p_{1Ai}) &= \mu_{1i}, & g(p_{1Bi}) &= \mu_{1i} + \delta_{1i} \\
g(p_{2Ai}) &= \mu_{2i}, & g(p_{2Bi}) &= \mu_{2i} + \delta_{2i} \\
(\delta_{1i}, \delta_{2i}) &\sim N \left( \left( \begin{array}{c} d_1 \\ d_2 \end{array} \right), \left( \begin{array}{cc} \tau_1^2 & \tau_1 \tau_2 \rho_b \\ \tau_2 \rho_b & \tau_2^2 \end{array} \right) \right) \quad (4)
\end{align*}
\]

Where \((d_1, d_2)\) are the mean effects on first and second outcome, \(\tau_1\) and \(\tau_2\) are the between studies heterogeneity parameters and \(\rho_b\) the between-studies correlation. Similarly as in the BRMA, between-studies correlation quantifies the relationship between the surrogate endpoint and the final outcome.

To implement the model in the Bayesian framework, we place prior distributions on unknown parameters such as, the baseline treatment effects \(\mu_{1,2i} \sim N(0,10^2)\), the mean effects \(d_{1,2i} \sim N(0,10^2)\), the between study standard deviations \(\tau_{1,2} \sim U(0,2)\) and in order to implement the natural constrain of \(-1 \leq \rho_b \leq 1\) we used the Fisher’s \(z\) transformation as, \(\rho_b = \tanh(z), z \sim N(0,1)\).

The main difference between this method and the BRMA model is the within-study level \(^3\). Here, we model the within-study variability using exact likelihood approach based on the binomial distribution avoiding to make the restrictive assumption of normality. This approach does not require continuity corrections, however, the model ignores the within-study association. This is very restrictive as the number of events in each arm on the first and the second outcomes are obtained from the same patients and hence are expected to be correlated.

### 2.3 Model with bivariate copula

In this section we propose an extension of the BRMA-IB using a copula representation to model the number of events in each arm on the first and the second outcome jointly. Copulas is a very flexible way to model multivariate data as they account for the dependence structure avoiding the restrictive assumption of normality. First, we introduce some background on copula models. In section 2.3.2 a copula model with binomial margins is presented.

#### 2.3.1 Overview of copula theory

A bivariate copula \(C\) is a bivariate cumulative function (CDF) restricted to the unit square with standard uniform marginal distributions\(^21\),\(^24\).

If \(H\) is a bivariate cdf with univariate cdf margins \(F_1, F_2\) then according to the Sklar’s theorem\(^23\) for every bivariate distribution there exists a copula representation \(C\) such that

\[
H(x_1, x_2, \theta) = C(F_1(x_1), F_2(x_2), \theta) \quad (5)
\]

The copula \(C\) is unique if \(F_1, F_2\) are continuous random variables; otherwise, there are many possible copulas if some of the margins have discrete components as emphasized by Genest and Neslehova\(^23\) but all coincide on the closure of \(\text{Ran}(F_1) \times \text{Ran}(F_2)\) where \(\text{Ran}(F)\) denotes the range of \(F\). While the derivation of the joint density is easy for the continuous case through partial derivatives, it is not that simple in the discrete case. In this case, the joint probability mass function (pmf) is obtained using finite differences

\[
\begin{align*}
h(x_1, x_2, \theta) &= C(F_1(x_1), F_2(x_2), \theta) - C(F_1(x_1 - 1), F_2(x_2), \theta) \\
&\quad - C(F_1(x_1), F_2(x_2 - 1), \theta) + C(F_1(x_1 - 1), F_2(x_2 - 1), \theta) \quad (6)
\end{align*}
\]

The key benefit of this theory is that copulas avoid the assumption of normality when modelling non-normal data and allow the marginal distributions and the dependence structure to be estimated separately as they provide a natural way to study and measure the dependence among random variables.

Next, we describe the set copulas we used in this paper. Archimedean copulas\(^23\) have the form,

\[
C(u_1, u_2, \theta) = \phi(\phi^{-1}(u_1, \theta) + \phi^{-1}(u_2, \theta), \theta)
\]

where \(\phi(u, \theta)\) is the Laplace transform of a univariate family of distributions of positive random variables, such as \(\phi()\) and its inverse have closed forms. We used Frank copula which is one of the most popular Archimedean copulas. It is a reflection symmetric copula without tail dependence\(^25\). In general, a bivariate copula \(C\) is reflection symmetric if its density satisfies \(c(u_1, u_2) = c(1-u_1, 1-u_2)\) for all \(0 \leq u_1, u_2 \leq 1\). Otherwise, the joint density is reflection asymmetric with more probability
in the upper tail or the lower tail. Tail dependence is another useful copula-based measure indicating dependence in extreme values. Frank copula is given by,

\[ C_F(u_1, u_2, \theta) = \theta^{-1} \log \left\{ 1 + \frac{e^{-u_1 \theta} - 1}{e^{-u_2 \theta} - 1} \right\}, \quad \theta \in (-\infty, \infty) \setminus \{0\}. \]

Frank copula interpolates from the Frechet lower bound \( \theta \to -\infty \) (perfect negative dependence) to the Frechet upper bound \( \theta \to \infty \) (perfect positive dependence) and hence, it is appropriate to model both kind of dependencies (negative and positive) between the surrogate endpoint and the final outcome. Many other copulas can also be used to model a variety of different dependence structures, but this is out of the scope of this research.

### 2.3.2 Bivariate random effects meta-analysis with bivariate copulas (BRMA-BC)

BRMA-IB model assumes independence of the summarised events across arms and outcomes. However, in the context of surrogate endpoints (or correlated binary outcomes) this assumption is fairly strong. At the within-study level, the summarised events in each arm on the first and the second outcome are obtained from the same patients. Therefore, they are correlated. A more rational modelling approach is to model the events on both outcomes jointly assuming some kind of association between them. This can be achieved by using a copula representation with discrete (binomial) marginals, as copulas account for the dependence between marginals and allow for modelling various dependence structures, providing a flexible representation of the bivariate distribution. Therefore, a joint density made with copulas can be much more flexible compared to the bivariate normal distribution which only allows for normal marginals and linear dependence structure.

At the within-study level, we assume that the summarised events in each arm on both outcomes follow bivariate distributions \( h(p_{1i}, p_{2i}, N_i, \theta_i) \) with binomial marginal distributions. The parameters \( p_{1Ai}, p_{2Ai}, p_{1Bi}, p_{2Bi} \) denote the true probabilities of the summarised events in each arm on the first and the second outcome, \( N_{Ai} \) and \( N_{Bi} \) are the number of patients in the control arm \( A \) and experimental arm \( B \) in trial \( i \). Additionally, \( \theta_{Ai}, \theta_{Bi} \) are the dependence parameters in each arm respectively and they are known when IPD are available.

\[
\begin{align*}
  &\begin{pmatrix} r_{1A1} \\ r_{2A1} \end{pmatrix} \sim h(p_{1A1}, p_{2A1}, N_{A1}, \theta_{A1}) \quad &\begin{pmatrix} r_{1B1} \\ r_{2B1} \end{pmatrix} \sim h(p_{1B1}, p_{2B1}, N_{B1}, \theta_{B1}) \\
  &g(p_{1A1}) = \mu_{1i}, \quad g(p_{2A1}) = \mu_{1i} + \delta_{1i} \quad &g(p_{1B1}) = \mu_{2i}, \quad g(p_{2B1}) = \mu_{2i} + \delta_{2i} \\
  &\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix} \sim N\left( \begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \begin{pmatrix} \tau_1 & \tau_1 \rho_b \\ \tau_1 \rho_b & \tau_2 \end{pmatrix} \right) 
\end{align*}
\]

where

\[
\begin{align*}
  &h(r_{1A1}, r_{2A1}|p_{1A1}, p_{2A1}, N_{A1}, \theta_{A1}) = C(F_1(r_{1A1}), F_2(r_{2A1}), \theta_{A1}) - C(F_1(r_{1A1} - 1), F_2(r_{2A1}), \theta_{A1}) \\
  &\quad - C(F_1(r_{1A1}), F_2(r_{2A1} - 1), \theta_{A1}) + C(F_1(r_{1A1} - 1), F_2(r_{2A1} - 1), \theta_{A1}) \\
  &h(r_{1B1}, r_{2B1}|p_{1B1}, p_{2B1}, N_{B1}, \theta_{B1}) = C(F_1(r_{1B1}), F_2(r_{2B1}), \theta_{B1}) - C(F_1(r_{1B1} - 1), F_2(r_{2B1}), \theta_{B1}) \\
  &\quad - C(F_1(r_{1B1}), F_2(r_{2B1} - 1), \theta_{B1}) + C(F_1(r_{1B1} - 1), F_2(r_{2B1} - 1), \theta_{B1}) \\
  &F_1(r_{1A1}), F_2(r_{2A1}) \quad \text{and} \quad F_1(r_{1B1}), F_2(r_{2B1}) \quad \text{are the CDFs of the binomial marginal distributions on the surrogate and the final outcome and} \ C(\cdot, \cdot) \quad \text{is the bivariate copula.}
\end{align*}
\]

We assume that within-study dependencies are different across studies and hence each study has a different dependence parameter. However, in cases where individual patient data are not available across all studies, we can relax this assumption having the same dependence across them. In the absence of IPD, we can construct informative prior distributions combining evidence from external sources such as observational studies. At the between-studies level, the model is exactly the same as BRMA-IB. The true probabilities of events \( p_{1Ai}, p_{2Ai}, p_{1Bi}, p_{2Bi} \) are transformed using a link function \( g(\cdot) \) and the true treatment effects on both outcomes are normally distributed. This model was implemented in the Bayesian framework assuming the same prior distributions as BRMA-IB.

### 3 SIMULATION STUDY

The proposed methods make different assumptions at the within-study level. BRMA-IB assumes that the summarised number of events across outcomes are independent and binomially distributed whereas, BRMA-BC models the summarised events on
both outcomes jointly accounting for the dependence structure between them. We carried out a simulation study to assess the performance of BRMA model and the two proposed methods and in particular to investigate the impact of the magnitude of within-study association on the performance of the three models.

3.1 Simulation scenarios varying within-study association, proportions of responders, number of participants

We simulated data under 18 scenarios generating 1000 replications for each of them. Across scenarios, Frank copula was used to simulate correlated IPD (which is also the copula function we use to implement BRMA-BC model). To measure the effect of the within-study association, we varied the strength of association by assuming weak, moderate and strong within-study associations (see details in step 6 of the data generation below). To test the effect of the proportions of events on the performance of the models, we also considered different baseline treatment effects. Baseline effects \( \mu_{1i,2i} \) were drawn from the bivariate normal distribution (see details in step 3 of the data generation below). As the baseline effects are transformed on the logit scale, the mean baseline effects \( \eta_{1,2} \) correspond to 50% proportion of events in the control arm (as \( \logit^{-1} \approx 0.5 \), and similarly, \( \eta_{1,2} = 3 \) correspond to 95% proportion of events and \( \eta_{1,2} = 4 \) imply that there are around 98% of events in the first arm and on both outcomes. Lastly, we considered two settings for study sizes. The study size in both arms of each study were drawn from the following normal distribution: \( n_{Ai,Bi} \sim N(m, 5) \) where \( i = 1, ..., N \) and rounded off to the nearest integer. Setting \( m = 300 \) and \( m = 80 \) covers the typical sizes of phase 3 and phase 2 trials in CML.

The generation process is the following:

1. Set the number of studies to thirty (\( N = 30 \)).
2. Simulate the heterogeneous arm sizes \( n_i \) of each study \( i \) from the following normal distribution (\( n_i \sim N(m, 5) \)) and then round off to the nearest integer.
3. Simulate the baseline treatment effects \( \mu_{1i,2i} \) from the following bivariate normal distribution (\( \mu_{1i,2i} \sim \mathcal{BV}N(\begin{bmatrix} \eta_1 \\ \eta_2 \end{bmatrix}, \begin{bmatrix} s_1^2 & s_1 s_2 \rho \\ s_1 s_2 \rho & s_2^2 \end{bmatrix}) \)) with \( s_1 = s_2 = 0.1 \) and \( \rho = 0.8 \).
4. Simulate the true treatment effects from (\( \delta_{1i,2i} \sim \mathcal{BV}N(\begin{bmatrix} d_1 \\ d_2 \end{bmatrix}, \begin{bmatrix} \tau_1^2 & \tau_1 \tau_2 \rho_b \\ \tau_1 \tau_2 \rho_b & \tau_2^2 \end{bmatrix}) \)) with \( d_1 = 0.4, d_2 = 0.2, \tau_1 = 0.5, \tau_2 = 0.5, \rho_b = 0.8 \).
5. Calculate the proportions of events from \( p_{1Ai} = \logit^{-1}(\mu_{1i}), p_{2Ai} = \logit^{-1}(\mu_{2i}), p_{1Bi} = \logit^{-1}(\mu_{1i} + \delta_{1i}), p_{2Bi} = \logit^{-1}(\mu_{2i} + \delta_{2i}) \) in each arm across outcomes.
6. To simulate (weakly, moderately and highly) correlated binary IPD, we used a joint density (made with Frank copula) of Bernoulli marginal distributions in both arms with dependence parameters \( \theta_A \) and \( \theta_B \). For each set of proportions of events (50%, 95%, 98%) we chose a different value of the dependence parameters to reflect low, moderate and high within-study association. The dependence parameters \( \theta_A \) and \( \theta_B \) for all the simulated scenarios along with the approximate value of corresponding Spearman’s correlation are presented in section A.5 of the supplementary material.

The dependence parameter of Frank copula \( \theta \) was obtained by transforming the corresponding Spearman’s correlation across scenarios.

7. Summarise the number of events in each arm and outcome by taking the sum of the binary responses.

This process gives us a dataset with correlated summarised events on the first and the second outcome in each arm, as well as, the original correlated binary IPD.

We fitted BRMA model, BRMA-IB model and BRMA-BC model with Frank copula to the generated data. As it was explained in Sections 2.1, 2.2.3, BRMA and BRMA-BC methods take into account the within-study associations. When IPD are available these parameters, the within-study correlation and the dependence parameter, can be estimated. To obtain the within-study correlations for BRMA and the dependence parameters of BRMA-BC model, bootstrapping methods were used (see supplementary material section A.3). The dependence parameters between the summary data had to be estimated as is different than the one use in the data generation process. This is because a Frank copula with Bernoulli marginals was used to generate IPD and a
copula with Binomial marginals is used to model summary binomial data. BRMA-BC models binomial data in each arm at the within-study level on both outcomes jointly using Frank copula with Binomial marginal distributions. However, the dependence parameter of its copula is not the same as the one from the generation process since the marginal distributions are different.

To evaluate which method estimates better the relationship between the surrogate endpoint and the final outcome and derives better estimates of true treatment effects, we stored the following: median between study correlation $\rho_b$; its 95% credible interval (CrI); coverage of $\rho_b$ across 95% CrIs; average bias of $\rho_b$; coverage, average bias and RMSE for the between-studies heterogeneity parameters $\tau_1$ and $\tau_2$, the mean treatment effects $d_1$ and $d_2$, and the true effects $\delta_{1i}$ and $\delta_{2i}$.

3.2 Results

The results of the simulation study are presented in Figures 1, 2, 3 and 4 covering all the scenarios. They present mean bias, coverage across replications and root mean square error (RMSE) for the following estimates: between study correlation estimate $\hat{\rho}_b$ (Fig. 1), between-studies heterogeneity estimate on the second outcome $\hat{\tau}_2$ (Fig. 2), the mean treatment effect estimate on the second outcome $\hat{d}_2$ (Fig. 3) and the true treatment effect estimates on the second outcome $\hat{\delta}_{2i}$ (Fig. 4).

3.2.1 Between-study correlation $\rho_b$

The between study correlation is the main parameter of interest in this paper as it quantifies the study level association between the treatment effects on the surrogate endpoint and the final outcome. Figure 1 shows the performance measures for the estimate of between-study correlation $\hat{\rho}_b$. It can be seen that when the mean true baseline effects on the first $\eta_1$ and the second outcome $\eta_2$ were 0 (left hand side (LHS) plots), BRMA and BRMA-BC models performed very similarly in terms of their average accuracy, coverage and RMSEs regardless of the sample size. As they both take into account the within-study association, there was no difference in their performance across the different strengths of within-study associations. On the other hand, when within-study association was moderate or strong, BRMA-IB was on average the least accurate method resulting also in slightly higher RMSEs and under-coverage compared to the other two methods. Concerning the effect of study sample size, the smaller was the sample size the higher were the average biases and RMSEs were across all methods.

When the proportions of events were approximately 95% (middle plots), BRMA-BC and BRMA-IB methods outperformed BRMA model across all scenarios regardless of the sample size. BRMA model underestimated significantly $\rho_b$ in particular when the arm sample size was small ($N = 80$) resulting in on average the lowest accuracy of the estimates and highest RMSEs. Additionally, in this set of scenarios (middle plots), BRMA-BC was more accurate compared to BRMA-IB when the within-study association was moderate or strong resulting in coverages closer to 95%. On the other hand the RMSEs of BRMA-BC were higher than RMSEs of BRMA-IB. This implies that despite BRMA-BC gave on average less biased estimates, the variance of the estimates was larger compared to BRMA-IB. The estimate of the between study correlation of BRMA-IB was upward biased when $N = 300$ and some under-coverage was also observed when the within-study association was strong.

In the remaining sets of scenarios (right hand side (RHS) plots), BRMA-IB was the best method in the majority of scenarios in terms of average accuracy and RMSE of the estimate of the between-study correlation. Only when the within-study association was strong and the sample size $N = 300$, it was slightly more biased than BRMA-BC. The other two methods substantially underestimated the between study association a lot, however, BRMA-BC was more accurate and its coverage was closer to 95% compared to BRMA across all these scenarios. BRMA model failed to estimate $\rho_b$ as the assumption of normality was unreasonable in these scenarios respectively.
FIGURE 1 Performance of $\hat{\beta}_b$ across 18 scenarios

N=300

Proportions $\approx 0.5$ Proportions $\approx 0.95$ Proportions $\approx 0.98$

Bias Coverage RMSE
Weak within-study association Moderate within-study association Strong within-study association

N=80

Proportions $\approx 0.5$ Proportions $\approx 0.95$ Proportions $\approx 0.98$

Bias Coverage RMSE
Weak within-study association Moderate within-study association Strong within-study association

Model • BRMA ▲ BRMA−BC ■ BRMA−IB
3.2.2 | Between-study variance $\tau_2$

To have a better understanding of the behaviour of the between-study covariance matrix we also monitored the between-study heterogeneity parameters $\tau_1$, $\tau_2$. In this section, we report only the performance of the estimate of $\tau_2$ as $\hat{\tau}_1$ performed in a very similar way. Figure 2 presents the performance of $\hat{\tau}_2$ in terms of average bias, coverage and RMSEs. When the proportions of events were close to 0.5 (LHS plots) all methods were on average accurate, with coverages very close to 95% and small RMSEs regardless of sample size. Only when within-study association was high, BRMA-IB slightly overestimated $\tau_2$ resulting in higher on average bias compared to BRMA-BC and BRMA.

When the proportions of events were approximately 0.95 (middle plots), BRMA model underestimated $\tau_2$ across all strengths of within-study association regardless of the sample size. When $N = 300$, the higher was the strength of the within-study association the more downward biased were the estimates from BRMA. On the other hand, when the sample size was small ($N = 80$) the estimates of $\tau_2$ were equally biased across all the strengths of the within-study association. This indicates that BRMA is performs worse when the sample size is small and the proportion of events is close to one or zero. Note that under- or overestimation of the heterogeneity parameters will affect the estimates of the between-studies correlation, which explains why $\rho_b$ obtained from BRMA was underestimated. BRMA-IB overestimated the heterogeneity parameter $\tau_2$ mainly when the within-study association was moderate or strong and in particular when the sample size was smaller, $N = 80$. This makes clear the upward biased results of $\rho_b$ from this method. Furthermore, some under-coverage was also observed from BRMA model when the within-study association was moderate or strong regardless the sample size and from BRMA-IB when the within-study association was moderate or strong and the sample size $N = 80$. BRMA-BC was the only accurate method in this set of scenarios resulting also in smaller RMSEs and acceptable coverages for $\hat{\tau}_2$.

In the final set of scenarios (RHS plots), BRMA-BC was again superior compared to BRMA and BRMA-IB models. It yielded the most robust results achieving acceptable coverages when $N = 300$, on average very accurate estimates and relatively small RMSEs. In contrast to BRMA-BC, BRMA and BRMA-IB models performed poorly having similar patterns as in the previous set of scenarios. In this case, they had even more biased estimates and larger RMSEs compared to the previous set of scenarios. Concerning the effect of within-study association when $N = 300$, the stronger is the association, BRMA model is expected to underestimate the heterogeneity parameters, whereas BRMA-IB to overestimate them. These findings show that BRMA model is completely inappropriate method in such scenarios. Furthermore, this indicates that BRMA-IB estimated $\rho_b$ unrealistically accurately, in scenarios where it was not possible due to the small sample size and the extremely high proportion of events, since it substantially overestimated the heterogeneity parameters. BRMA-IB was also the most sensitive method to the effect of sample size as its RMSEs were significantly larger compared to any other method when the sample size was small ($N = 80$) and its biases were much larger compared to the set of scenarios with $N = 300$. 
FIGURE 2 Performance of $\hat{\tau}$ across 18 scenarios

N=300

| Proportions $\approx 0.5$ | Proportions $\approx 0.95$ | Proportions $\approx 0.98$ |
|--------------------------|--------------------------|--------------------------|
| Bias                     |                          |                          |
| Coverage                 |                          |                          |
| RMSE                     |                          |                          |

N=80

| Proportions $\approx 0.5$ | Proportions $\approx 0.95$ | Proportions $\approx 0.98$ |
|--------------------------|--------------------------|--------------------------|
| Bias                     |                          |                          |
| Coverage                 |                          |                          |
| RMSE                     |                          |                          |

Model: BRMA, BRMA-BC, BRMA-IB
3.2.3 True treatment effects $\delta_{2i}$ and mean treatment effects $d_2$

In this section we present the results from the pooled estimate $d_2$ across all the models and scenarios, as well as, the true treatment effects $\delta_{2i}$. In the general meta-analytic framework the mean treatment effects are the main parameters of interest. However, in the context surrogate endpoints $\delta_{2i}$ correspond to the true treatment effects on the final outcome. These are the effects we aim to predict using the true treatment effect of a surrogate endpoint. Therefore, it is crucial to assess and compare the performance of the estimates of $\delta_{2i}$ from BRMA model and the proposed methods.

First we discuss the performance of the pooled estimate $\hat{d}_2$. Figure 3 presents the performance of $\hat{d}_2$ by monitoring the average bias, the coverage and RMSEs across the 18 scenarios. We decided to present results from $\hat{d}_2$ and $\hat{\delta}_{2i}$, as the estimates on the the first outcome performed almost identical. When the proportions of events were approximately 0.5 (LHS plots) and the sample size $N = 300$ all methods performed well and in a very similar way. BRMA-IB was the most sensitive to the effect of sample size resulting in higher biases and reduced coverages compared to BRMA and BRMA-BC when the sample size was small and the within-study association moderate or strong.

When then the proportions of events were approximately 95% (middle plots) BRMA gives downward biased estimates of $d_2$, reduced coverages and for scenarios with $N = 300$ higher RMSEs compared to the proposed methods, indicating that the assumption of normality was not reasonable. Another interesting finding was the effect of within-study association on the estimates of $d_2$. The stronger was the within-study association the more downward biased were the estimates from BRMA. On the other hand, BRMA-BC was quite accurate across all the scenarios for $N = 300$ and having the lowest RMSEs across scenarios for $N = 80$.

In the remaining scenarios (RHS plots) BRMA-BC and BRMA-IB performed very similarly. However, when the sample size was small and the proportion of events high ($\eta_{1,2} = 4$ and $N = 80$) BRMA-IB performed poorly. The estimates from BRMA model remained biased method across these scenarios, although it copes slightly better with the small sample size and the high proportion of events compared to BRMA-IB.

Figure 4 presents the average bias, the coverage and RMSEs of $\hat{\delta}_{2i}$ across the 18 scenarios. The main findings were very similar to the analysis of $\hat{d}_2$ and $d_2$. When the proportions of events 50% (LHS plots), BRMA model and BRMA-BC performed well. BRMA-IB is slightly more biased when the within-study association was strong resulting in under-coverage and larger RMSEs of the estimates of $\hat{\delta}_{2i}$.

BRMA model was more biased compared to the other two methods when the proportions of events were 95% and 98%. When the within-study association was weak or moderate, the estimates of the true treatment effect on the second outcome from BRMA-IB and BRMA-BC performed similarly in terms of average accuracy, RMSE and coverage. BRMA-BC outperformed BRMA-IB when the within-study association was moderate or strong resulting in lower RMSEs.
FIGURE 3 Performance of $\hat{d}_2$ across 18 scenarios
**FIGURE 4** Performance of $\hat{\beta}_{21}$ across 18 scenarios

### N=300

| Proportions = 0.5 | Proportions = 0.95 | Proportions = 0.98 |
|-------------------|--------------------|--------------------|
| Bias              | Coverage           | RMSE               |

- Weak within-study association
- Moderate within-study association
- Strong within-study association

### N=80

| Proportions = 0.5 | Proportions = 0.95 | Proportions = 0.98 |
|-------------------|--------------------|--------------------|
| Bias              | Coverage           | RMSE               |

- Weak within-study association
- Moderate within-study association
- Strong within-study association

Model: • BRMA ▲ BRMA-BC ■ BRMA-IB
3.3 | Key findings

A short summary of the key findings from the simulation study is given below:

- The simulation study showed that the normal approximation fails for binary outcomes when the proportions of events are close to one or zero. This confirms findings by Hamza et al.\(^8\) for the univariate case and extends their finding to the bivariate cases. In our simulation study we focused on the performance of the parameters describing the between-studies variability: the between-studies correlation \(\rho_b\) and heterogeneity parameters \(\tau_1, \tau_2\). When the proportions of events are close to 0.5 (\(\eta_{1,2} = 0\)), there is no clear difference between BRMA model and BRMA-BC as they performed very similarly and sufficiently well. However, when the proportions of events are high, BRMA yielded poor coverages, large RMSEs and biased estimates of \(\rho_b, \tau_{1,2}, d_{1,2}\) and \(\delta_{1,2}\). Therefore, BRMA model is not appropriate to estimate the study level association for binary outcomes with very large probabilities of events.

- Another aim of the simulation study was to explore the impact of the within-study association on the estimation of the between-studies variability across methods. BRMA-IB model was the most sensitive method by far. This model assumes that events are independent and binomially distributed across outcomes. This assumption makes the model quite robust when the proportions of events are high and the within-study association is small, but inappropriate when the within-study association is moderate or strong. When the proportions of events were high, higher within-study association led to poorer coverage and larger RMSEs. Overall, BRMA-IB is a reliable method only when within-study association is small. In any other case it should be avoided as it overestimates the between study heterogeneity and gives estimates of true treatment effect with higher RMSEs compared to BRMA-BC. This behaviour leads to unrealistically accurate and precise estimates of \(\rho_b\) in some scenarios where, study size is small and the proportions extremely high (small within-study variability).

- The simulation study also investigated the effect of sample size by having two sets of scenarios. Overall, smaller sample size results in higher biases and larger RMSEs across all methods. BRMA-IB model was most sensitive to the effect of sample size. Small sample and proportions of events close to one or zero make BRMA-IB model inappropriate for modelling correlated binary outcomes. For instance, when \(N = 80\) and the proportions of events were 98%, BRMA-IB performed worse than BRMA in terms of bias and RMSE of \(\hat{\tau}_2, \hat{d}_2\) and \(\hat{\delta}_2\) in this scenario. On the other hand when sample size was large (\(N = 300\)), BRMA model yielded more biased estimates as the strength of within-study association increased. We did not, however, observe the same behaviour when the sample size was small (\(N = 80\)). Overall, BRMA-BC was less sensitive to the effect of sample size across all scenarios.

- BRMA-BC is the most appropriate method to investigate the study level association between treatment effects on two binary outcomes. The model performed sufficiently well under any setting without over/underestimating the between-studies variances. There were scenarios in the simulation study, where it failed to estimate \(\rho_b\) as accurately and precisely as BRMA-IB. This was due to the extremely high proportion of events. In practice, investigating between-studies association between binomial endpoints with proportions of events close to one or zero will require sufficiently large sample size. This will allow the model to estimate the between-studies correlation accurately and with good precision.

4 | DATA EXAMPLE

CML is a myeloproliferative neoplasm of hematopoietic stem cells associated with a characteristic chromosomal translocation called the Philadelphia chromosome. The main characteristic is that CML is regarded as a slow progressive disease. Before the molecular pathogenesis of the disease was well understood, the median survival was 6 years, with a predicted 5-year overall survival (OS) of 47.2%.\(^{13}\) However, the introduction of tyrosine kinase inhibitor (TKI) therapies has led to dramatically improved long-term survival rates since 2001 resulting in high response rates of complete cytogenetic response (CCyR) at 12 months and very few events such as loss of response (e.g complete cytogenetic response, major molecular response etc.), progression to accelerated phase (AP) or blast crisis (BC) and death from any cause. To illustrate the proposed methods and compare them with BRMA model we identified 10 studies comparing first generation TKI therapies (e.g 400mg imatinib) with second generation TKIs (e.g. dasatinib, nilotinib,busotinib) or different doses of first generation TKIs (600mg or 800mg imatinib). We selected to evaluate the study level association between two binary outcomes, CCyR at 12 months and event-free survival (EFS) at 24 months. We chose CCyR at 12 months as it has been extensively used in the literature as a gold standard for a good measure of response and EFS at 24 months as it is very significant in view of the dismal prognosis of the patients.
proceeding to advanced stages or losing response. Table 1 presents the summarised responses in the treatment and the control arm on both outcomes along with the sample size per arm and outcome. To work with positive correlations we measured the number of patients who were event-free at 24 months EFS.

### TABLE 1 Summarised data in CML

| Study name     | Control arm | Treatment arm | Control arm | Treatment arm |
|----------------|-------------|---------------|-------------|---------------|
| Cortes 2012    | 252         | 171           | 250         | 175           |
| Kantarjian 2010| 260         | 189           | 259         | 216           |
| Radich 2012    | 61          | 42            | 70          | 59            |
| Saglio 2010    | 243         | 184           | 236         | 219           |
| Baccarani 2009 | 108         | 63            | 108         | 69            |
| Preudhomme 2010| 158         | 92            | 160         | 104           |
| Hehlmann 2011  | 306         | 151           | 328         | 206           |
| Cortes 2010    | 157         | 103           | 319         | 223           |
| Deininger 2013 | 49          | 33            | 41          | 35            |
| Wang 2015      | 133         | 107           | 134         | 104           |

4.1 Results

The aim of our analysis was to evaluate the study level surrogate relationship between the candidate endpoint (CCyR) at 12 months and the final outcome (EFS) at 24 months using the proposed methods and the BRMA model. As IPD were not available from any of these studies, we were unable to estimate the dependence parameters of BRMA-BC and Pearson’s within-study correlation of BRMA and instead we placed informative prior distributions on these parameters. To construct informative prior distributions we used three cohort studies. These studies measured the impact of achieving a CCyR at 12 months on longer term outcomes by reporting rates of EFS for patients who did or did not achieve CCyR at 12 months. Having these rates we could create pseudo IPD, and hence calculate the within-study association parameters with uncertainty by using a double bootstrap method (see more details in the section A.4 of the supplementary material). Figure 5 shows the three probability densities derived from the external evidence using the double bootstrap method. The first density corresponds to the Pearson’s within-study correlation $\rho_w$ used to populate BRMA model and the other two are prior distributions for the dependence parameters $\theta_A$ and $\theta_B$ of BRMA-BC.

![FIGURE 5 Within-study associations](image)
We assumed the same prior knowledge for the within-study association parameters across all studies. The remaining parameters have the same prior distributions as in the simulation study. Figure 6 presents the posterior distributions from the between-studies correlation parameter $\rho_b$ across models.

**FIGURE 6** Posterior distributions of $\rho_b$ across models

BRMA model yielded a posterior distribution of $\rho_b$ with significantly smaller median (0.37), while the scale and the shape of the posterior distribution was flatter compared to the posterior distribution of BRMA-IB and BRMA-BC. In the simulation study BRMA underestimated the study level association in similar sets of scenarios, hence we can infer that BRMA model fails to capture part of the between-studies association due to high proportions of events across studies on EFS. On the other hand, the shape of the posterior distributions from BRMA-BC and BRMA-IB were very similar. The median of the posterior distribution of BRMA-IB was 0.60 and the median of BRMA-BC was 0.52. This can potentially imply that the estimate from BRMA-IB was slightly biased, as in the simulation study the estimates of $\rho_b$ from BRMA-IB were upward biased in most of the scenarios.

To investigate further the performance of the models we monitored the between-study heterogeneity parameters $\tau_1$ and $\tau_2$ as well as the pooled treatment effects $d_1$ and $d_2$. Table 2 presents the results of the between-studies estimates.

**TABLE 2** Between-studies estimates across models

| Models | BRMA | BRMA-BC | BRMA-IB |
|--------|------|---------|---------|
| Measures | Mean(Median) | 95% CrI | Median(Mean) | 95% CrI | Median(Mean) | 95% CrI |
| Parameters | | | | | | |
| $\rho_b$ | 0.23(0.37) | (-0.93, 0.97) | 0.35(0.52) | (-0.87, 0.97) | 0.44(0.60) | (-0.84, 0.98) |
| $\tau_1$ | 0.40(0.38) | (0.11, 0.83) | 0.45(0.42) | (0.17, 0.90) | 0.46(0.43) | (0.14, 0.95) |
| $\tau_2$ | 0.25(0.21) | (0.01, 0.72) | 0.28(0.24) | (0.01, 0.81) | 0.33(0.30) | (0.01, 0.91) |
| $d_1$ | 0.45(0.45) | (0.14, 0.78) | 0.48(0.48) | (0.15, 0.82) | 0.49(0.49) | (0.12, 0.83) |
| $d_2$ | 0.27(0.27) | (-0.05, 0.61) | 0.30(0.29) | (-0.02, 0.63) | 0.30(0.29) | (-0.04, 0.70) |

BRMA-BC and BRMA-IB yielded higher values for the estimates of between-studies heterogeneity parameters compared to BRMA model. This agrees with the findings of the simulation study, as when the response rates were high, BRMA model underestimated the between-study heterogeneity. On the other hand, since BRMA-IB ignored the within-study association it yielded more uncertainty around the estimates of pooled effects. This is in agreement with the findings by Riley et al. They proved the importance of taking into account the within-study correlation when BRMA model is used. When BRMA model ignores the within-study association it also yields pooled estimates with larger uncertainty. BRMA-BC resulted in increased uncertainty around the pooled estimate $d_1$ compared to BRMA model. This potentially is related to the smaller values of between-studies variance or to the accuracy of the bootstrap method. Overall, the study level association was suboptimal as the credible intervals of $\rho_b$ were very wide, spanning almost from -1 to 1. This implies that CCyR at 12 months is not valid surrogate endpoint for EFS at 24 months. This is possibly due to the lack of evidence of treatment effect on EFS at 24 months, as many studies
have previously reported\cite{Papanikos2014,Papanikos2016}. It indicates that long-term outcomes should be used for the validation of CCyR at 12 months. However, this is not feasible, as very few studies report EFS at 5 or 7 years.

5 | DISCUSSION

We have developed two methods for bivariate random effects meta-analysis of binomial data which allow for modelling the within-study variability using exact binomial likelihoods. The proposed methods offer a robust framework for meta-analysis of binary outcomes avoiding the use of an unreliable approximation of normality for log odds ratios. In this paper, we used these methods for the evaluation of study level surrogate relationship between treatment effects on binary outcomes for novel targeted therapies, where the increased effectiveness of these treatments often leads to high number of responses and reduced number of events. In our case study of highly effective TKI therapies in CML, the validation of CCyR as a surrogate endpoint to EFS (or OS) has been extremely challenging, due to such high response rates and very few events recorded over the duration of each trial. Standard meta-analytic methods, such as BRMA model, can model the observed treatment effects at the within-study level using a bivariate normal distribution of log odds ratios. Although this approach takes into account the within-study association, the assumption of normality is often unreasonable leading to biased results. BRMA-IB model is a more restrictive method of the two we propose. It models the within-study variability using binomial likelihoods, however, these likelihoods are independent therefore the method does not take into account the within-study association. BRMA-BC is more flexible as it models the summarised events on the surrogate endpoint and the final outcome in each arm jointly. This is more appropriate as the number of events on both outcomes are obtained from the same patients.

BRMA-IB model performs well when the proportions of events are high and the within-study association is weak, giving more accurate estimates and smaller RMSEs compared to BRMA model. However, in scenarios where the within-study association is strong or moderate the model fails to estimate well the between-study heterogeneity, giving upward biased estimates of the between-studies correlations and standard deviations; $\rho_b$ and $r_{1,2}$, higher RMSEs and unreasonably low coverage probabilities. In the extreme set of scenarios (proportions of events $\approx 0.98$), the method estimated $\rho_b$ unrealistically well. This occurred due to the heterogeneity parameters and the true treatment effects being substantially overestimated by this model.

BRMA-BC is the most robust model to quantify the study level association as it takes into account within-study associations whilst avoiding the use of the assumption of normality at the within-study level. In particular the model does not over/underestimate the heterogeneity parameters $r_{1,2}$. This lead to more reasonable estimates of the between-study correlation $\rho_b$. Overall, across the 18 scenarios of the simulation study, BRMA-BC model was superior to BRMA model. However, there were some extreme scenarios where it failed to yield as accurate estimates of $\rho_b$ as BRMA-IB model. For instance, when the proportions of events were $\approx 0.98$, BRMA-BC model yielded on average downward biased estimates of $\rho_b$ regardless of sample size. However, this was due to small sample and the very small number of non-events which makes the estimation of $\rho_b$ extremely difficult. Therefore, when the proportions of events are extremely high, we need very large sample sizes in order to estimate $\rho_b$ accurately and precisely.

In the illustrative example, all methods found the study level association between CCyR at 12 months and EFS at 24 months suboptimal as the 95% CrI of $\rho_b$ was extremely wide, spanning almost from -1 to 1. However, BRMA-BC model gave larger estimates of the median between-study correlation $\rho_b$ and the median between-studies standard deviations $r_1, r_2$ compared to BRMA model. Overall, the posterior distribution of $\rho_b$ from BRMA model was much flatter compared to the other two models. This behaviour is in agreement with the findings from the simulation study. Additionally, BRMA-BC model gave slightly better predictions in terms of uncertainty and errors.

Although BRMA-BC model provided robust results in a variety of scenarios, potential limitations should always be kept in mind. First, in order to perform Bayesian inference, we had to run Hamiltonian Monte Carlo (HMC) with Rstan\cite{Stan2018}. The model was very sensitive to initial values, making difficult the initiation of the HMC process. We solved this problem by fitting BRMA-IB or BRMA models first and then we used their estimates as initial values for BRMA-BC model.

A limitation of the illustrative example was the lack of IPD. We informed the prior distributions of within-study association parameters using 3 cohort studies. We constructed binary pseudo IPD and hence calculated the within-study association between the number responses on the surrogate endpoint and the within-study association between the number of events on the final outcome by using a double bootstrap method to account for uncertainty. Furthermore, the definition of EFS varies across these studies. Some studies present it as PFS, some others include more types of events in their definition than others. However, by excluding a small studies where EFS was defined slightly differently did not affect the results and our inferences.
BRMA-BC can be extended in a number of ways. For instance, it can be extended by using also a copula at the between-study level in a similar way as in Nikolopoulos et al. This will allow to model the study level association on the true scale (proportions of events) with beta marginal distributions avoiding the logit transformation. Furthermore, taking advantage of the setting proposed by Bujkiewicz et al., BRMA-BC can be extended to allow for modelling multiple surrogate endpoints (or the same surrogate endpoint but reported at multiple time points) via a vine-copula. Furthermore, we used only Frank copula to construct the joint densities at the within-study level of BRMA-BC model, but other copulas with various dependence structures can be used. However, this is out of the scope of this paper. We performed a short sensitivity analysis fitting BRMA-BC with Gumbel copula and the performance of the model was very similar. In general, when data are sparse (such as in meta-analysis of aggregate data) it is very challenging to capture the exact dependence structure, and therefore different copula functions have small impact on the performance of the model in such cases.

In summary we developed Bayesian hierarchical meta-analytic methods to perform bivariate meta-analysis of binary outcomes and particularly, to quantify the study level surrogate relationship. In our view, BRMA-BC is a preferred model for modelling binary outcomes in the context of surrogate endpoints, as well as, in the general meta-analytic framework. The model can improve the process of the validation of surrogate endpoints in the era of personalised medicine where the increased effectiveness of targeted treatments often leads to high number of responses and reduces the number of events.

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