Received: 17 January 2024 | Revised: 9 May 2024 | Accepted: 26 June 2024

DOI: 10.1002/jrsm.1737

RESEARCH ARTICLE

Research Synthesis Methods WILEY

Calculating the power of a planned individual participant data meta-analysis to examine prognostic factor effects for a binary outcome

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Funding information
Engineering & Physical Sciences Research Council (EPSRC), Grant/Award Number: EP/Y018516/1; Medical Research Council - National Institute for Health and Care Research (MRC-NIHR), Grant/Award Number: MR/V038168/1; Cancer Research UK, Grant/Award Number: C49297/A27294

Abstract

Collecting data for an individual participant data meta-analysis (IPDMA) project can be time consuming and resource intensive and could still have insufficient power to answer the question of interest. Therefore, researchers should consider the power of their planned IPDMA before collecting IPD. Here we propose a method to estimate the power of a planned IPDMA project aiming to synthesise multiple cohort studies to investigate the (unadjusted or adjusted) effects of potential prognostic factors for a binary outcome. We consider both binary and continuous factors and provide a three-step approach to estimating the power in advance of collecting IPD, under an assumption of the true prognostic effect of each factor of interest. The first step uses routinely available (published) aggregate data for each study to approximate Fisher's information matrix and thereby estimate the anticipated variance of the unadjusted prognostic factor effect in each study. These variances are then used in step 2 to estimate the anticipated variance of the summary prognostic effect from the IPDMA. Finally, step 3 uses this variance to estimate the corresponding IPDMA power, based on a two-sided Wald test and the assumed true effect. Extensions are provided to adjust the power calculation for the presence of additional covariates correlated with the prognostic factor of interest (by using a variance inflation factor) and to allow for between-study heterogeneity in prognostic effects. An example is provided for illustration, and Stata code is supplied to enable researchers to implement the method.

KEYWORDS

individual participant data (IPD) meta-analysis, power, predictor effects, prognostic factor effects, sample size

Highlights

What Is Already Known?

- The use of individual participant data (IPD) for a meta-analysis can increase the quantity and quality of data, often improving the power available to examine the effects of a prognostic factor over using a single study or a traditional meta-analysis.
- However, IPD meta-analysis studies can be costly and time consuming, hence reassurance is needed that the project will be worth the additional resource and time, especially with respect to the power available.

What Is New?

- We provide analytic solutions to estimate the power of a planned IPD meta-analysis project, where the primary objective is to examine the (unadjusted or adjusted) effect of a prognostic factor on a binary outcome.
- The calculations provided allow the power to be estimated prior to IPD collection, using data that is usually reported in study publications such as the total number of events, participants in each group of a binary prognostic factor, or characteristics of a continuous factor (e.g., mean and standard deviation)

Potential Impact for *Research Synthesis Methods* Readers

- The methods provided can be used by researchers in any field conducting an IPD meta-analysis to analyse the effects of a binary or continuous factor on a binary outcome, helping them decide on the benefit of the IPD approach in advance of collecting their IPD.
- It could potentially save years' worth of wasted time, or provide reassurance to both researchers and funders that the project will be valuable.

1 | INTRODUCTION

There is a growing demand for meta-analyses that use individual participant data (IPD), which refers to participant level data in a research study. The availability of IPD from existing studies can increase the quantity and quality of data,[1] often improving the power to examine the effects of a covariate compared to using single studies or a traditional meta-analysis of published aggregate data. However, IPD meta-analysis studies can be costly and time consuming. They can take upwards of 2 years to obtain, clean, harmonise and then meta-analyse the IPD. Researchers and funders therefore need reassurance that IPD meta-analysis projects are worth the additional resource and time, especially with respect to the number of studies that are likely to provide IPD and the power of an IPD meta-analysis using this data.

Power and sample size calculations are seldom considered in protocols and publications of IPD meta-analysis projects, but if known prior to data collection that the project would have high power, it could give reassurance to researchers and funders that the project is worth investing in. Conversely, if the planned IPD meta-analysis has low power to detect a clinically important effect then researchers may reconsider the design or funders may reconsider investing in the project.

Previous work has focused on calculating (before IPD collection) the power of an IPD meta-analysis of randomised trials to identify a treatment-covariate interaction for continuous,[2] binary[3] and survival outcomes.[4] However, IPD meta-analysis projects have many other potential research questions, enabling many types of analysis to be performed that are not feasible with only aggregate data. One common application is to identify prognostic factors—variables (covariates) whose values are associated with changes in outcome risk (e.g., stage of disease in cancer prognosis). Prognostic factors inform clinical decision making and the development of prognostic

models.[5,6] IPD improves meta-analysis of prognostic effects allowing for better modelling of continuous prognostic factors (e.g., without dichotomisation) and routine adjustment for known prognostic factors already used in practice.

In this article, we propose methodology to estimate the power of a planned IPD meta-analysis project, before IPD collection, where the primary objective is to examine the effect of a (potential) prognostic factor on a binary outcome. The outline of the paper is as follows. In Section 2, we lay the foundation of the work presented by describing a two-stage approach to estimating a prognostic effect in an IPD meta-analysis with a binary outcome. Section 3 describes the method for calculating the variance of a binary and continuous prognostic effect estimate in a single study. Section 4 uses these methods in a three-step approach to estimate the power of the planned IPD meta-analysis of prognostic factors. Briefly, the three steps are: (1) estimate the anticipated variance of the prognostic factor effect for each study separately; (2) estimate the anticipated variance of the prognostic factor effect from the planned IPD meta-analysis; (3) use this estimated variance to calculate the corresponding power of the planned IPD meta-analysis. The methods are extended in Section 4.4, adjusting for the presence of additional adjustment factors correlated with the prognostic factor of interest by using a variance inflation factor. Section 5 provides an example illustration of the proposed methods. Section 6 provides a further extension to allow for between-study heterogeneity and we discuss our work in Section 7.

2 | A TWO-STAGE APPROACH TO ESTIMATING A PROGNOSTIC EFFECT IN AN IPD META-ANALYSIS WITH A BINARY OUTCOME

Let us assume that IPD are available from multiple (S) cohort studies with a binary outcome. In the first stage of a two-stage IPD meta-analysis, the effect parameters are estimated using the IPD for each study individually. In the second stage, the prognostic effect estimates are pooled using a meta-analysis model.[7] We focus on this two-stage approach as by only pooling prognostic effect parameters derived from within-study information (i.e., based at the participant-level), it automatically avoids study-level confounding and aggregation bias that may occur in meta-regression based on across-study information,[8,9] or in one-stage IPD meta-analysis models that do not separate out within-study and across-study prognostic relationships.[10] Both stages of the two-stage approach can be implemented using *ipdmetan* in Stata,[11] or using R packages (e.g., metafor[12]) that implement the second stage.

2.1 | First-stage

For each of S cohort studies, consider a variable x_{ij} denoting a participant level prognostic factor of interest (e.g., the sex of participant j in study i), observed for all participants in each study, and a variable y_{ij} denoting a binary outcome of interest (i.e., $y_{ij} = 0$ or 1, where 0 denotes no event and 1 denotes event occurred). To estimate the prognostic factor parameter in each study separately, S logistic regression models could be fitted:

$$\begin{aligned} y_{ij} &\sim \text{Bernoulli}\left(p_{ij}\right) \\ \ln\left(\frac{p_{ij}}{1-p_{ij}}\right) &= \alpha_i + \beta_i x_{ij} \end{aligned} \tag{1}$$

where p_{ij} is the probability of the outcome event for participant j in study i, and estimated using maximum likelihood estimation. The prognostic factor parameter for each study is denoted by β_i, which represents the unadjusted log odds ratio (change in log odds) for a 1-unit increase in x_{ij}. This first stage leads to S estimates of the parameter, one for each of the $i = 1$ to S studies included in the IPD.

For a continuous prognostic factor, the model assumes the effect of the factor on the log odds of the outcome event is linear. Although in practice non-linear trends might be modelled, we provide a power calculation assuming linear effects as this makes the approach more practical in advance of getting the actual IPD, as specifying an assumed linear trend is easier than a non-linear trend. However, we suspect larger sample sizes would be needed to detect a non-linear relationship. In this section we focus on unadjusted effects, adjustment for additional prognostic factors will be considered in Section 4.4.

2.2 | Second stage

The first stage of an IPD meta-analysis produces S estimates of the prognostic effect parameter ($\hat{\beta}_i$) and its variance ($\text{var}(\hat{\beta}_i)$). In the second stage, the $\hat{\beta}_i$ values are combined using either a common-effect model (i.e., the true prognostic effect is assumed the same in all studies, denoted by β),

$$\hat{\beta}_i \sim N\left(\beta, \text{var}\left(\hat{\beta}_i\right)\right) \quad (2)$$

or a random-effects model (i.e., the true prognostic effects are assumed random across studies, drawn randomly from a normal distribution with a mean of β and between-study variance of τ^2):

$$\begin{aligned} \hat{\beta}_i &\sim N\left(\beta_i, \text{var}\left(\hat{\beta}_i\right)\right) \\ \beta_i &\sim N\left(\beta, \tau^2\right) \end{aligned} \quad (3)$$

Restricted maximum likelihood (REML) is recommended to fit model Equation (3).[13] The summary estimate of β will be a weighted average and summarises the difference in the log odds in participants with a one unit increase in x.

For the common-effect model, the variance of the summary prognostic effect parameter is:

$$\text{var}\left(\hat{\beta}\right) = \frac{1}{\sum_{i=1}^{S}\left(\text{var}\left(\hat{\beta}_i\right)\right)^{-1}} \quad (4)$$

where S is the total number of studies in the IPD meta-analysis.

For the random-effects model, the variance of the summary prognostic effect parameter is:

$$\text{var}\left(\hat{\beta}\right) = \frac{1}{\sum_{i=1}^{S}\left(\text{var}\left(\hat{\beta}_i\right) + \hat{\tau}^2\right)^{-1}} \quad (5)$$

To consider the potential power of an IPD meta-analysis project, the expected value of the variance of $\hat{\beta}$ (i.e., $\text{var}\left(\hat{\beta}\right)$) needs to be determined in advance. Fundamentally, this depends on the study variances (i.e., the $\text{var}\left(\hat{\beta}_i\right)$), and so Section 3 describes how these may be ascertained in advance of IPD collection.

3 | ESTIMATING THE VARIANCE OF AN UNADJUSTED PROGNOSTIC EFFECT ESTIMATE FOR A BINARY OUTCOME IN A SINGLE STUDY

In the following sections we propose methods to use and amend previous work by Demidenko et al.[14] and Riley et al.[3] to estimate the variance of a prognostic factor effect to then calculate the power of a planned IPD meta-analysis examining prognostic effects in studies with a binary outcome.

3.1 | Binary prognostic factor

Let x_{ij} be a binary covariate, such as $x_{ij} = 1$ for males and $x_{ij} = 0$ for females. After fitting the logistic regression model in Equation (1) to the IPD in a single study, the variance of $\hat{\beta}_i$ is:

$$\text{var}\left(\hat{\beta}_i\right) = \boldsymbol{I}_{\boldsymbol{i}}^{-1}(2,2)/n_i \quad (6)$$

where n_i is the total sample size of study i, and $\boldsymbol{I}_{\boldsymbol{i}}^{-1}(2,2)$ denotes the 2,2 element of the inverse of Fisher's unit information matrix ($\boldsymbol{I}$).

Let the design matrix $\boldsymbol{X} = \left(1, x_{ij}\right)'$, then the 2 by 2 unit information matrix for a particular study can be expressed as:

$$\boldsymbol{I}_{\boldsymbol{i}} = E_{x_i}\left(p_{ij}\left(1-p_{ij}\right)\boldsymbol{X}\boldsymbol{X}'\right) \quad (7)$$

where $E_{x_i}\left(p_{ij}\left(1-p_{ij}\right)\boldsymbol{X}\boldsymbol{X}'\right)$ refers to the expected value of $p_{ij}\left(1-p_{ij}\right)\boldsymbol{X}\boldsymbol{X}'$ over the distribution of x_i, and:

$$p_{ij} = \frac{\exp\left(\alpha_i + \beta_i x_{ij}\right)}{1 + \exp\left(\alpha_i + \beta_i x_{ij}\right)}$$

and

$$\boldsymbol{X}\boldsymbol{X}' = \begin{bmatrix} 1 & x_{ij} \\ x_{ij} & x_{ij}^2 \end{bmatrix}$$

Note that technically $\boldsymbol{X}$ might be labelled $\boldsymbol{X}_{\boldsymbol{i}}$, to emphasise it is study-specific (as each study is analysed in the first stage of the two-stage approach), but we retain just $\boldsymbol{X}$ for brevity here.

Hence, recognising that x_{ij} is binary, so is equal to either 0 or 1, the Fisher's unit information matrix in Equation (6) can be simplified to:

$$\boldsymbol{I}_{\boldsymbol{i}} = E_{x_i}\left(\frac{\exp\left(\alpha_i + \beta_i x_{ij}\right)}{\left(1 + \exp\left(\alpha_i + \beta_i x_{ij}\right)\right)^2}\begin{bmatrix} 1 & x_{ij} \\ x_{ij} & x_{ij} \end{bmatrix}\right) \quad (8)$$

An expansion of the simplification of the Fisher's unit information in Equation (6) to the solution in Equation (8) can be found in the Supplementary Material. For a binary covariate, this can be expanded to a closed-form solution of,

$$\boldsymbol{I_i} = \frac{\exp(\alpha_i)}{(1+\exp(\alpha_i))^2}\boldsymbol{M}_1 \Pr(x_{ij}=0) + \frac{\exp(\alpha_i+\beta_i)}{(1+\exp(\alpha_i+\beta_i))^2}\boldsymbol{M}_2 \Pr(x_{ij}=1) \quad (9)$$

where $\Pr(x_{ij}=0)$ and $\Pr(x_{ij}=1)$ denote the marginal probability of x being 0 and 1, respectively, and:

$$\boldsymbol{M}_1 = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix} \boldsymbol{M}_2 = \begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}$$

Thus, to derive the unit information matrix after fitting the logistic regression of Equation (1) to a particular study, the assumed values of parameters α_i and β_i need to be specified along with the probabilities $\Pr(x_{ij}=0)$ and $\Pr(x_{ij}=1)$, which are estimated as the proportion of participants in the study classified as $x=0$ and the proportion classified as $x=1$. The asymptotic variance of the prognostic effect estimate can then be derived using Equation (6). This will be extended to the IPD meta-analysis setting in Section 4.

3.2 | Continuous prognostic factor

For a continuous covariate, using both Equations (6) and (8) again, the Fisher unit information matrix for each study separately can be written as:

$$\begin{aligned} \boldsymbol{I_i} &= E_{x_i}\left(\frac{\exp(\alpha_i+\beta_i x_{ij})}{(1+\exp(\alpha_i+\beta_i x_{ij}))^2}\boldsymbol{X}\boldsymbol{X}'\right) \\ &= E_{x_i}\left(\frac{\exp(\alpha_i+\beta_i x_{ij})}{(1+\exp(\alpha_i+\beta_i x_{ij}))^2}\begin{bmatrix} 1 & x_{ij} \\ x_{ij} & x_{ij}^2 \end{bmatrix}\right) \\ &= E_{x_i}(\boldsymbol{B}) \end{aligned} \quad (10)$$

where $\boldsymbol{B}$ is a 2 by 2 matrix.

The expected value $(E_{x_i}(\boldsymbol{B}))$ now depends on the distribution of the continuous covariate and on the values of the logistic regression parameters (α_i and β_j). Hence, it is not possible to modify Equation (8) into a closed form solution for $\boldsymbol{I_i}$. One way to derive $E_{x_i}(\boldsymbol{B})$ post estimation is to calculate each of the 4 components of $\boldsymbol{B}$ for each participant in the study using the estimated logistic regression parameters and then their means provide the expected values and thus form $\boldsymbol{I}$. The asymptotic variance of the prognostic effect parameter can then be derived using Equation (6).

4 | ESTIMATING THE POWER OF A POTENTIAL IPD META-ANALYSIS PROJECT TO ESTIMATE A PROGNOSTIC EFFECT WITH A BINARY OUTCOME USING A THREE-STEP PROCESS

Assuming that studies from which IPD are requested have not reported prognostic effects for the factor of interest (and their variances), and that information regarding number of outcome events in each group of a binary prognostic factor are not available, we aim to estimate the power of an IPD meta-analysis project in advance of the collecting the IPD.

The overall power of the IPD meta-analysis is a function of the estimated variances of the study-specific prognostic factor effects ($\text{var}(\hat{\beta}_i)$), rather than simply the sum of the power of each study. We now propose a three step approach to calculate the power.

Step 1 describes how to derive an estimate of the anticipated variance of the prognostic factor ($\text{var}(\hat{\beta}_i)$) for each study using routinely reported aggregate data from study publications, alongside assumptions about the prognostic effect size in each study and (for continuous factors) the distribution of the prognostic factor. Step 2 uses these estimated variances to derive an estimate of the anticipated variance of the meta-analysis summary result for the prognostic effect parameter. Then step 3 derives the power of the planned IPD meta-analysis using the values obtained in step 1 and step 2.

4.1 | Step 1: Estimate the variance of the prognostic factor effect separately for each study in the planned IPD meta-analysis

4.1.1 | Binary prognostic factor

The first step is to apply Equation (9) in each study promising IPD, followed by Equation (6) to obtain an estimate of $\text{var}(\hat{\beta}_i)$.

To approximate this before IPD collection, the following aggregate data are needed from each study:

1. Total participants in the study (n_i)
2. Total number of events (e_i)
3. Total participants with $x_{ij}=1$ ($n_{i,1}$)
4. Total participants with $x_{ij}=0$ ($n_{i,0}$)

Assumptions need to be made about the values of parameters α_i and β_i. Previous work[3,6,15] suggests identifying a minimally important value for β_i via discussion

with clinical experts within the IPD meta-analysis project team. It is possible to consider a range of potential β_i values and assess the change in power dependent on the assumed value of β_i. It is simplest to assume β is common for all studies (i.e., $\beta_i = \beta$).

Based on the assumed value of β, and the aggregate data extracted, α_i can be estimated using the number of outcome events, the total number of participants and the proportion of $x_{ij} = 1$. If $p_{i,0}$ is defined as the risk (i.e. number of events / total number of participants) of the event occurring in participants with $x = 0$ in study i, and $p_{i,1}$ is the risk of the outcome occurring in patients with $x = 1$ in study i, then by definition:

$$\begin{aligned}\alpha_i &= \ln\left(\frac{p_{i,0}}{1-p_{i,0}}\right) \\ &= \ln\left(\frac{p_{i,1}}{1-p_{i,1}}\right) - \beta_i\end{aligned} \tag{11}$$

Note that a weighted average of $p_{i,0}$ and $p_{i,1}$ can be taken to give an approximation of the overall log odds,

$$\ln\left(\frac{p_i}{1-p_i}\right) = \frac{\left(\ln\left(\frac{p_{i,0}}{1-p_{i,0}}\right)n_{i,0} + \ln\left(\frac{p_{i,1}}{1-p_{i,1}}\right)n_{i,1}\right)}{n_i} \tag{12}$$

where p_i is the overall risk in study i, which is assumed to be available alongside $n_{i,0}$ and $n_{i,1}$.

By rearranging Equation (12), an approximation of the log odds in participants with $x = 1$ can be derived:

$$\ln\left(\frac{p_{i,1}}{1-p_{i,1}}\right) = \frac{\left(\ln\left(\frac{p_i}{1-p_i}\right)n_i - \alpha_i n_{i,0}\right)}{n_{i,1}} \tag{13}$$

where p_i represents the overall risk, n_i is the total sample size, and $n_{i,0}$ and $n_{i,1}$ represent the numbers in each group, in study i. Equation (13) can then be substituted into Equation (11) to obtain an estimate of α_i:

$$\alpha_i = \ln\left(\frac{p_i}{1-p_i}\right) - \frac{n_{i,1}}{n_i}\beta_i \tag{14}$$

Further details on Equation (14) are provided in the Supplementary Materials.

Based on the values of α_i (derived from Equation 14) and β_i (assumed based on clinical discussion), and the necessary aggregate data extracted (i.e., p_i, n_i and $n_{i,1}$) from each study, Equation (9) can then be applied followed by Equation (6) to obtain an estimate of $\text{var}(\hat{\beta}_i)$ in each study.

4.1.2 | Continuous prognostic factor

The approach to estimate $\text{var}(\hat{\beta}_i)$ for a continuous covariate is similar, with added specification of the assumed distribution of the continuous prognostic factor. For simplicity, we can assume this to be a normal distribution, with mean and standard deviation (SD) of continuous prognostic factors often reported in study publications.

The aggregate data required from each study publication are:

1. Total participants in the study (n_i)
2. Number of outcome events (e_i)
3. Characteristics to define the continuous prognostic factor's assumed distribution (e.g. mean and SD)

As with the binary prognostic factor setting, assumptions are needed about the values of parameters α_i and β_i. Centring the prognostic factor, x_{ij}, by its mean allows α_i to be approximated by the overall log-odds of the outcome in study i, which is a transformation of the overall risk and should be available from the study publication. Again, it is advised to identify a minimally important value of β_i via discussion with clinical experts or to consider a range of values.

An estimate of $\text{var}(\hat{\beta}_i)$ for each study can then be obtained by estimating Fisher's information matrix as described in Section 3.2. To do this, the following is implemented for each study:

1. Generate a large dataset (e.g., 1 million participants) that mimics the study aggregate data provided with respect to the proportion of patients with the outcome and the distribution of x (e.g., a normal distribution with a specified mean and SD);
2. Calculate $\boldsymbol{I_i} = E_{x_i}(\boldsymbol{B})$ conditional on the specified α_i and β_i values for that study (Equation 10)
3. Use Equation (6) to calculate $\text{var}(\hat{\beta}_i) = \boldsymbol{I_i}^{-1}(2,2)/n_i$

Our Stata code automates this process.

4.2 | Step 2: Estimate the variance of the prognostic factor effect from the planned IPD meta-analysis

Step 1 produces S estimates of $\text{var}(\hat{\beta}_i)$, one for each study. The anticipated variance of the summary prognostic factor parameter estimate from an IPD meta-analysis of these studies can then be estimated, depending on whether step 1 assumed β_i was common or random across studies. When assuming β_i is common (i.e., $\beta_i = \beta$),

Equation (5) can be used to calculate the anticipated estimate of $\mathrm{var}(\hat{\beta})$ for the IPD meta-analysis project:

$$\mathrm{var}(\hat{\beta}) = \frac{1}{\sum_{i=1}^{S}\left(\mathrm{var}(\hat{\beta}_i)\right)^{-1}} \quad (15)$$

4.3 | Step 3: Calculate the power of the planned IPD meta-analysis

The final step is to calculate the power of the planned IPD meta-analysis project to detect β. Assuming a common prognostic factor effect for all studies, and based on a Wald-test and a 5% statistical significance level, the power is approximately:

$$\text{Power} = \Phi\left(-1.96 + \frac{\hat{\beta}}{\sqrt{\mathrm{var}(\hat{\beta})}}\right) + \Phi\left(-1.96 - \frac{\hat{\beta}}{\sqrt{\mathrm{var}(\hat{\beta})}}\right) \quad (16)$$

Here, $\Phi(z)$ is the probability of sampling a value $< z$ from a standard normal distribution, $\mathrm{var}(\hat{\beta})$ is the anticipated variance of the summary prognostic effect estimate (as obtained in step 2), and $\hat{\beta}$ can be replaced with the assumed true β (as defined in step 1). This power estimate is usually multiplied by 100 and reported as a percentage.

4.4 | Adjusting for other prognostic factors

The proposed three-step method assumes that the prognostic effect of any other covariate is zero. However, existing prognostic factors are likely to be included and adjusted for in the model and may be correlated with the prognostic factor of primary interest. Hence, the described power formulae would not be valid.[15]

Whittemore[16] has shown that in settings where multiple continuous covariates are adjusted for, the variance of the prognostic factor of interest ($\mathrm{var}(\beta)$) can be approximated by inflating the variance of β obtained in the one covariate (unadjusted) model by the variance inflation factor (VIF). The VIF, ranging upwards from 1, is a measure of the amount of correlation between a set of covariates in a model, measuring how much the variances of estimated regression coefficients are inflated when compared to having uncorrelated covariates. The VIF is defined as:

$$VIF = \frac{1}{1-\rho^2}$$

where ρ is the multiple correlation coefficient, the proportion of the variation in the outcome that is predictable from the prognostic factors, and ranges from 0 to 1. Hsieh et al.[17] has shown that the same VIF also works well for binary covariates.

Hence, to gain a more accurate estimate of the power of a planned IPD meta-analysis when there are other prognostic factors to be adjusted for, step 1 can be completed as described for an unadjusted prognostic effect, but then prior to beginning step 2, each of the S estimates of $\mathrm{var}(\hat{\beta}_i)$ should be multiplied by the VIF to provide estimates of the inflated variances for the S studies. These inflated estimates of $\mathrm{var}(\hat{\beta}_i)$ can then be used in step 2 to estimate the anticipated variance of the summary prognostic factor parameter, which can then be used in step 3 to calculate the power. To allow the estimation of the inflated variances, an assumption of the correlation coefficient value is needed. A pragmatic approach, when information is unavailable, is to assume a moderate value of ρ (e.g., 0.5) or to examine a range of values (e.g., 0.25 to 0.75).

5 | APPLIED EXAMPLE: PROGNOSTIC EFFECT OF AGE AND SEX ON GASTROINTESTINAL BLEEDING IN PATIENTS WITH CIRRHOSIS AND OESOPHAGEAL VARICES

The proposed methods are now applied to an example for illustration. The example considers the power of an IPD meta-analysis conducted by Poynard et al.[18] The project aimed to examine the efficacy of beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding for patients with cirrhosis and oesophageal varices. IPD were obtained from four randomised trials involving a total of 286 patients randomised to active treatment and 383 to a control (placebo).

Here we pretend that IPD are not yet available with the aim to assess whether collecting IPD would allow sufficient power to examine prognostic factors. The data in each trial would be analysed as a cohort study to estimate the prognostic effect of binary sex and continuous age (individually) on the occurrence of gastrointestinal bleeding (rather than treatment effects as in the original trials).

The aggregate trial data are shown in Table 1. Aggregate data in the publications were given by treatment/

Trial	Total participants	Total Events	Age in years: mean (SD)	Male, %
1	230	49	54 (10)	71
2	174	44	54 (11)	70
3	79	12	54 (8)	72
4	106	26	56 (11)	75

TABLE 1 Aggregate data from four randomised trials included in the IPD meta-analysis project of Poynard et al.[18]

control groups, however, as the data have been combined for the purpose of this example, a weighted mean age was calculated as,

$$\text{Overall mean} = \frac{n_C\mu_C + n_T\mu_T}{\text{total participants}}$$

where n_C and n_T are the number of participants in the control and treatment groups, respectively, and μ_C and μ_T are the mean age reported in the control and treatment groups, respectively. The corresponding SD for age was calculated as (see Supplementary Data for more details):

$$\text{SD} = \sqrt{\frac{(n_C-1)\text{SD}_\text{C}^2 + (n_T-1)\text{SD}_\text{T}^2}{n_C+n_T-1} + \frac{n_C n_T(\mu_C-\mu_T)^2}{(n_C+n_T)(n_C+n_T-1)}}$$

The question of interest here is: based on this aggregate data, what is the estimated power of a planned IPD meta-analysis to estimate prognostic effects of sex and age (individually)? We use the three-step process described in Section 4 to undertake the power calculations.

A value (or values) of β need to be assumed to be able calculate the power. Focusing on unadjusted prognostic effect, we assume a range of values from $\beta = \ln(0.5)$ to $\beta = \ln(3)$ and $\beta = \ln(0.95)$ to $\beta = \ln(1.05)$ for the sex and age covariates, respectively. Age is assumed normally distributed in each study, with a mean and SD as given in Table 1.

A selection of the results of the power calculations between the ranges of assumed β values are shown in Supplementary Table 1 for sex and Supplementary Table 2 for age (where ρ=0, VIF = 1), and plots of the calculated powers over the full range of assumed values are given in Figure 1 (where ρ=0). There is a power of 91% to detect the unadjusted assumed prognostic effect of sex with an odds ratio of 0.5, and 99% power to detect an odds ratio of 3. The power decreases significantly the closer the assumed unadjusted odds ratio gets to 1, with only 8% power to detect an odds ratio of 0.9 and 17% power to detect an odds ratio of 1.25. For age (assuming a linear prognostic effect), there is 99% power of detecting an unadjusted odds ratio of 0.95 or 1.05, which again decreases significantly the closer the assumed odds ratio is to 1, with 19% power of detecting an unadjusted odds ratio of 0.99 and 55% power of detecting an odds ratio of 1.02.

5.1 | Adjusting for additional prognostic factors

The methods used for the unadjusted example were repeated for scenarios including additional covariates correlated with the prognostic factor of interest. We assume each factor's unadjusted and adjusted effects are the same; sometimes adjusted effects are more attenuated towards zero, but this is not always the case, and so we considered them to be the same in the calculations that follow for simplicity. Also, the assumed effect represent clinically relevant sizes of interest.

The individual variances of β_i for each study ($\text{var}(\beta_i)$) were multiplied by a VIF prior to calculate the variance of the summary prognostic factor effect. Three different values of ρ (0.25, 0.5 and 0.75) were used to calculate three VIFs, to assess the impact on the power of varying levels of correlation between the prognostic factors.

The results of the power calculations after inflating the variances for the sex covariate, using the same values of β as previously, are given in Supplementary Table 1 and the results for age are given in Supplementary Table 2. Plots of the calculated powers over the range of values for each of the VIFs are given in Figure 1.

The results show that inflating the variances by a VIF of 1.0666 (i.e. $\rho = 0.25$) has a relatively small impact on the power, lowering it by 2.8 percentage points for an assumed OR of 0.6 for sex. However, as ρ is increased, the VIF has a greater impact on the power, reducing it by over 50% when ρ is 0.75 for certain values of β. For example, when the OR for sex is assumed to be 1.5, the power reduces from 41.23% when no adjustment for other covariates is made to 20.98% when adjustment is made with an assumed correlation coefficient of 0.75.

In practice, without other information, assuming a moderate correlation of 0.5 may be a pragmatic choice. In this scenario, this IPD meta-analysis project would be

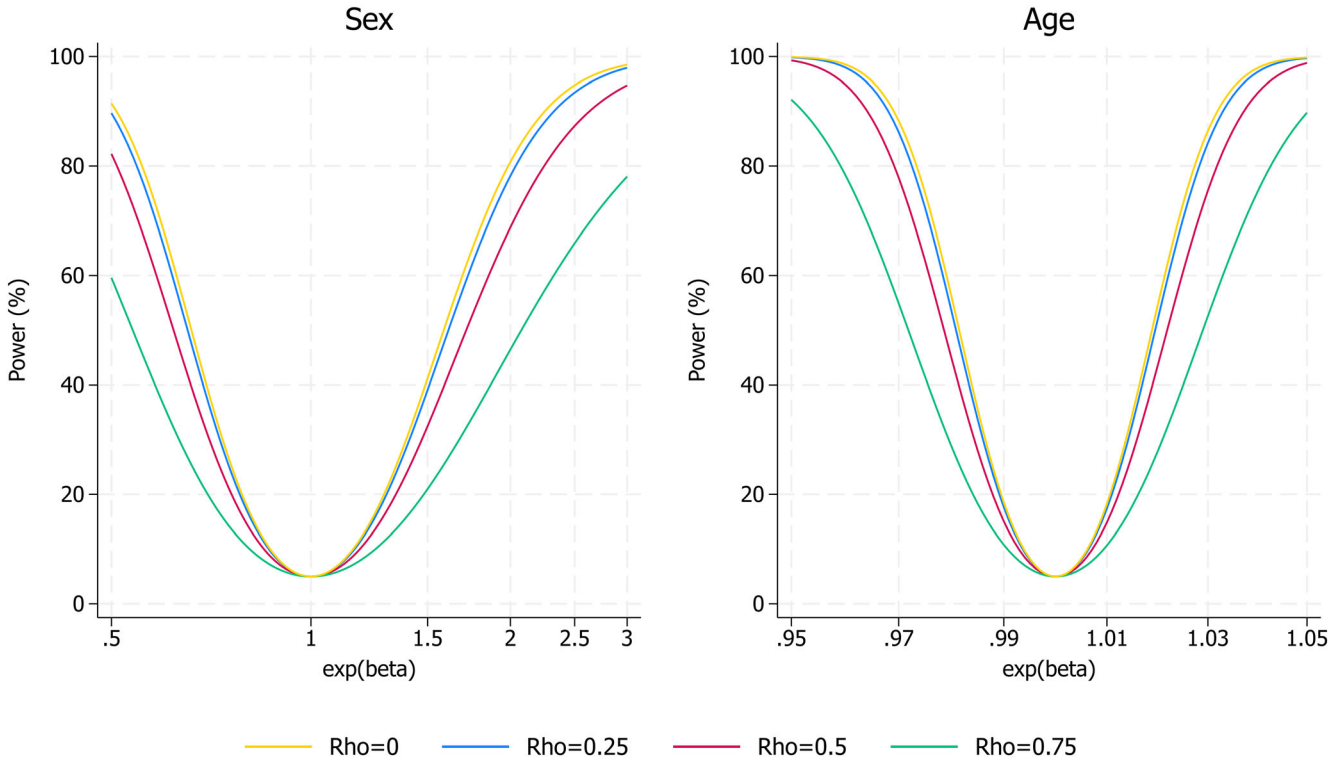

FIGURE 1 Results of the power calculations for the applied example for a range of beta values (presented as odds ratios) for different values of the VIF. VIF, variance inflation factor.

unlikely to provide enough power to test the prognostic ability of sex, as for an OR of 0.6, there would only be 56% power, and the OR would likely be much closer to one than this in reality (Poynard et al.[18] found a hazard ratio of 0.89). However, there may be enough power to detect a prognostic effect of age, dependent on the expected size of the effect. It is estimated that there would be 93% power to detect an OR of 1.04, which may be a reasonable OR to expect (however, in practice, this would require clinical input).

6 | EXTENSION: ALLOWING FOR HETEROGENEITY

So far, we have assumed a common-effect model in the second stage of the meta-analysis, which assumes the true prognostic effect is the same in each study. We now allow for between-study heterogeneity in the prognostic factor effect, based on the proposed approach by Riley et al.[3] for an IPD meta-analysis of interactions.

To allow for between-study heterogeneity, a random-effects model must be assumed (Equation 3), which requires additional assumptions about the magnitude of the heterogeneity. The power calculation can be extended to allow for between-study heterogeneity in the prognostic effect:

$$\text{Power} = \text{T}\left(-t_{S-1,0.975} + \frac{\hat{\beta}}{\sqrt{\text{var}\left(\hat{\beta}\right)}}\right) + \text{T}\left(-t_{S-1,0.975} - \frac{\hat{\beta}}{\sqrt{\text{var}\left(\hat{\beta}\right)}}\right) \quad (17)$$

where $\text{T}(x)$ is the probability of sampling a value $< x$ from a t-distribution with a mean of zero and $S-1$ degrees of freedom, and S is the number of studies expected to provide their IPD. The variance of the prognostic factor, $\text{var}\left(\hat{\beta}\right)$, now needs to be estimated from Equation (5), hence, an assumed value of $\hat{\tau}$ (the between-study SD of the prognostic factor effect) must also be given.

As with the Hartung-Knapp-Sidik-Jokman (HKSJ) approach for deriving 95% confidence intervals after fitting a random-effects meta-analysis,[19,20] which uses a t-distribution rather than a normal distribution, a t-distribution is used here to help reflect the extra uncertainty due to $\hat{\tau}$ being estimated rather than already known.

Riley et al.[3] suggest that Equation (17) is likely to over-estimate the power as it assumes τ is known, when actually it will be estimated. This will be of greatest concern when there are small numbers of studies providing

TABLE 2 Comparison of the power in the common-effect model and random-effect model for an assumed OR for age of 1.04 in the applied example, considering a range of values for τ.

	Without adjustment for other covariates ($\rho = 0$)		With adjustment for other covariates ($\rho = 0.5$)	
τ	$SE\left(\hat{\beta}\right)$	Power	$SE\left(\hat{\beta}\right)$	Power
Common-effect model				
-	0.00981	97.93%	0.01132	93.37%
Random-effect model				
0.001	0.00982	76.45%	0.01134	60.38%
0.0025	0.00990	75.63%	0.01141	59.63%
0.005	0.01018	72.71%	0.01165	57.05%
0.0075	0.01064	67.91%	0.01205	53.04%
0.01	0.01123	61.53%	0.01258	48.03%
0.015	0.01274	46.64%	0.01396	37.19%
0.02	0.01454	33.56%	0.01564	27.95%

Note: α: Trial 1 = −1.307, Trial 2 = −1.083, Trial 3 = −1.720, Trial 4 = −1.124.

IPD, and when the true τ is close to zero, as then τ would be poorly estimated and often too high (as the estimate is bounded at zero). A simulation-based approach would be a better reflection of the uncertainty in that situation.[2]

Returning to the example from Section 5, Table 2 below shows the estimated power to detect a prognostic factor effect of β=ln(1.04) for age, both before and after adjustment for other covariates. For the random-effects model, the power calculation from Equation (17) was used, deriving the variance using Equation (5) for a range of assumed τ values. When adjusting for other covariates, the correlation coefficient (ρ) was assumed to be 0.5. For an assumed τ of 0.005, the power is now estimated to be 72.7% when not adjusting for other covariates, which is considerably lower than when assuming a common-effect model (97.9%). This is even further reduced when adjusting for other covariates, to 57.1% (from 93.4% for the common-effect model). As expected, the greater the value of τ, the greater the reduction in the estimated power. The drop off in power is slightly greater for this example when τ increases above 0.005.

7 | DISCUSSION

Power and sample size are important considerations when planning and funding IPD meta-analysis projects. In this article, we have proposed a new method to estimate the power when designing an IPD meta-analysis project to estimate the effect of a prognostic factor for a binary outcome. We have extended this method to enable the power to be adjusted for the presence of additional correlated adjustment factors and to allow for between-study heterogeneity. An example was provided illustrating the use of the proposed methods.

A three-step approach is proposed using an asymptotic solution for calculating variances of prognostic factor effect estimates, which allow the power of the planned IPD meta-analysis project to be calculated in advance of IPD collection, using aggregate data that are frequently reported in study publications. The three-step approach first uses the aggregate data to derive the Fisher's information matrix and an approximate estimate of the variance of each studies prognostic factor effect estimate, which then enables the variance of the summary effect estimate to be calculated from a two-stage IPD meta-analysis and finally the power of the IPD MA project can then be calculated.

If these results from the power calculations are known in advance of IPD collection, this would allow the researchers planning the project and the potential funders to decide whether the project would be worth their investment. It could also provide incentive to pursue IPD from additional studies, if they exist, to increase the power if necessary.

As with any power calculation, the approach is pragmatic to help gauge potential power under plausible assumptions, and the actual power will change depending on various modelling assumptions. For example, the power could change if not all the available IPD can be obtained. Other reasons that the power could change are if the assumed prognostic factor effects are incorrect, if the assumed distribution of a continuous covariate is wrong, if there is larger heterogeneity in prognostic effects than expected, or if the amount of correlation between the prognostic factor and adjustment covariates

is incorrect. Hence, for funding applications it would be wise to display a range of power calculations based on a range of assumptions, as shown in the example in this article.

A key issue when applying the proposed methods is the ability to obtain the necessary aggregate data for each of the potential studies to be included. Basic study information, such as the number of participants and number of outcome events should be available from study publications. However, information about covariate distributions may be more difficult to obtain, particularly for covariates other than the standard covariates such as age and sex, which are likely to be summarised in the baseline characteristics. In this situation, the study investigators can be contacted and asked to provide the summary information needed, which should hopefully be a reasonable request if they have already agreed to provide their IPD.

A further limitation of the proposed approach is the need to approximate α for the binary covariate scenario. It is approximated by using a weighted average of the risks in each group as an approximation for the overall log-odds of the outcome in study i, which can then be rearranged to approximate α. Further work is needed to evaluate how robust the power calculation is to deviations from this approximation of α. Extension to non-linear effects of continuous prognostic factors is also needed.

Consideration should also be given to the amount of correlation between the prognostic factor and adjustment variables, as it has been shown in the example above that this can have a substantial impact on the power of the project, and therefore the presence of additional adjustment covariates should not be ignored when calculating the power of a planned IPD meta-analysis project. Additionally, the assumption about the true effect size may need to change when adjusting for other prognostic factors, as the adjusted effect may sometimes be lower than the unadjusted effect, which would in turn lower the power. However, this is difficult to gauge in advance and so in our examples we assumed the size of clinically relevant effects was the same for unadjusted and adjusted situations, but recognise that further research on this issue would be welcome.

For the main part of this article, a common-effect meta-analysis model was assumed, which assumes the true prognostic effect is the same in each study. This approach taken was for pragmatic reasons, as using a random-effects model, as demonstrated in Section 6, would require additional assumptions about the magnitude of the heterogeneity, which may be difficult to ascertain. Section 6 extended the approach to allow for heterogeneity, which showed a dramatic change in the estimated power dependent on what value of τ is assumed. This further highlights the need for allowing for heterogeneity in the power calculations. However, it also highlights the potential for drastically overestimating the power of the planned IPD meta-analysis project if heterogeneity is not accounted for.

Although this paper focused on the power of an IPD meta-analysis, there are many reasons why an IPD meta-analysis might still be taken even if the power is insufficient. For example, without IPD, meta-analysis of prognostic factor studies would be restricted by poor presentation of aggregate data in primary studies, selective outcome reporting, and dichotomisation of continuous factors, whereas IPD would allow more complex analyses allowing all outcomes to be assessed and continuous variables to modelled more appropriately.[5]

In summary, we have proposed a novel analytic method to estimate the power of an IPD meta-analysis to examine prognostic factor effects with binary outcomes, based on published study aggregate data, and we hope that researchers will use this to help them decide on the benefit of the IPD approach in advance of collecting IPD, potentially savings years worth of wasted time, or providing reassurance to both researchers and funders that the project will be valuable.

AUTHOR CONTRIBUTIONS

Rebecca Whittle: Data curation; formal analysis; methodology; visualization; software; writing – original draft; writing – review and editing. **Joie Ensor:** Funding acquisition; methodology; software; supervision; writing – review and editing. **Miriam Hattle:** Methodology; writing – review and editing. **Paula Dhiman:** Funding acquisition; writing – review and editing. **Gary S. Collins:** Funding acquisition; methodology; writing – review and editing. **Richard D. Riley:** Conceptualization; funding acquisition; methodology; software; supervision; visualization; writing – review and editing.

ACKNOWLEDGMENTS

We would like to thank two reviewers for constructive suggestions that helped improve this paper upon revision.

FUNDING INFORMATION

This paper presents independent research supported (for RW, JE, RDR, PD, GSC) by an Engineering & Physical Sciences Research Council (EPSRC) for 'Artificial intelligence innovation to accelerate health research' (number: EP/Y018516/1); (for RDR, JE, MH and GSC) by an Medical Research Council - National Institute for Health and Care Research (MRC-NIHR) (MR/V038168/1); and (for RW, RDR, MH and JE) by the NIHR Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. Professor Riley and Professor Collins are

National Institute for Health and Care Research (NIHR) Senior Investigators. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. GSC is supported by Cancer Research UK (programme grant: C49297/A27294).

CONFLICT OF INTEREST STATEMENT

Richard Riley is the lead Editor on the book 'Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research' for which he receives royalties. The other authors confirm that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The work presented involves applying equations using aggregated data, and therefore no actual individual-level data is available for sharing. Example code is provided in the Supplementary Material, and aggregate data for an applied example is shown in the paper itself and supplied in a data file (Data S2).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Whittle R, Ensor J, Hattle M, Dhiman P, Collins GS, Riley RD. Calculating the power of a planned individual participant data meta-analysis to examine prognostic factor effects for a binary outcome. *Res Syn Meth*. 2024;1-12. doi:10.1002/jrsm.1737