**Supporting Information S2**

***Model 1***

*One-stage fixed-effect model*

$$logit\left(p\_{ij}\right)=log\left(\frac{p\_{ij}}{1-p\_{ij}}\right)=α\_{i}+βx\_{ij}$$

Where pij is the probability of an event for person j in trial i, xij denotes the treatment received, αi is the baseline risk in each trial and βi is the log odds ratio of the treatment effect. To obtain the log relative risk, replace the logit link with a log link function.

*R code:* glm(event~trial+treat, family=binomial)

*Or for relative risk:* glm(event~trial+treat, family=binomial(link=”log”))

***Model 2***

*One-stage random-effects model*

$$\begin{matrix}logit\left(p\_{ij}\right)=α\_{i}+β\_{i}x\_{ij}\\β\_{i}\~N\left(θ,τ^{2}\right)\end{matrix}$$

 Here treatment effect varies across trials, distributed normally around the overall effect θ, with heterogeneity τ2.

*R code:* glmer(event~trial+treat+(treatn-1|trial), family= binomial)

 *\* treatn is a numerical coding for treatment (Experimental=1, Control=0)*

***Model 3***

*One-stage random-effects model with treatment-covariate interaction (Turner et.al. (2000))*

$$\begin{matrix}logit\left(p\_{ij}\right)=α\_{i}+β\_{i}x\_{ij}+γz\_{ij}+δx\_{ij}z\_{ij}\\β\_{i}\~N\left(θ,τ^{2}\right)\end{matrix}$$

Where zij is the coding for the covariate, γ is the baseline effect of the covariate and δ the treatment-covariate interaction.

*R code:* glmer(event~trial+treat\*covar+(treatn-1|trial), family= binomial)

***Model 4***

*One-stage random-effects model with treatment-covariate interaction (Simmonds (2005))*

$$\begin{matrix}logit\left(p\_{ij}\right)=α\_{i}+β\_{i}x\_{ij}+γ\_{i}z\_{ij}+δx\_{ij}z\_{ij}\\β\_{i}\~N\left(θ,τ^{2}\right)\end{matrix}$$

This model allows for independent effects of the covariate on risk across trials ($γ\_{i}$ rather than the $γ$ of Turner *et.al.*).

*R code:* glmer(event~trial\*covar+treat\*covar+(treatn-1|trial), family= binomial)

***Model 5***

*One-stage random-effects model allowing for aggregation bias (Simmonds-Riley).*

$$\begin{matrix}logit\left(p\_{ij}\right)=α\_{i}+β\_{i}x\_{ij}+γ\_{i}z\_{ij}+ξx\_{ij}(z\_{ij}-\overbar{z\_{i}})+ηx\_{ij}\overbar{z\_{i}}\\β\_{i}\~N\left(θ,τ^{2}\right)\end{matrix}$$

Where $\overbar{z}\_{i }$ is the mean of the covariate within-trial i, ξ is the desired within-trial interaction and $η$ is the across-trials interaction. This model may be expressed as:

$$\begin{matrix}logit\left(p\_{ij}\right)=α\_{i}+β\_{i}x\_{ij}+γ\_{i}z\_{ij}+δx\_{ij}z\_{ij}+κx\_{ij}\overbar{z\_{i}}\\β\_{i}\~N\left(θ,τ^{2}\right)\end{matrix}$$

Where $δ=ξ$ and$ κ=η-ξ$, thus κ is a measurement of aggregation bias.

*R code:* glmer(event~trial\*covar+treat\*covar+intermean+(treatn-1|trial),family=binomial)

*\* Where* intermean *is a new variable being zero in the control group and equal to the trial-level covariate mean in the experimental group (i.e treatn\*mean covariate).*

***Model 6***

*One-stage model with random treatment and interaction effects*

$$\begin{matrix}logit\left(p\_{ij}\right)=α\_{i}+β\_{i}x\_{ij}+γ\_{i}z\_{ij}+δ\_{i}x\_{ij}z\_{ij}\\\left(\begin{matrix}β\_{i}\\δ\_{i}\end{matrix}\right)\~N\left(\begin{matrix}\left(\begin{matrix}θ\\δ\end{matrix}\right),&\left(\begin{matrix}τ^{2}&c\\c&τ\_{δ}^{2}\end{matrix}\right)\end{matrix}\right)\end{matrix}$$

Where the interaction term δ has a random effect which may be correlated with the treatment random effect. Model 6 is a useful and novel alternative to model 5 for nominal covariate data (e.g. disease stage), where separation of within and across trial treatment interactions is not possible, as the additional random effect term minimises the impact of aggregation bias.

*R code:* glmer(event~trial\*covar+treat\*covar+(treatn+treatn:covar-1|trial), family= binomial)