



Methodological Considerations in Model-Based Meta-Analysis (MBMA): Concepts, Applications, and Implementation

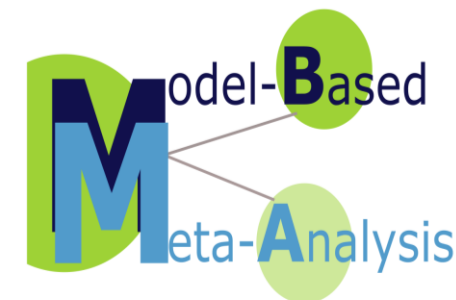
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- Jaap Mandema
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- Paul Diderichsen
- Eugene Cox

Note: Many of these slides have been derived from prior presentations

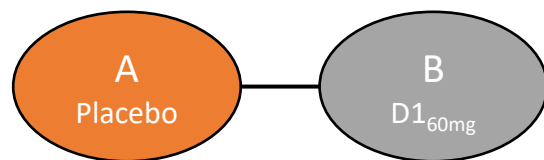
Tutorial Agenda

1. Introduction to meta-analysis and MBMA
 - Different types of meta-analysis
 - Key concepts and value proposition of MBMA
 - Case studies
2. MBMA methodology and best practices
 - How to account for between-study heterogeneity
 - Unstructured placebo response vs. parametric placebo model
 - Understanding prognostic vs predictive covariates
 - Data weighting and variable/model transformation
 - Model implementation
 - Covariate exploration and model evaluation

MBMA is an Extension of Network Meta-Analysis

Pairwise Meta-Analysis

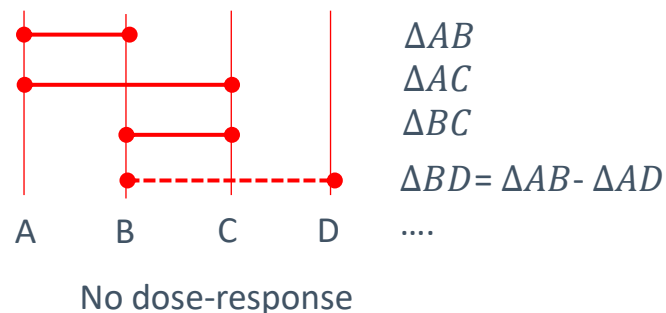
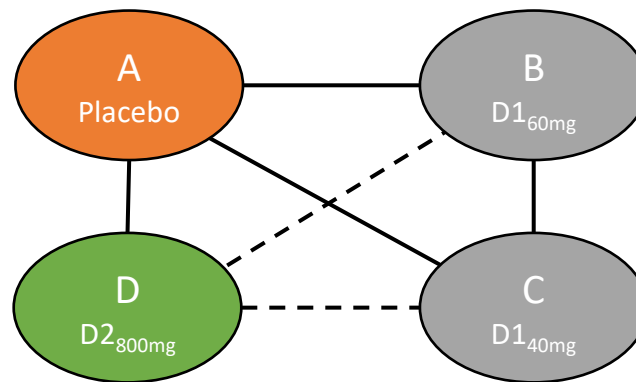
Only compares the same treatment vs control



Each treatment comparison analyzed independently
No indirect comparisons
No dose-response

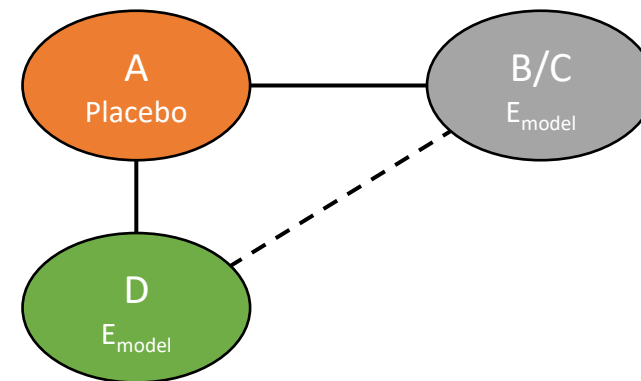
Network Meta-Analysis

Compares treatments not studied together, but for limited doses and time points



Model-Based Meta-Analysis

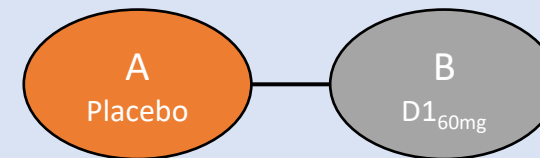
Uses pharmacologic (PD) models to incorporate the totality of available data (all doses and times)



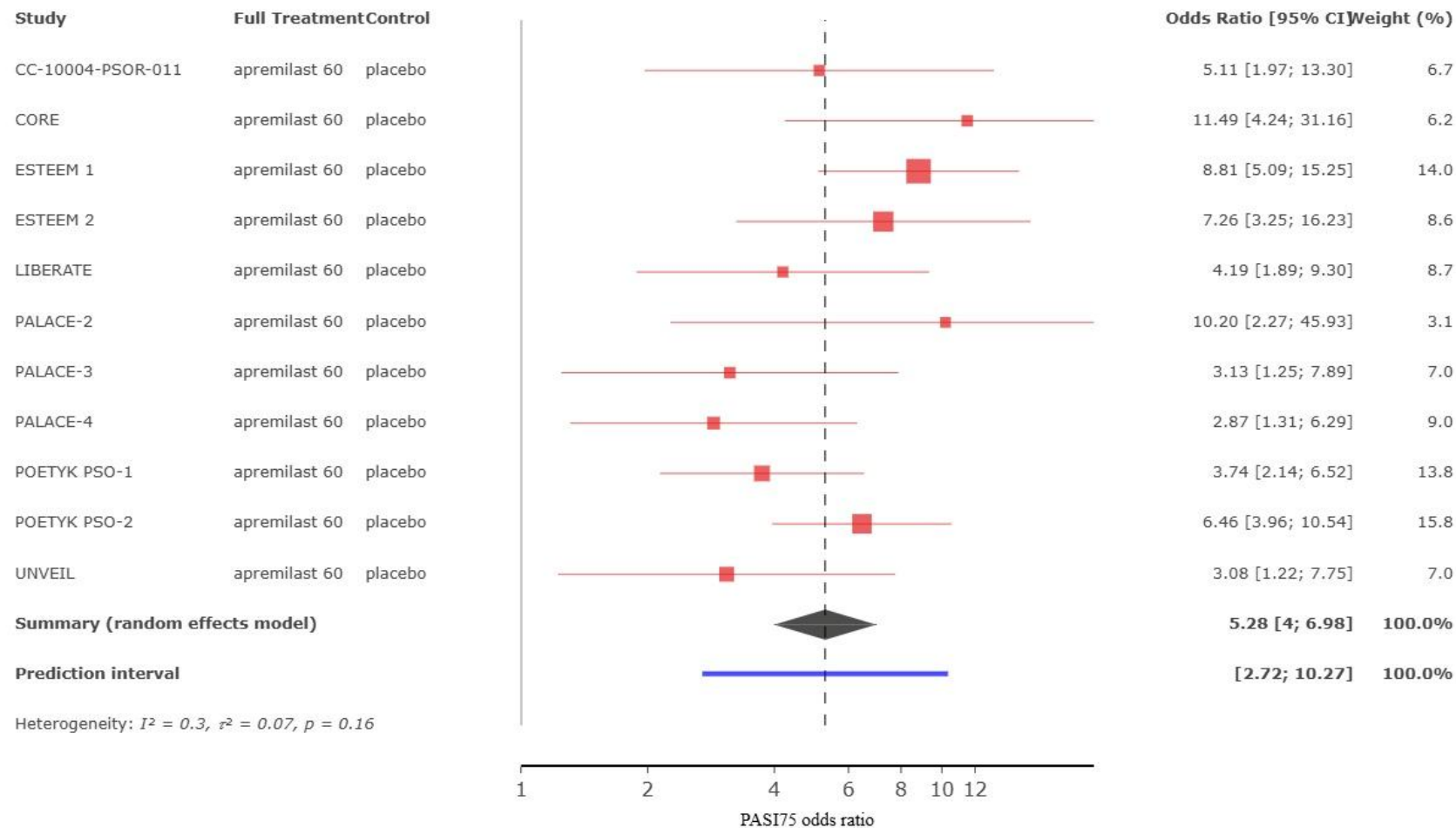
Dose-response relationships and longitudinal effects quantified
Other effect modifiers can account for additional heterogeneity in treatment effects

Pairwise Meta-Analysis (PMA) in PsO

week 16 PASI75 OR vs. placebo (single treatment)

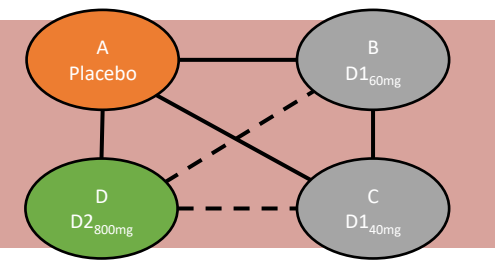


PMA of 11 studies with a single treatment (apremilast 60 mg/day) vs. placebo shows a precise treatment effect at week 16

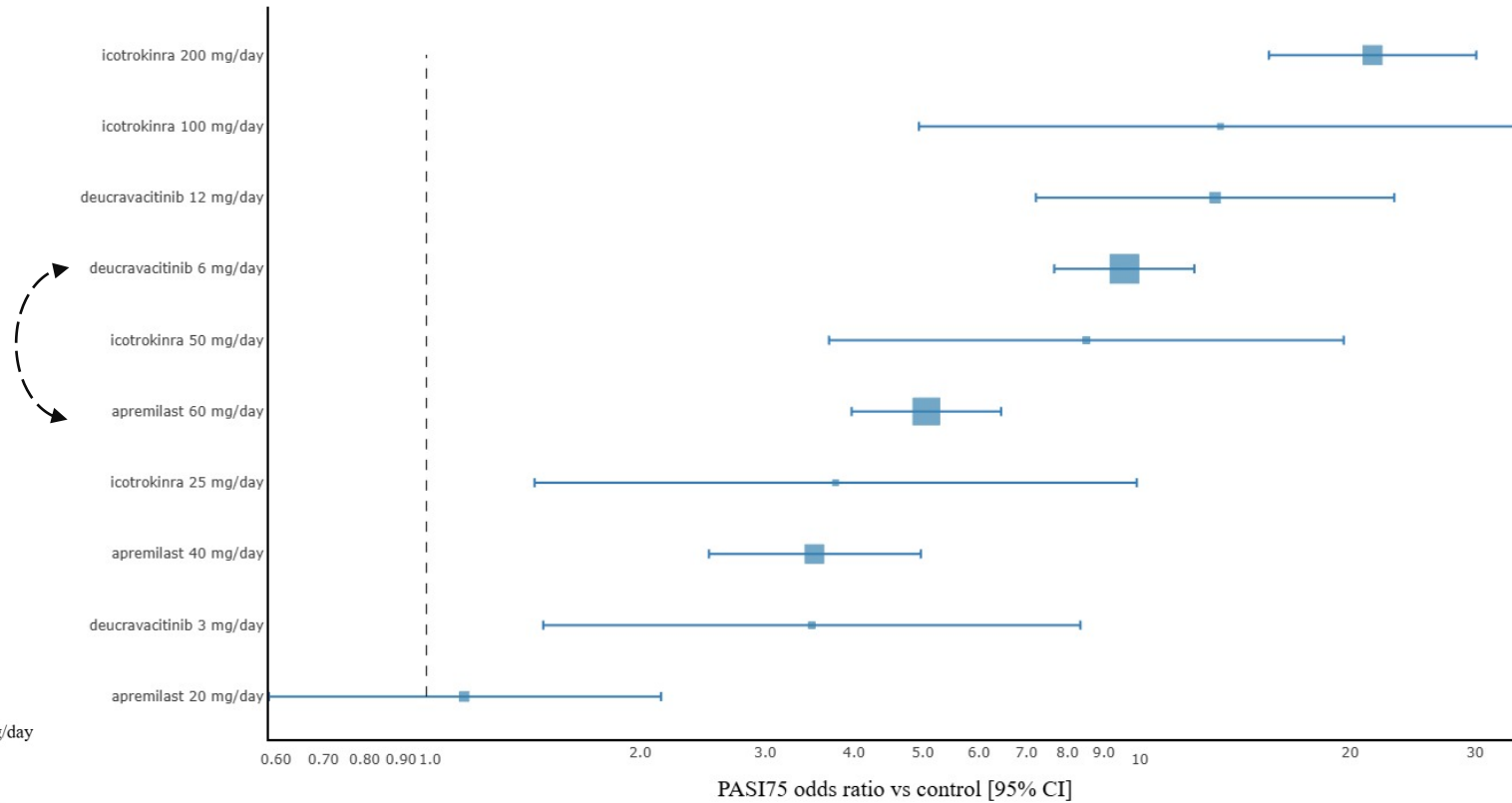
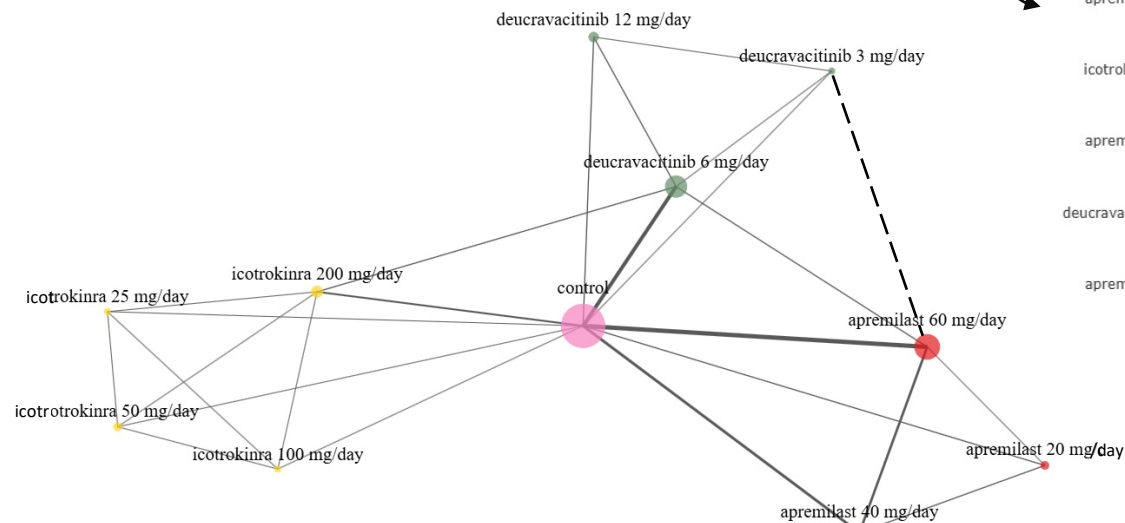


Network Meta-Analysis (NMA) in PsO

week 16 PASI75 OR vs. placebo (by specific treatment)

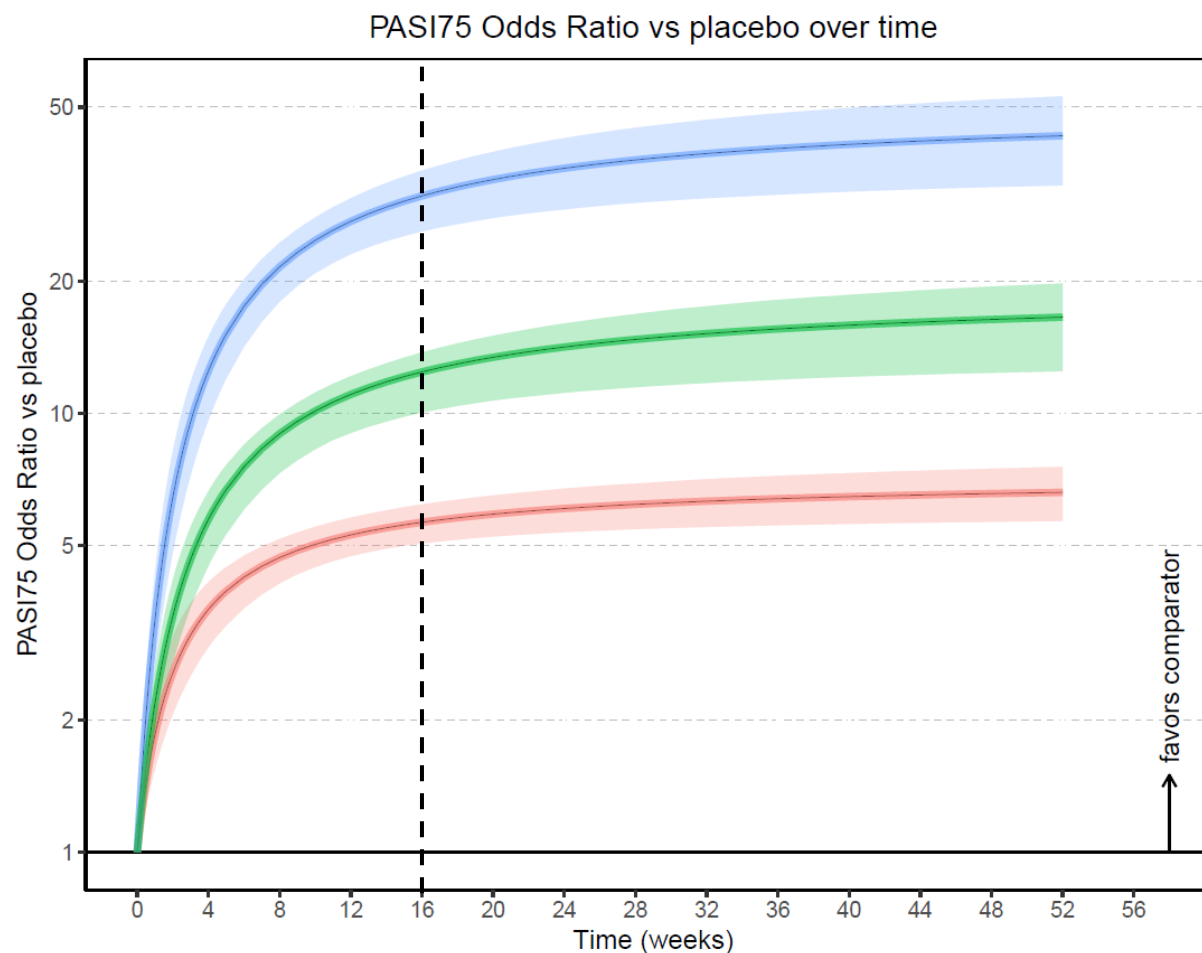
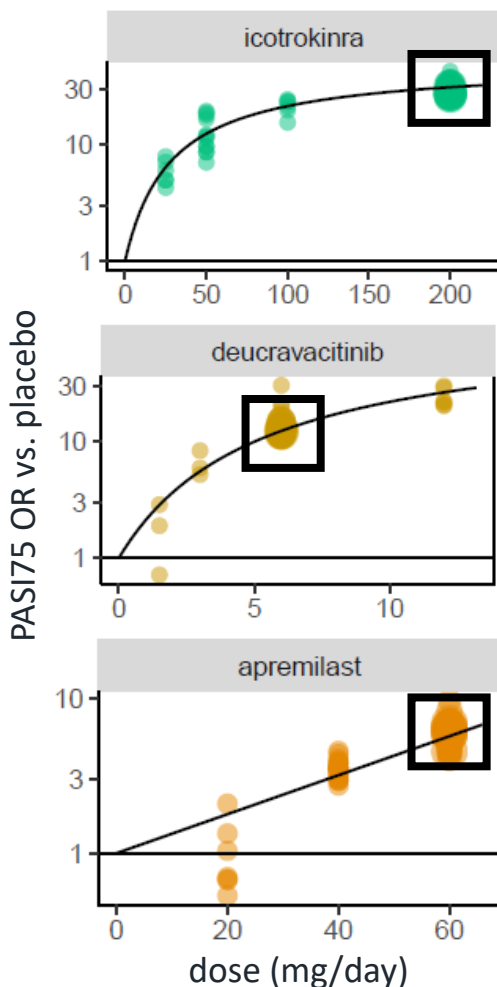
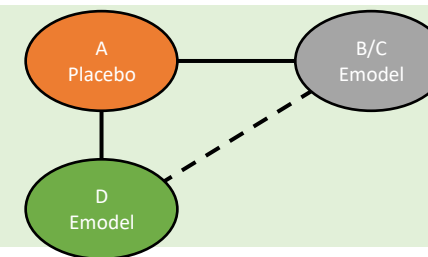


NMA of 23 studies, 66 study arms, ~11,000 patients (with various doses of apremilast, deucravacitinib, and icotrokinra) highlights differences in relative effects across treatments at week 16



MBMA in PsO

longitudinal PASI75 OR vs. placebo (w/ dose-response)



MBMA captures effect onset and dose-response, allowing for simulations at different dose and time

Drug Dose

- apremilast 30 mg bid
- deucravacitinib 6 mg/day
- icotrokinra 200 mg qd

2005: First published MBMA in Migraine

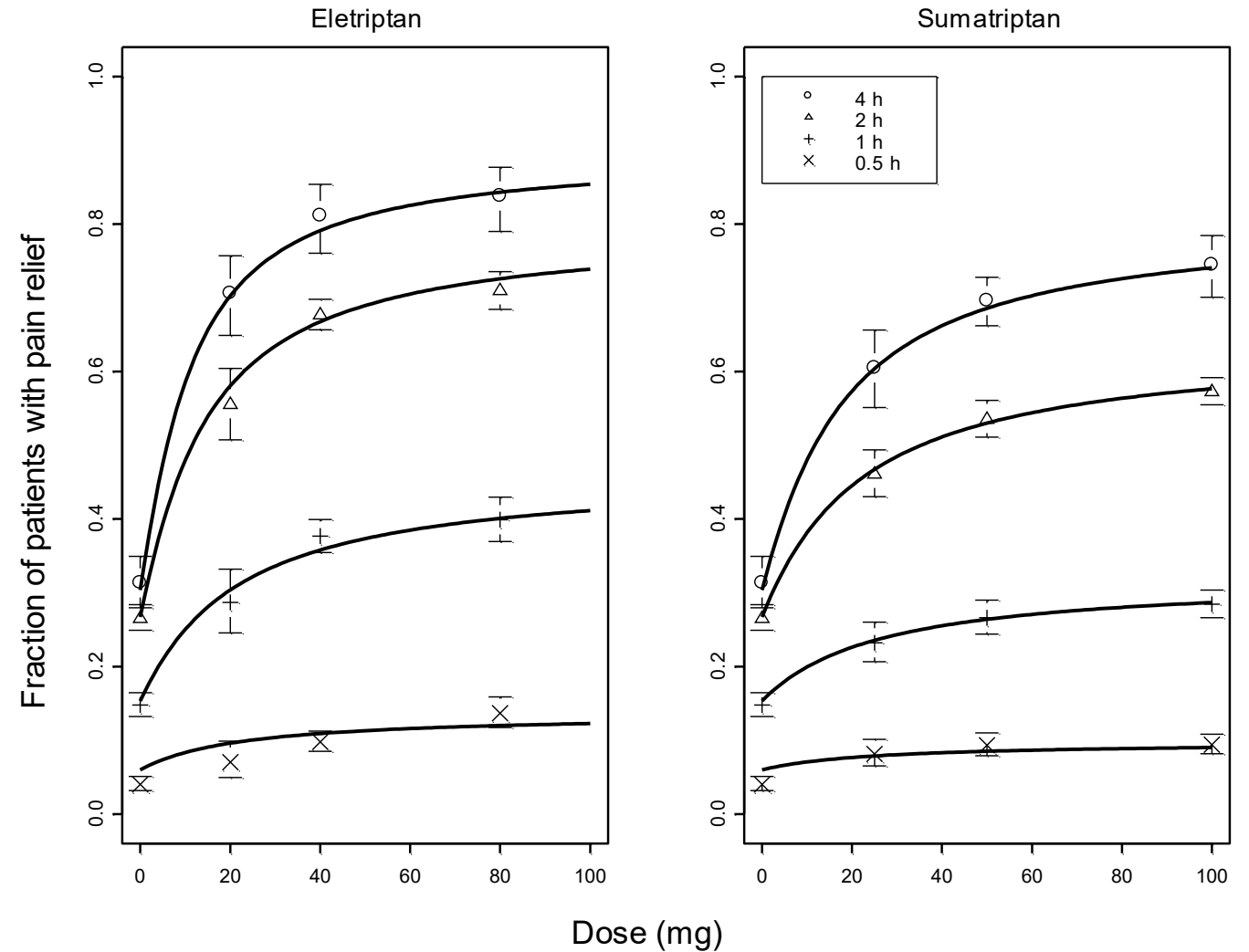
Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain – results of a model-based meta-analysis that accounts for encapsulation

JW Mandema^{1*}, E Cox¹ & J Alderman²

¹Pharsight Corporation, Mountain View, CA and ²Pfizer Inc, New York, USA

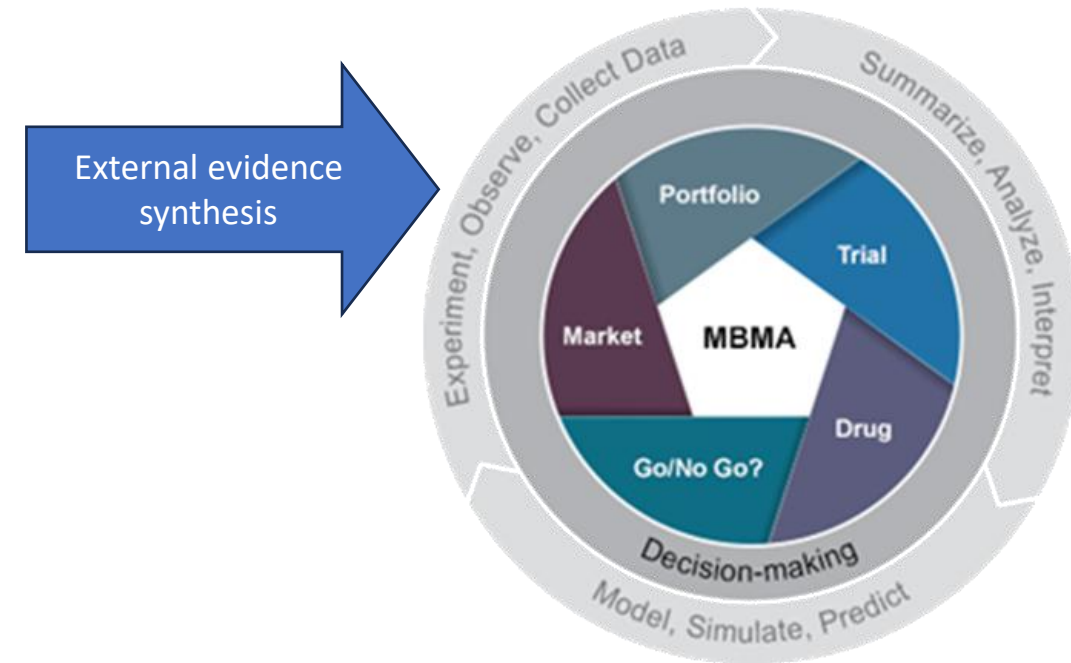
MBMA quantified the impact of dose and time (onset) on migraine pain relief for eletriptan and sumatriptan, suggesting eletriptan was faster-acting and more potent than sumatriptan

Figure 1. Longitudinal and Dose-Response Model of Responders



MBMA (What and Why): Quantitative Framework to Leverage External Data for Development, Regulatory, & Commercial Decisions

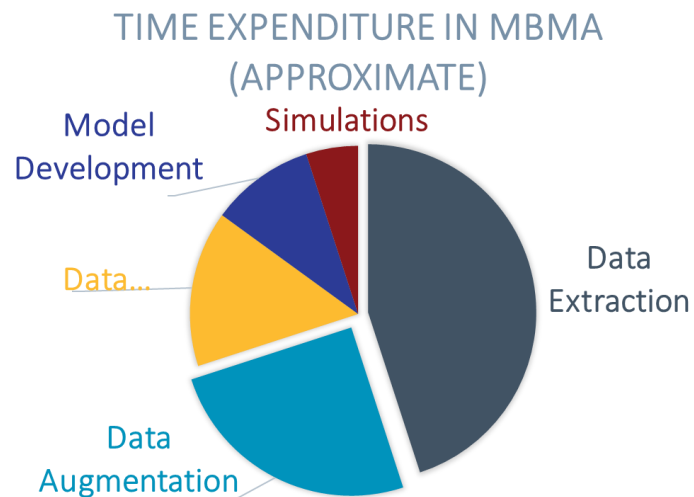
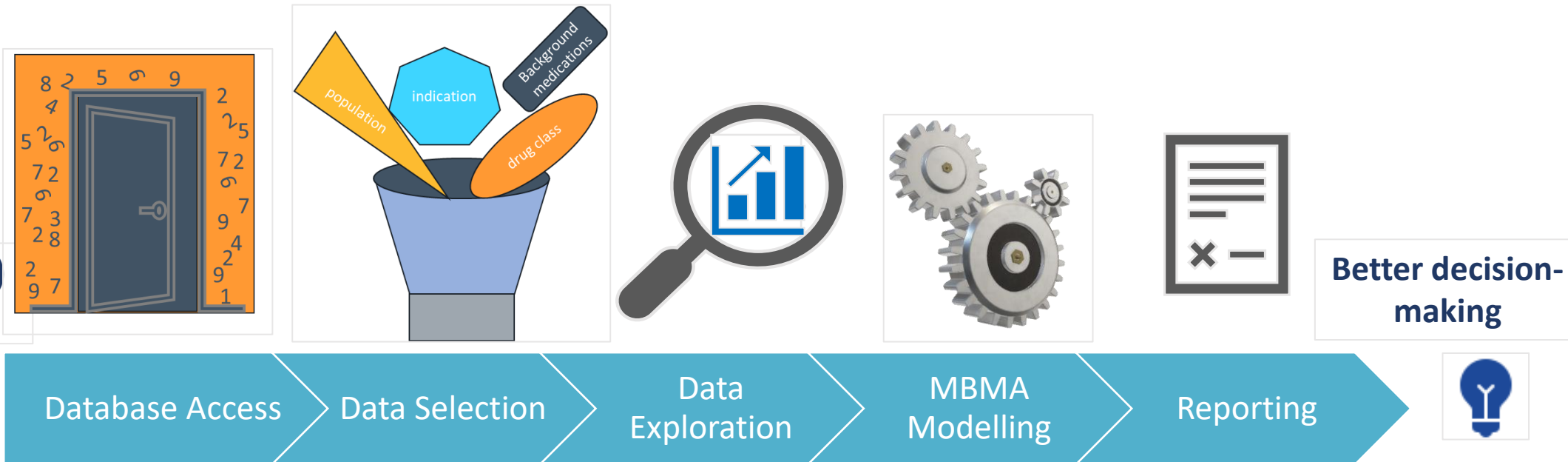
- **Leveraging existing information to inform decisions and optimize trial designs**
 - Global/class-specific impact of covariates on treatment effect, including dose-response relationships
- **Comparative safety and efficacy**
 - Rigorously establish safety/efficacy targets for differentiation against existing or emerging treatments
 - Evaluate new treatment's probability of achieving differentiation, supporting **go/no-go decisions**, dose selection, and trial/program/portfolio strategy
- **Endpoint-to-Endpoint relationships**
 - Predicting clinical outcomes from early biomarker/endpoint responses
 - Bridging across indications
- **Create synthetic control arms**
 - Adjusting for known and accounting for unknown factors that impact heterogeneity
- A rigorous assessment of the competitive landscape **provides regulatory, marketing, and reimbursement support** and bolsters due diligence efforts



MBMA Roadmap (How and When)

Clinical question(s)
(e.g. design, dose)

?



- Pre-curated clinical outcomes databases expedite the development and application of a predictive MBMA
- To maximize the utility of MBMA, develop and maintain comparator models well in advance of key decision points

MBMA (What and Why): Case Studies

- **Leveraging existing information to inform decisions and optimize trial designs**
 - Global/class-specific impact of covariates on treatment effect, including dose-response relationships
- **Comparative safety and efficacy**
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A broader list of case studies
can be found in the
supplementary material

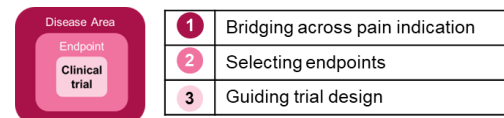
Case study 1

Case study 2



Case Study 1 - MBMA in Chronic Pain to Bridge across Indications to Guide Clinical Development

- Understanding the relative effects between different types of associated pain indications to inform the clinical development strategy within each broad category: (i.e. bridging relative effects within neuropathic pain (NP) indications as well as within musculoskeletal (MSK) pain indications to support phase 3 strategy)
 - NP: The landmark MBMA of change from baseline measures of average pain intensity (NRS or VAS by daily diary) showed a 43% greater treatment effect [15% to 71%] in PHN when compared to DPN.



Musculoskeletal (MSK)

Osteoarthritis (OA)

NRS
numerical rating scale



WOMAC
registrational subscale



Chronic low back pain (CLBP)

Different pathophysiology

Neuropathic (NP)

Diabetic Peripheral Neuropathic Pain (DPNP)

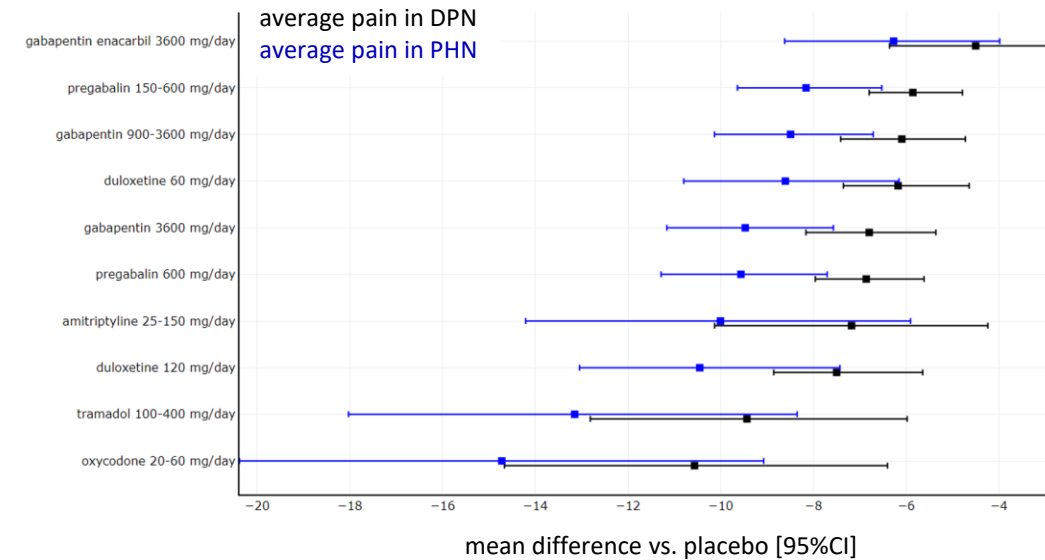


- Time course (week 6 vs. week 12)
- Baseline (+/- 10 units)
- Drop out (BOCF vs. LOCF)
- Study years (<2000 vs. >2000)



Post-Herpetic Neuralgia (PHN)

Estimated treatment effect (with 95% CI) at 12 weeks for selected treatments in DPN vs. PHN



Case Study 2 - MBMA in Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) to create a synthetic control for Regulatory Support

- MBMA functioned as a **synthetic control arm to support accelerated approval** of blinatumomab in adult patients with R/R ALL based on **single arm trial** (MT103-211) with 185 patients
- Evaluated the expected relative effect (survival HR) of blinatumomab versus existing salvage therapies using meta-analysis models and **clinical trial simulations**
- Referenced by FDA and EMA for impact on approval process:

2.7.4. Conclusions on the clinical efficacy

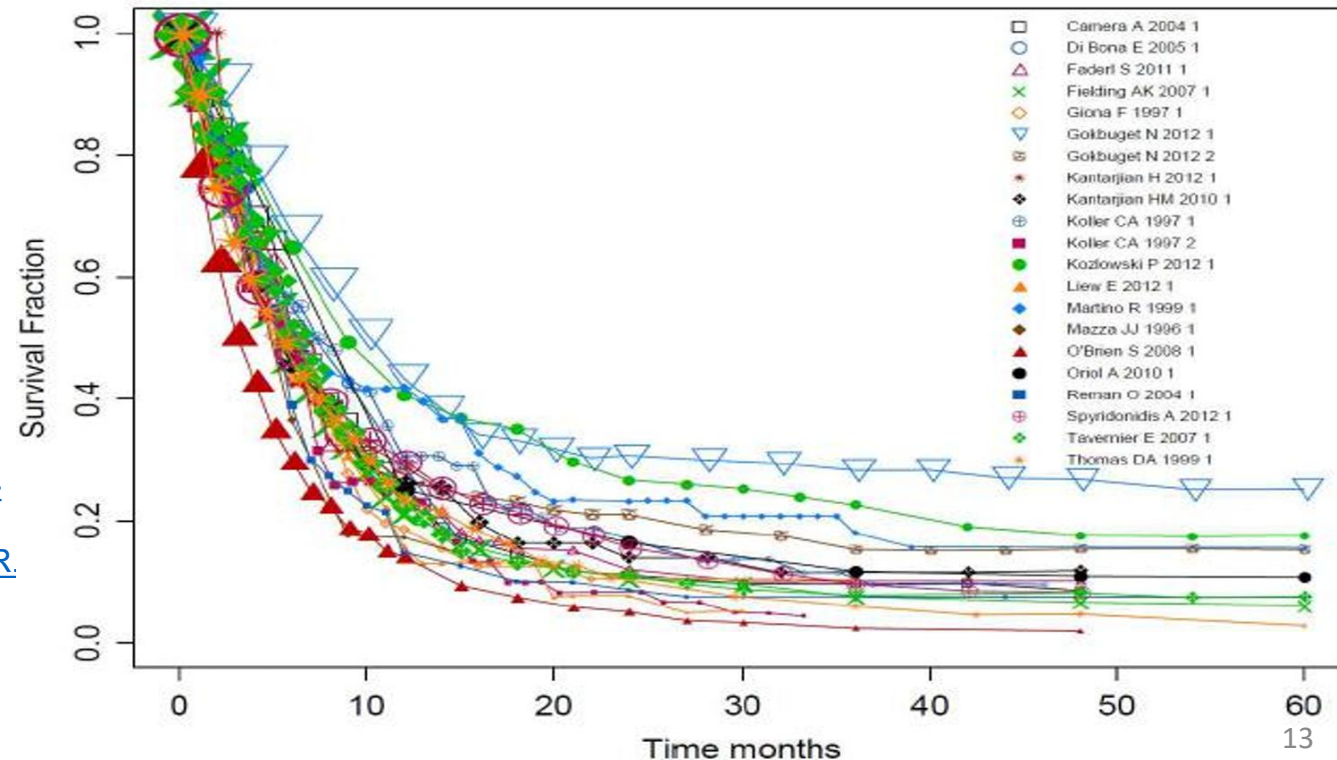
Data from pivotal study MT103-211 showed a clinically significant response rate to blinatumomab in a high risk population of relapsed/refractory adult ALL patients for whom results obtained with conventional chemotherapy are usually unsatisfactory. These results are further supported by the high rates of negative MRD responses observed throughout all the clinical studies, and by the estimation of clinical responses obtained with conventional chemotherapy as provided by the historical comparator study 20120310 and by a model-based meta-analysis.

However efficacy results from direct comparison with chemotherapy regimens are needed in order to better quantify the magnitude of the effect.

- Accelerated FDA approval on Dec 3, 2014
- Full FDA approval granted on July 11, 2017, after confirmatory

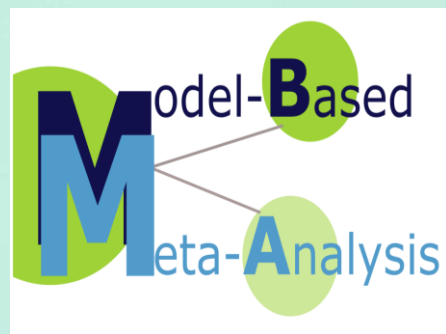
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https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125557Orig1s000StatR

Figure 1. Overall Survival Curves Across Included Studies with Salvage Therapies



Key Concept Overview

- MBMA provides a quantitative and cost-effective framework for integrating external and internal drug development data, thereby maximizing knowledge and optimizing decision-making
- MBMA differs from “traditional” meta-analysis in that it uses pharmacological models to account for the effect of dose, time, and/or other covariates of interest
- As illustrated in the case studies, knowledge gained through MBMA is having a critical impact on a growing number of drug development programs and therapeutic areas



MBMA Best Practices

Heterogeneity



Origins and Implications of Heterogeneity

- The trials from which data are combined are likely to differ in their design and patient population characteristics (i.e., trial-level covariates)
- Due to these differences, there could be heterogeneity in trial results, i.e., more between-trial variability in the results than expected on the basis of chance (sample size) alone
 - This applies to both **absolute outcomes** and **relative treatment effects**
- Because the trials are not randomized with respect to trial-level covariates, estimates of the relative treatment effect can be biased
 - Understanding heterogeneity is critical
- One of the major benefits of MBMA is accounting for the impact of trial-level treatment effect modifiers by including *predictive covariates** in the set of model parameters
- Random effects models are used to account for any remaining unexplained between-trial differences

Heterogeneity in Absolute Outcomes and Relative Effects

- Each study has a different placebo (control) effect that contributes to between-study heterogeneity
- A parametric placebo model aims to explain placebo response heterogeneity with influential factors as *prognostic covariates*^[1] and with random effects
- However, clinical trials typically aim to characterize relative efficacy and/or safety (e.g., relative to placebo/comparator), thus a typical MBMA should focus on relative effects
 - Between-study heterogeneity in relative effects tends to be smaller than in absolute outcomes, but it is still critical to understand
- A simpler approach uses a fixed effect placebo parameter for each trial (unstructured placebo) ^[2-4]
 - The unstructured placebo approach implicitly captures heterogeneity in placebo effects and enables direct exploration of heterogeneity in relative effects (e.g., with *predictive covariates*^[1])
 - This approach reduces the risk of bias in the relative treatment effect estimates
 - Drugs with limited data (e.g., with fewer and smaller studies) are most susceptible to this bias
- If placebo response (or disease progression with prognostic factors) is of primary interest, a model based on data from only placebo arms is recommended ^[2]

Supportive references:

[1] [Clark GM. Mol Oncol. 2007 Dec 8;1\(4\):406–412.](#)

[2] [Mawdsley D, et al. CPT Pharmacometrics Syst Pharmacol. 2016 Aug;5\(8\):393-401.](#)

[3] [Piepho HP and Madden LV. Res Synth Methods. 2022 Nov;13\(6\):821-828.](#)

[4] [Piepho HP, Madden LV, Williams ER. Res Synth Methods. 2024 Sep;15\(5\):747-750.](#)

FIXED EFFECT MODEL

General Unstructured Placebo Model: One Observation per Treatment Arm

$$Y_{ij} = Eo_i + f(\theta_k) + \varepsilon_{ij}$$

$$\varepsilon_{ij} \sim N(0, \sigma_{ij}^2 / N_{ij})$$

- Y_{ij} is the observed mean response in the j^{th} arm of the i^{th} study
- Eo_i represents the placebo response for the i^{th} study (one for every study)
 - This captures between-study heterogeneity in absolute outcomes
 - Note: active-controlled studies (without placebo) can still be included (i.e., Eo_i is still estimated)
- $f(\theta_k)$ is the relative treatment effect (e.g., dose-response) model with parameters $\theta_{1..k}$
 - Note: there is no random-effects heterogeneity in relative effects in this example
- ε_{ij} is the residual variability, assumed to be normally distributed with variance σ_{ij}^2 / N_{ij}
 - σ_{ij}^2 is the observed between-subject variance in the j^{th} arm of the i^{th} study and N_{ij} is the sample size
 - This allows data from different studies/arms to be weighted differently

RANDOM EFFECT MODEL

General Unstructured Placebo Model: One Observation per Treatment Arm

$$Y_{ij} = Eo_i + f(\theta_{ki}) + \varepsilon_{ij}$$

$$\boxed{\theta_{ki} \sim N(\theta_k, \Omega)} \quad \varepsilon_{ij} \sim N(0, \sigma_{ij}^2 / N_{ij})$$

- Y_{ij} is the observed mean response in the j^{th} arm of the i^{th} study
- Eo_i represents the placebo response for the i^{th} study (one for every study)
 - This captures between-study heterogeneity in absolute outcomes
- $f(\theta_{ki})$ is the relative treatment effect (e.g., dose-response) model with parameters $\theta_{1..k}$ for each study
 - Note: Study-specific model parameters θ_{ki} are assumed to be normally distributed with between-study variance matrix Ω (illustrating relative effect heterogeneity)
- ε_{ij} is the residual variability, assumed to be normally distributed with variance σ_{ij}^2 / N_{ij}
 - σ_{ij}^2 is the observed between-subject variance in the j^{th} arm of the i^{th} study and N_{ij} is the sample size
 - This allows data from different studies/arms to be weighted differently

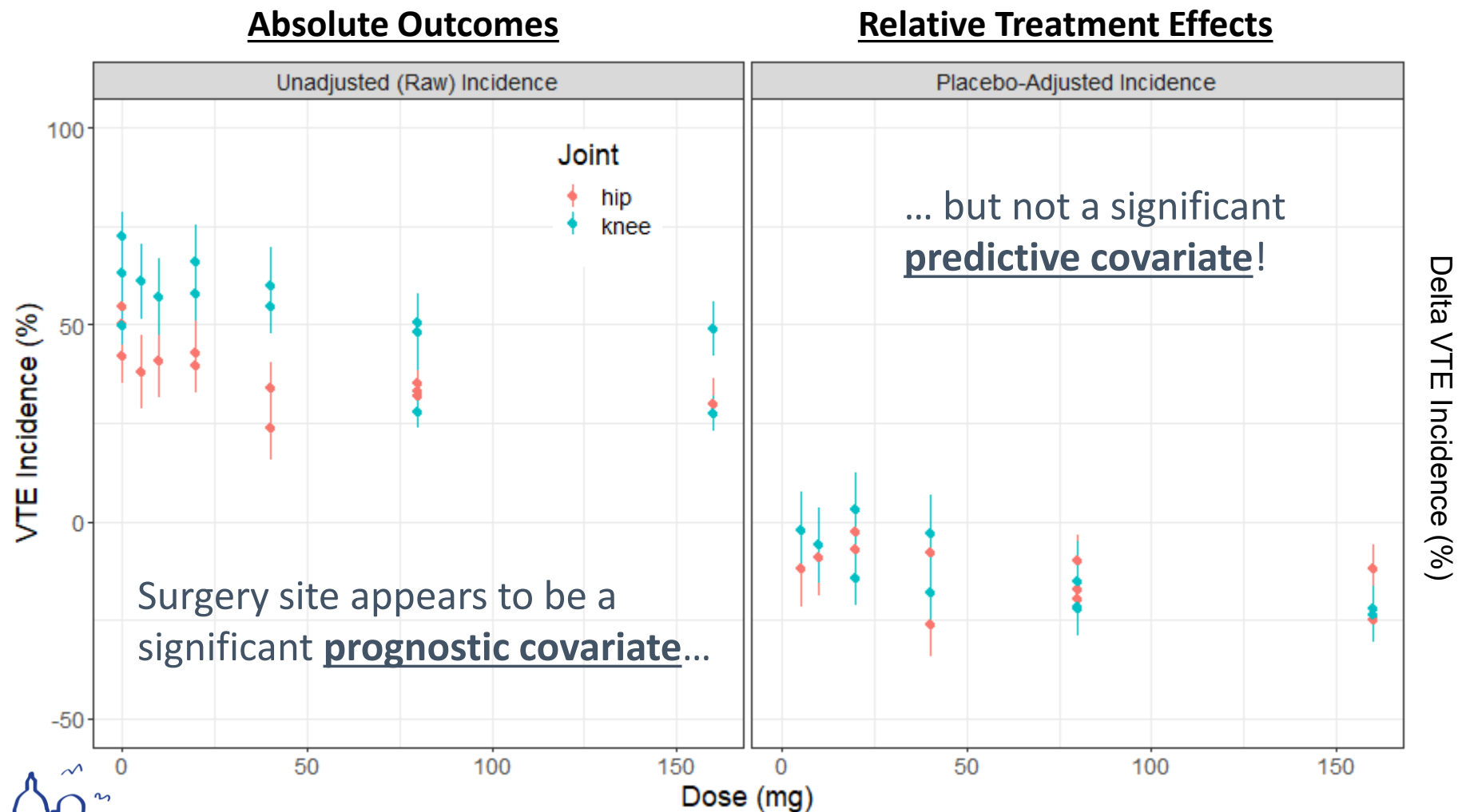
Example with Heterogeneity in Absolute Effect on VTE

Impact of a hypothetical factor Xa inhibitor on venous thrombo-embolism (VTE) after knee or hip surgery in a US patient population

Study	Surgery	N/Arm	Doses Arms (mg)	% With VTE
1	hip	100	0, 5, 10, 20, 40, 80	50, 38, 41, 43, 24, 33
2	hip	200	0, 20, 40, 80, 160	42, 40, 34, 32, 30
3	hip	400	0, 80, 160	55, 35, 30
4	knee	100	0, 5, 10, 20, 40, 80	63, 61, 57, 66, 60, 48
5	knee	200	0, 20, 40, 80, 160	72, 58, 54, 50, 49
6	knee	400	0, 80, 160	50, 28, 28

Note: Endpoint is only reported once at the end of each study, which is also often the case for safety endpoints.

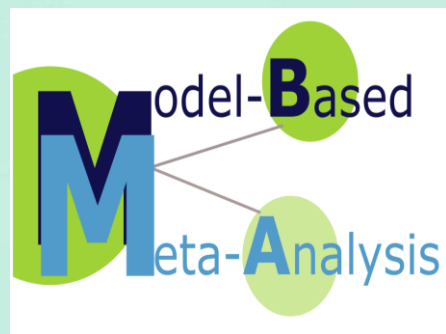
Exploratory Plots for the VTE Data



When to Focus the Model on Absolute Outcomes

- Again, the primary interest of an RCT (and typical MBMA) is the comparison of treatment versus control (i.e., relative effect)
- However, when the goal is to understand prognostic factors causing between-trial heterogeneity in absolute outcomes, a model on absolute outcomes is most appropriate
 - I.e., a parametric model for placebo response or disease progression
- This is common for indications where single-arm trials are prevalent (e.g., many oncology indications), or when modeling only placebo (or SoC) data
 - It is recommended to only model data from one treatment (e.g., placebo) with this approach
- Random effects and prognostic covariates should always be included in models that focus on absolute outcomes

See case study #2 (slide 13) for an example



MBMA Best Practices

Data Weighting



Accounting for Differences in the Precision of Observations

One of the most important differences between MBMA and models using patient-level data (e.g., pop PK/PD models) is the weighting of each data point

- In a typical pop PK/PD model, each data point is equally weighted (by patient)
- However, each data point in a MBMA represents a population of N patients, and larger populations should be more heavily weighted than smaller population
 - The weighting is actually based on the precision ($1/SE^2$) of the modeled endpoint, where $SE = \frac{\sigma}{\sqrt{N}}$
- This weighting is applied through the residual (ε) error in the model, where $\text{var}(\varepsilon) = \frac{\sigma^2}{N}$

$$Y_{ij} = Eo_i + f(\theta_k) + \boxed{\varepsilon_{ij}}$$

$$\boxed{\varepsilon_{ij} \sim N(0, \sigma_{ij}^2 / N_{ij})}$$

Weighting recommendations for different types of endpoints

Continuous endpoints (e.g., mean change from baseline, ΔY)

$$\varepsilon_{ij} \sim N(0, \sigma_{ij}^2 / N_{ij})$$

- Can use observed σ_{ij}^2 / N_{ij}
- Can also use global estimate of σ^2 as weighted average of observed σ_{ij}^2
- Or, can estimate σ^2 in MBMA

Binary endpoints (e.g., proportion of patients, p)

- Only need sample size and number of events: $Ne_{ij} \sim \text{binomial}(p(\text{event})_{ij}, N_{ij})$

- Binomial distribution approximated using p_{ij} as dependent variable with $\varepsilon_{ij} \sim N\left(0, \frac{p_{ij}(1-p_{ij})}{N_{ij}}\right)$
- $p_{ij} = \frac{Ne_{ij}}{N_{ij}}$

Event rates as endpoints (e.g., annualized event rate, r)

- Need sample size, number of events, and duration of interval (time): $Ne_{ij} \sim \text{Poisson}(\lambda_{ij})$

- Poisson distribution approximated using rate (r_{ij}) as dependent variable with $\varepsilon_{ij} \sim N\left(0, \frac{r_{ij}}{\sum_{k=1}^{N_{ij}} \text{time}_{ijk}}\right)$
- $r_{ij} = \frac{Ne_{ij}}{\sum_{k=1}^{N_{ij}} \text{time}_{ijk}}$

A quick note on imputing missing weights

- Precision of the modeled endpoint may not be reported in every study
 - Note: proportions and rates do not need to use reported precision, as the variable itself is sufficient to define SE (based on distribution assumptions)
- Instead of omitting studies with missing precision information, one can impute the missing information and keep the study in the analysis in different ways, e.g.,
 - Use weighted average of SD from studies reporting precision, then divide by $\sqrt{N_{ij}}$ to derive SE
 - Identify factors that are related to SD and use regression on SD to impute appropriate weights
- Similar imputation rationale can be applied to missing covariate data

Back to the VTE example...

Modeling the absolute response variability in the VTE data

- The number of patients with a VTE event in treatment arm (j) of a trial (i) is assumed to follow a binomial distribution, depending on sample size N_{ij} and probability $p(\text{event})_{ij}$:

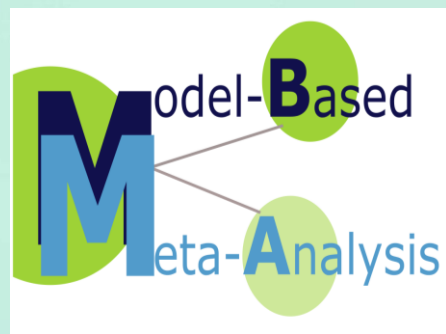
$$N_{event,ij} \sim \text{binomial}(p(\text{event})_{ij}, N_{ij})$$

$$\text{logit}(p) = \log\left(\frac{p}{1-p}\right)$$

$$p(\text{event})_{ij} = f\left\{E_{0i} - \frac{I_{\max} \cdot \text{Dose}}{\text{Dose} + ED_{50}}\right\} + \varepsilon_{ij}$$

$$\text{logit}^{-1}(x) = \frac{e^x}{1+e^x}$$

- $f\{x\} = \text{logit}^{-1}(x)$ for binomial distribution assumption and to keep modeled p between 0 and 1
- E_0 = logit VTE incidence in the absence of drug (e.g., placebo effect) for the i^{th} study
- $I_{\max}$ = maximum drug-related reduction in logit VTE incidence
 - $I_{\max}$ can be interpreted as the maximum log(OR) of placebo vs drug; i.e., $\text{OR vs pbo} = \exp\left(\frac{-I_{\max} \cdot \text{Dose}}{\text{Dose} + ED_{50}}\right)$
- ED_{50} = dose which achieves 50% of $I_{\max}$
- $\varepsilon_{ij} \sim N\left(0, \sigma_{ij}^2 = \frac{p_{ij}(1-p_{ij})}{N_{ij}}\right)$  Accounts for difference in weighting across VTE studies



MBMA Best Practices

Implementation



MBMA implementation (code)

- The following slides show specific coding suggestions using the nlme() library* within the R programming language
- However, like any model development, MBMA can utilize many different optimization programs (e.g., NONMEM, Monolix, WinBUGS, Matlab, etc.)

* Pinheiro, J., Bates, D., & R Core Team (2026). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-169.

Implementing the VTE Model in R

1. Ignore all between-trial heterogeneity (not recommended!)

```
fit.0 <- gnls(#Data are fit using generalized least squares
```

Model and Data Set Specification

```
y0 ~ invlogit(e0 - imax*dose/(dose+exp(led50))),  
data=vte.dat,
```

Structural Model

Parameter Dependencies and Initial Estimates

```
params=list(e0~1, imax~1, led50~1),  
start=list(e0=logit(0.6), imax=1.8, led50=log(30)),
```

Note: Only one value for each parameter is estimated for the entire data set. The number of initial estimates must match the number of parameters.

Weighting and Optimization Settings

```
weights= varPower(form=~fitted.)*(1-fitted.)/n,fixed=0.5),  
control=gnlsControl(sigma=1)
```

```
)#end of function call
```

Parameter	Value
e0	0.181
imax	1.43
led50	4.40

A Few Words on Weighting and Optimization Settings

```
weights= varPower(form=~fitted.)*(1-fitted.)/n, fixed=0.5),  
control=gnlsControl(sigma=1)
```

- **varPower** is a variance function which uses the following format for variance of the residuals: $\text{Var}(\varepsilon_{ij}) = \sigma^2 |f_{ij}|^{2\delta}$, where f_{ij} is the function specified using the 'form' statement and δ is specified with 'fixed'
- In this case, $f_{ij} = \frac{p(1-p)}{N_{ij}}$, the normal approximation for the variance of a sample proportion. Since the true probability of a VTE event (p) is unknown, we use the current best estimate from the fitting algorithm, **fitted(.)**
- **Fixing $\delta = 0.5$ and sigma (σ) = 1** essentially tells the fitting algorithm that f_{ij} exactly specifies the residual variance and no re-optimization of the weights is desired

$$\text{i.e., } \text{Var}(\varepsilon_{ij}) = \sigma^2 |f_{ij}|^{2\delta} = 1 * \left| \frac{p(1-p)}{N_{ij}} \right|^{2*0.5} = \frac{p(1-p)}{N_{ij}}$$

2. Incorporating Between-Study Variability on Placebo Effect: Placebo Model with Random Effect Method* (also not recommended)

nlme* instead of gnl
for random effects;
need to specify
“fixed” for fixed effect
parameters

```
fit.1 <- nlme(y0 ~ invlogit(e0 - imax*dose/(dose+exp(led50))),
```

```
data=vte.dat,
```

```
fixed=list(e0~1, imax~1, led50~1),
```

```
start=list(e0=logit(0.6),imax=1.8,led50=log(30)),
```

```
random=e0~1 | study,
```

```
weights= varPower(form=~fitted.)*(1- fitted.)/n,fixed=0.5),
```

```
control=nlmeControl(sigma=1))
```

Additional random
effect input to model;
additive effect applied
to e0, grouped by study

* The nlme() function allows you to specify random effects, gnl() does not

Parameter	Value
e0	0.233
imax	1.09
led50	3.52
e0.sd	0.382

3. Incorporating Between-Study Variability on Placebo Effect: Unstructured Placebo Method (recommended approach)

Specifies that separate values of e_0 should be estimated for each study; include -1 to avoid a reference intercept

Initial e_0 estimates must be included for all 6 trials

```
fit.2 <- gnls(y0 ~ invlogit(e0 - imax*dose/(dose+exp(led50))),  
             data=vte.dat,  
             params=list(e0~as.factor(study)-1, imax~1, led50~1),  
             start=list(e0=rep(logit(0.6),6),  
                       imax=1.8,led50=log(30)),  
             weights= varPower(form=~fitted.)*(1- fitted.)/n,fixed=0.5),  
             control=gnlsControl(sigma=1))
```

Parameter	Value
e0.as.factor(study)1	-0.126
e0.as.factor(study)2	-0.071
e0.as.factor(study)3	0.135
e0.as.factor(study)4	0.749
e0.as.factor(study)5	0.808
e0.as.factor(study)6	-0.069
imax	1.08
led50	3.47

Comparison of Model Fits

1. No Heterogeneity in Placebo (fit.0)

Parameter	Value	Std.Error	t-value	p-value
e0	0.181	0.050	3.64	0.0013
imax	1.43	0.252	5.69	0.0000
led50	4.40	0.434	10.1	0.0000

Differing numbers of e0 estimates

2. Heterogeneity with Random Effects in Placebo Model (fit.1)

Parameter	Value	Std.Error	t-value	p-value
e0	0.233	0.175	1.33	0.1969
imax	1.09	0.150	7.28	0.0000
led50	3.52	0.486	7.25	0.0000
e0.sd	0.382			

3. Heterogeneity with Unstructured Placebo (fit.2)

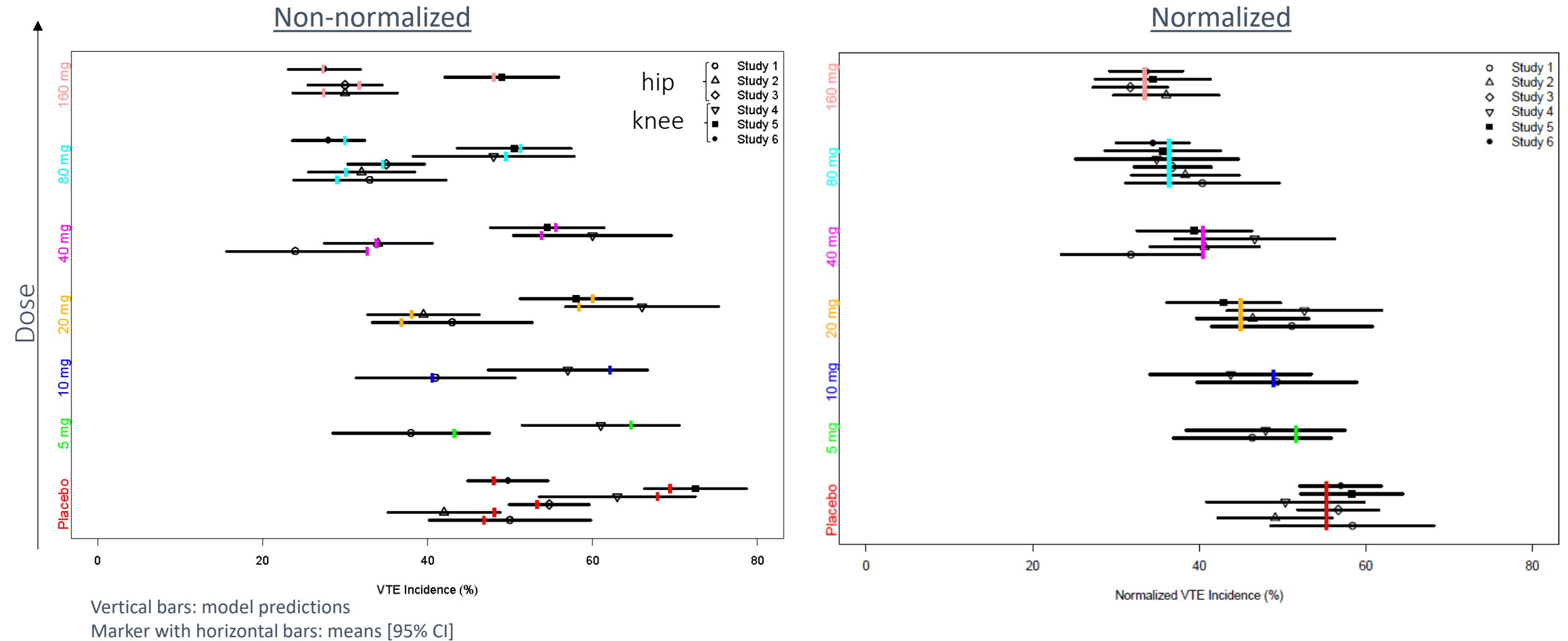
Parameter	Value	Std.Error	t-value	p-value
e0.as.factor(study)1	-0.126	0.100	-1.26	0.2232
e0.as.factor(study)2	-0.071	0.083	-0.85	0.4066
e0.as.factor(study)3	0.135	0.072	1.87	0.0763
e0.as.factor(study)4	0.749	0.101	7.45	0.0000
e0.as.factor(study)5	0.808	0.082	9.80	0.0000
e0.as.factor(study)6	-0.069	0.073	-0.94	0.3588
imax	1.08	0.132	8.18	0.0000
led50	3.47	0.451	7.70	0.0000

Improvement is highly significant at each step

Likelihood Ratio Test for Nested Models

Model	df	AIC	BIC	logLik	Test	L.Ratio	p-value
fit.0	3	73.6	77.6	-33.8		NA	NA
fit.1	4	-76.7	-71.4	42.4	fit.0 vs. fit.1	152.3	<0.0001
fit.2	8	-96.2	-85.5	56.1	fit.1 vs. fit.2	27.5	<0.0001

Dose-Response predictions shown with forest plot



Normalizing to a “typical” E0 gives a clearer view of dose-response

It is helpful to normalize model fits using partial residual plots

ARTICLE

Partial Residual Plots as an Integrated Model Diagnostic Tool in Model-Based Meta-Analysis

John Maringwa^{1,*} , Paul Matthias Diderichsen²  and Chandni Valiathan³

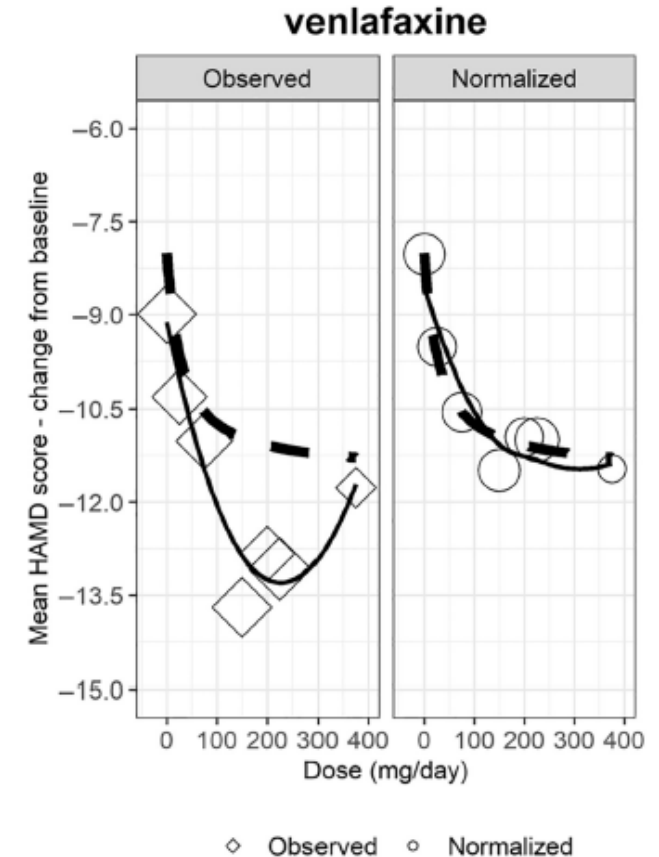
$$Y_{ij} = f(E0_i, dose_{ij}, \theta) + \varepsilon_{ij}; \quad \varepsilon_{ij} = Y_{ij} - f(E0_i, dose_{ij}, \theta)$$

$$Yn_{ij} = f(E0_{fix}, dose_{ij}, \theta) + \varepsilon_{ij}$$

$$Yn_{ij} = Y_{ij} + \left(f(E0_{fix}, dose_{ij}, \theta) - f(E0_i, dose_{ij}, \theta) \right)$$

“PRPs provide a robust integrated diagnostic tool in MBMA that uses all data to show the correlation between response and any covariate while controlling for other covariates included in the model.”

[Maringwa J, Diderichsen PM, Valiathan C. Partial Residual Plots as an Integrated Model Diagnostic Tool in Model-Based Meta-Analysis. Clin Pharmacol Ther. 2024 Sep 8. doi: 10.1002/cpt.3418.](#)



Model prediction (dashed line) in comparison to observed/normalized data points. The model prediction is based on a typical placebo estimate of -8 and mean baseline HAMD score of 23. The continuous lines show a LOESS curve.

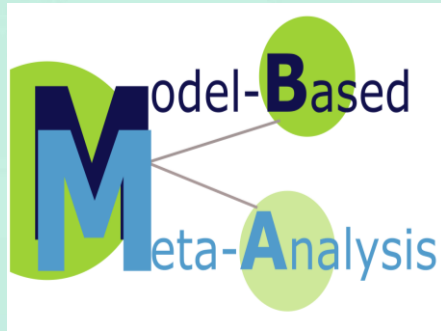
Extending to Longitudinal Models with Multiple Observations per Arm

- It is critical to account for correlation in longitudinal data to avoid inflated precision in parameter estimates
- Compound symmetry example:

$$Y_{ijt} = Eo_{it} + f(\theta_{ki}) + \eta_{ij} + \varepsilon_{ijt}$$

$$\theta_{ki} \sim N(\theta_k, \Omega) \quad \eta_{ij} \sim N(0, \omega^2 / N_{ij}) \quad \varepsilon_{ijt} \sim N(0, \sigma^2 / N_{ij})$$

- Notation is same as before: Y_{ijt} is the mean response at time t for the j^{th} arm in the i^{th} trial
- η_{ij} reflects the random differences in the mean due to between-arm variability ω^2
- ε_{ijt} reflects the random residual error due to within-arm (between-subject) variability σ^2
- The variance and correlation of the means of an arm within the trial is:
 - $\text{var}(Y_{ijt}) = \frac{\omega^2 + \sigma^2}{N_{ij}}; \quad \text{cov}(Y_{ijt_1}, Y_{ijt_2}) = \frac{\omega^2}{N_{ij}}; \quad \text{corr}(Y_{ijt_1}, Y_{ijt_2}) = \frac{\omega^2}{\omega^2 + \sigma^2}$
- Different temporal correlation structures (e.g., CAR1) can also be specified to ensure an adequate variance profile is captured:
 - $\text{corr}(\varepsilon_{ijk}, \varepsilon_{ij(k+\delta)}) = \rho^\delta$, at time points k and $k+\delta$ in arm j of trial i



MBMA Best Practices

Covariates and Model Diagnostics

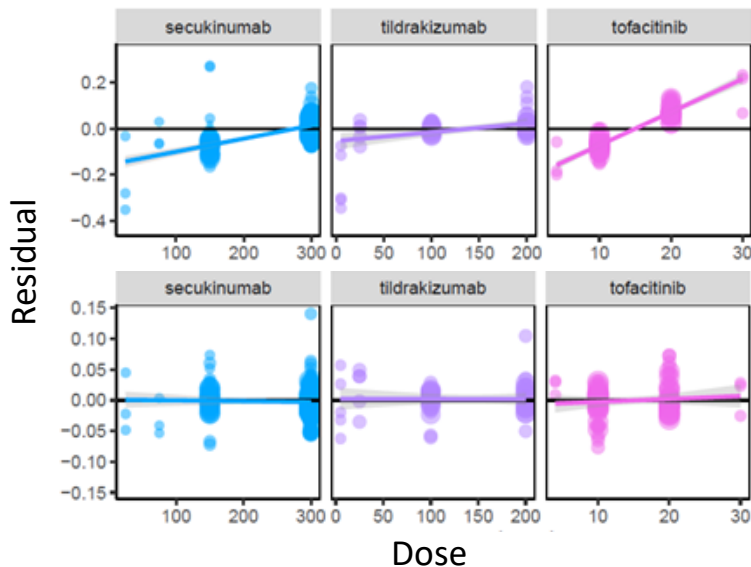


Explore covariates after accounting for treatment

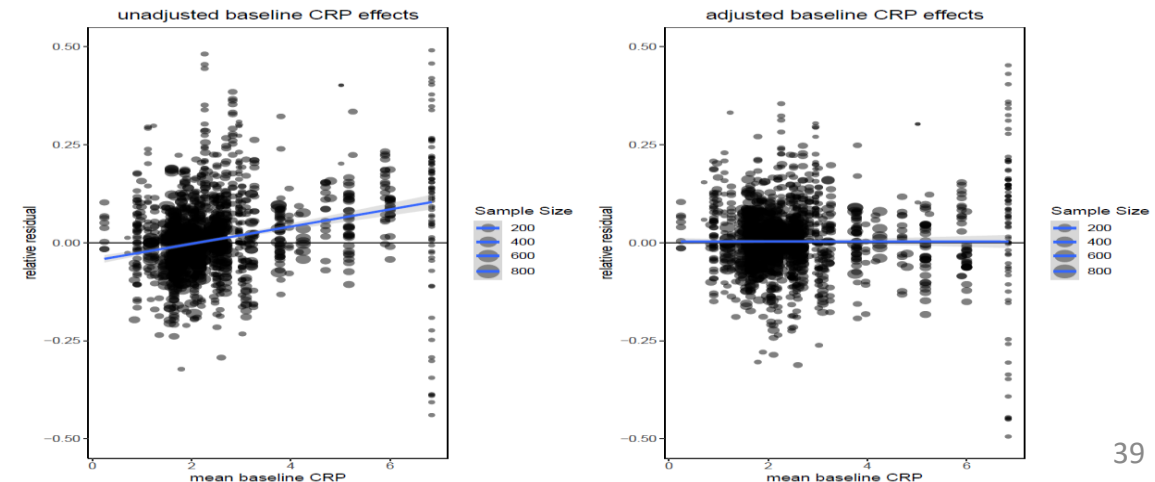
Covariates should be explored after adjusting for other known influential factors (e.g., treatment)

- Plots of raw outcomes vs covariates should be explored only if plotted separately for each known influential categorical factor, like treatment
- A preferred approach would be to plot residuals from the current model vs covariates
 - Residual plots implicitly account for influential factors already in the model
 - For transformed data, it may be more appropriate to use difference in observed and predicted outcomes in the domain where the covariates will act (e.g., log or logit domains)
 - To explore predictive covariates on treatment effects, use “relative residuals” (res.active – res.control)
 - These are only available for studies with the reference control treatment (e.g., placebo)

Base model

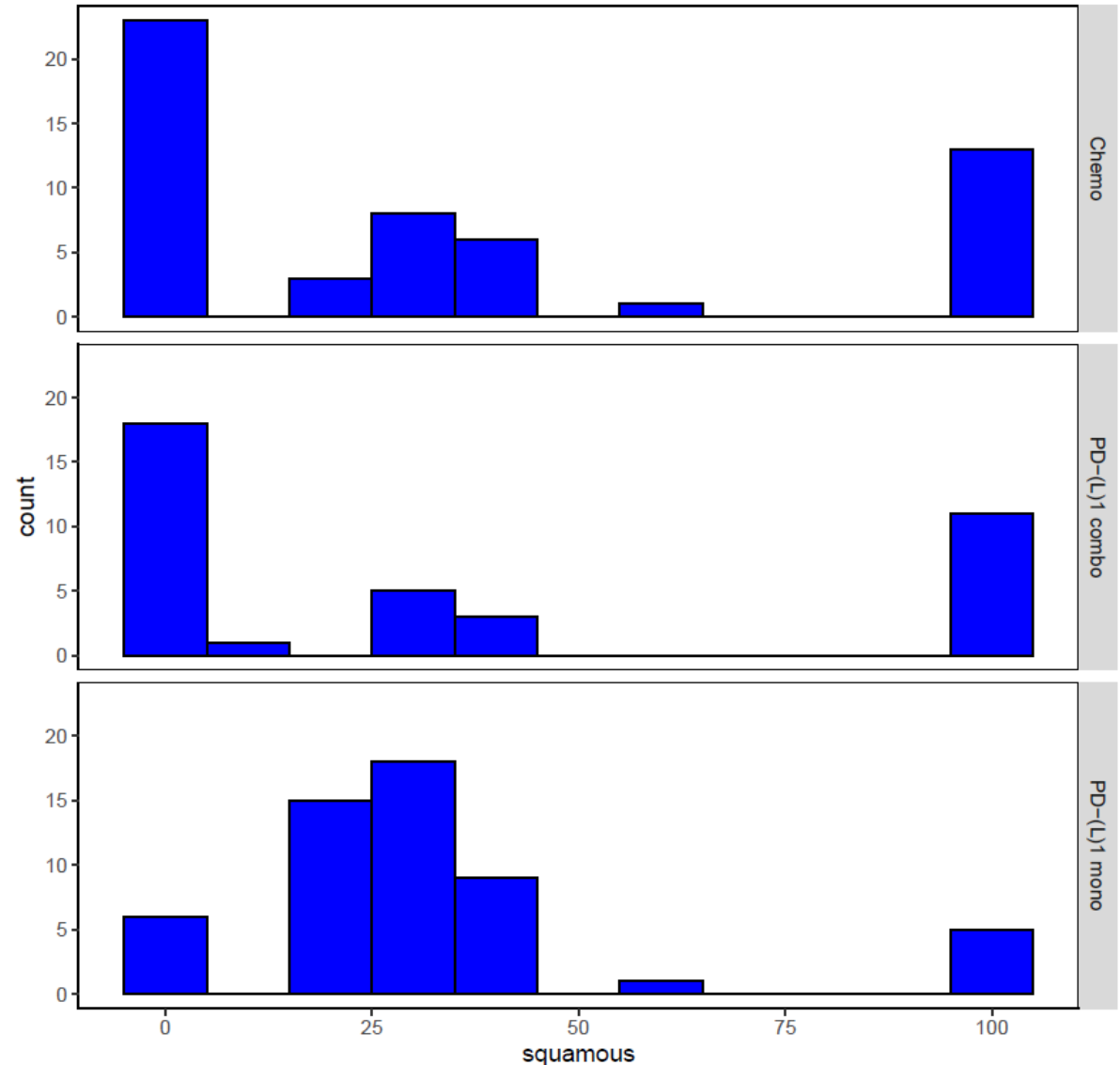


Final model



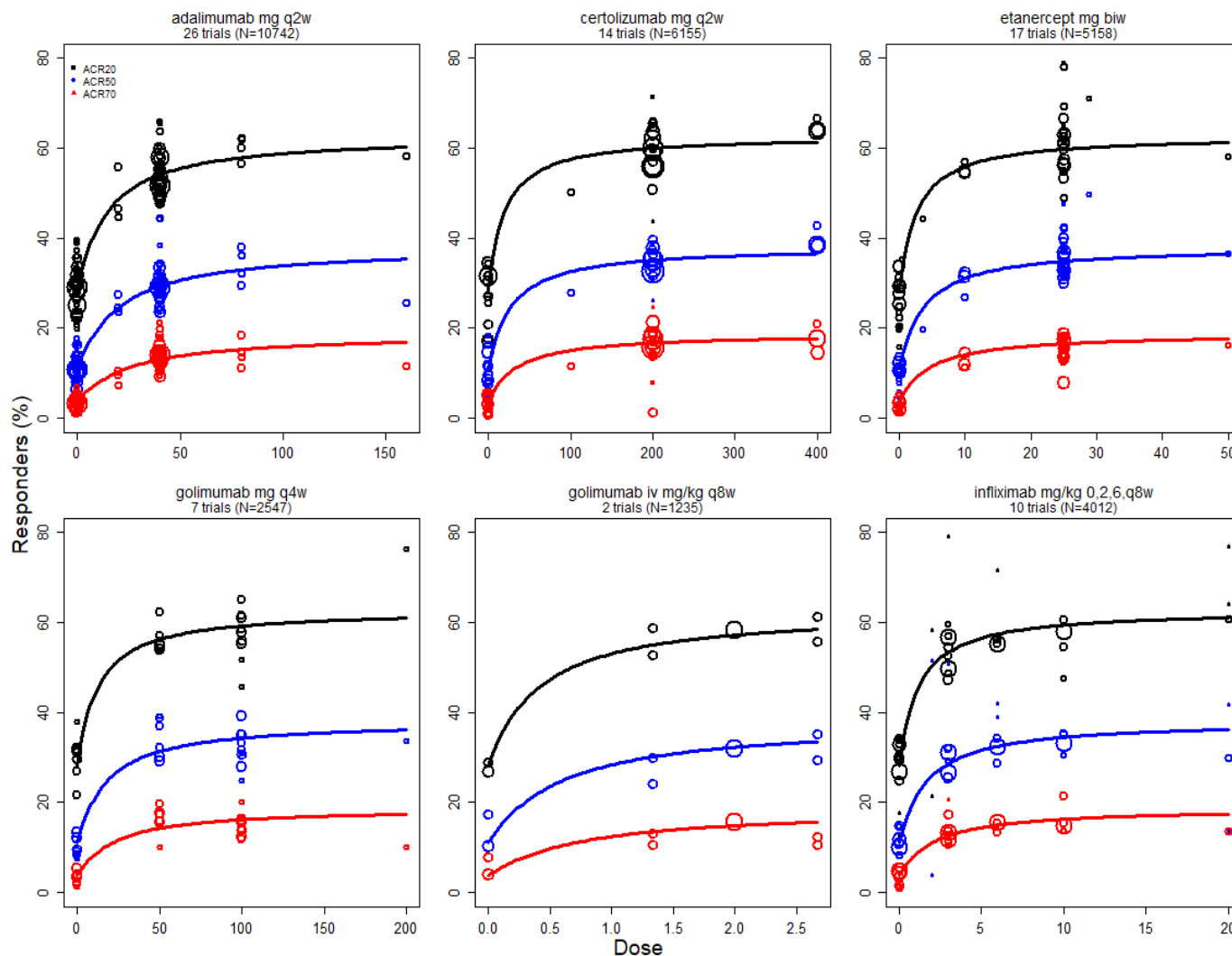
Explore covariate content (and effects) by treatment/class

- As treatment is a critical factor in an MBMA, covariate parameter estimates are only informed by treatments that have a range of covariate values across studies/strata
 - That is, treatments with few studies or treatments whose studies are all in similar populations will not inform covariate parameter estimates
 - Treatments included in studies that report results stratified by covariate categories are most informative
- Simple data summaries showing the range of covariate values available for each treatment allows the analyst to understand the sources of estimated covariate influences



Use Dose-Response Plots to Explore The Drug Effect

Dose-response relationship is consistent and well characterized across trials, elucidating the competitive landscape in RA



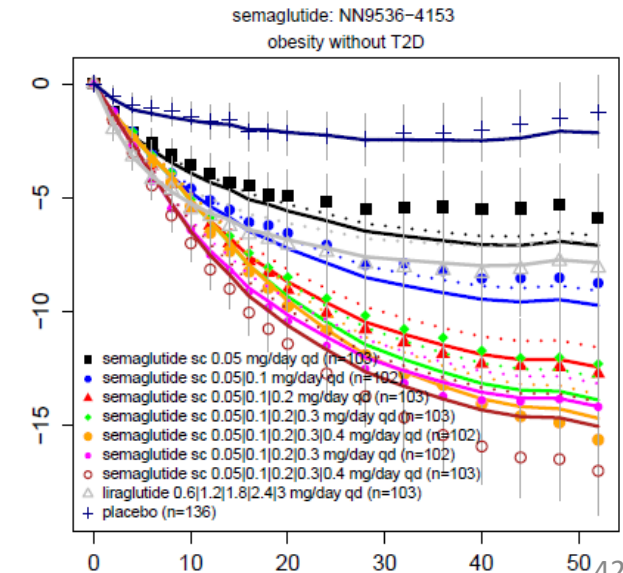
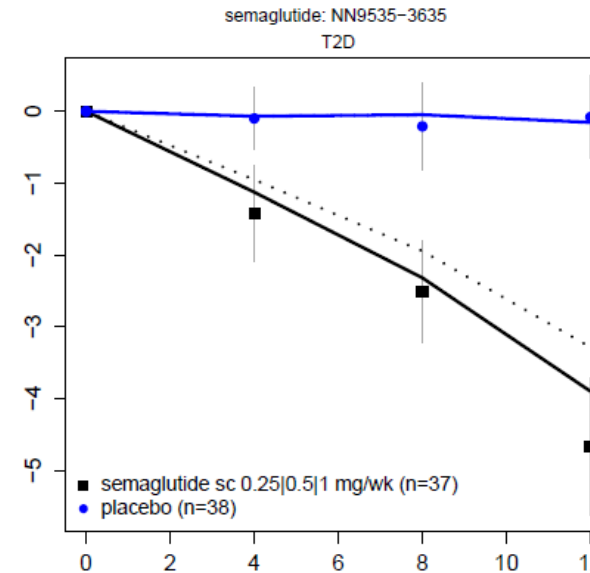
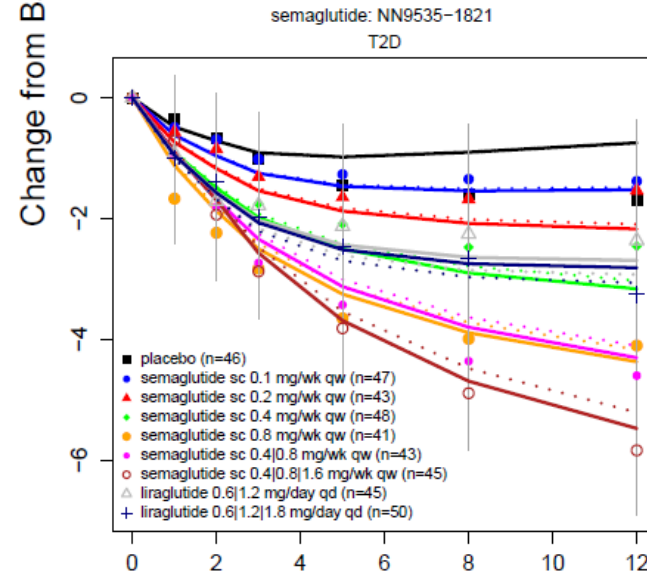
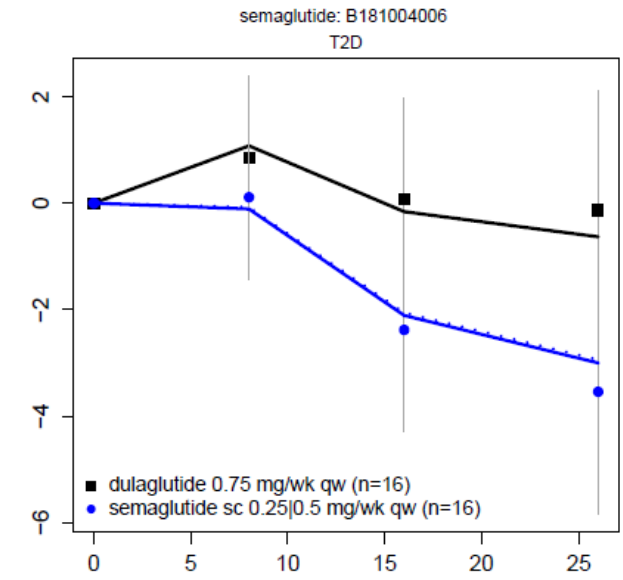
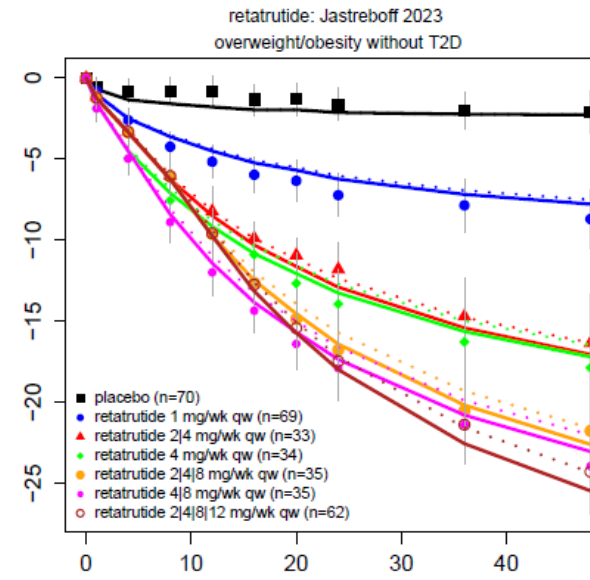
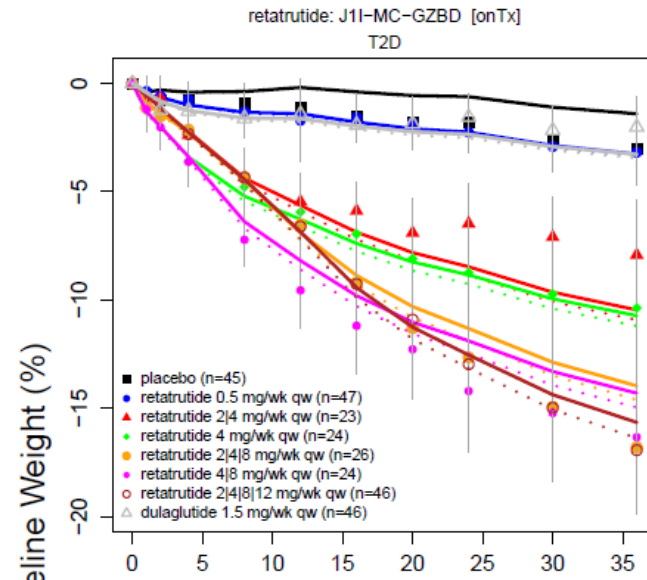
$$P(ACR)_{ijkt} = \text{logit}^{-1} \left(Eo_{itk} + f(\text{Drug}_{ij}, \text{Dose}_{ij}, t, X_i, \theta_{ik}) * e^{\eta_{ik}} \right)$$

Model Description

- Eo_{itk} represents a fixed-effect placebo estimate for every study, time, and endpoint (i.e., ACR20/50/70). This captures variability in absolute response, and no prognostic covariates are necessary.
- $f(\text{Drug}_{ij}, \text{Dose}_{ij}, t, X_i, \theta_{ik})$ is the model for the relative treatment effect for each drug, dose, time, endpoint, and predictive covariates:
 - Baseline CRP
 - % of patients on background MTX
 - Asian/non-Asian (especially for JAKs)
- Trial-to-trial variability in relative treatment effect (OR) is described by study-specific random effects η_{ik}

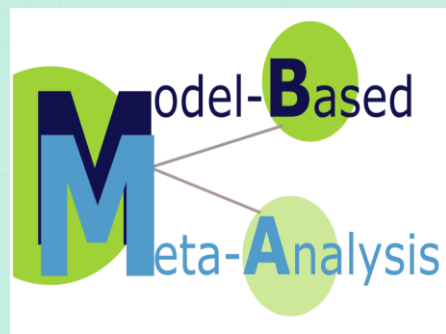
Use Time Course Plots to Evaluate Time Dependencies

Effect onset, including impact of dose-titration, is captured consistently well across studies involving weight loss drugs



Key Methodology Overview

- Dealing with heterogeneity between treatment arms and studies is critical in MBMA
- Prognostic covariates explain heterogeneity in absolute outcomes, independent of treatment
- Predictive covariates explain heterogeneity in relative treatment effects
- Literature data must be appropriately weighted according to the precision of each observation (variability and sample size)
- Relative response is generally of primary interest in MBMA. Unstructured placebo approaches greatly simplify the modeling process and avoid biased treatment effect estimates
 - Parametric approaches are appropriate if placebo response* (or disease progression) or synthetic control (e.g., when single-arm studies are prevalent) is the primary interest
 - * Best to separately model absolute outcomes using only placebo data
- When modeling longitudinal data, correlation between serial observations within a treatment arm should be accounted for
- Covariates should be explored after adjusting for other known influential factors (e.g., treatment)



Thank you!

Questions?



Selected References

1. [The Many Flavors of Model-Based Meta-Analysis: Part I-Introduction and Landmark Data](#) by M Boucher and M Bennetts
2. [Many Flavors of Model-Based Meta-Analysis: Part II - Modeling Summary Level Longitudinal Responses](#) by M Boucher and M Bennetts
3. [Applications of Model-Based Meta-Analysis in Drug Development](#) by Phyllis C et. al.
4. [Direct Oral Anticoagulants Vs. Enoxaparin for Prevention of Venous Thromboembolism Following Orthopedic Surgery: A Dose–Response Meta-analysis](#) by Boyd RA et. al.
5. [Quantitative Evaluations of Time-Course and Treatment Effects of Systemic Agents for Psoriasis: A Model-Based Meta-Analysis](#) by Checchio T et. al.
6. [Model-based meta-analysis of non-small cell lung cancer with standard of care PD-1 inhibitors and chemotherapy for early development decision making](#) by Turner DC et al.
7. [Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain--results of a model-based meta-analysis that accounts for encapsulation](#) by J W Mandema, E Cox, and J Alderman
8. [Model-based meta-analysis for comparative efficacy and safety: application in drug development and beyond](#) by JW Mandema et al.
9. [Quantitative Model-Informed Dose Selection for a Milvexian Phase III Study in Patients With Atrial Fibrillation](#) by W Zhou et al.
10. [Comparative Efficacy of Relapsing Multiple Sclerosis Therapies: Model-Based Meta-Analyses for Confirmed Disability Accumulation and Annualized Relapse Rate](#) by B Hennessy et al.
11. CPT-PSP MBMA themed issue 2026

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Statistics & Pharmacometrics



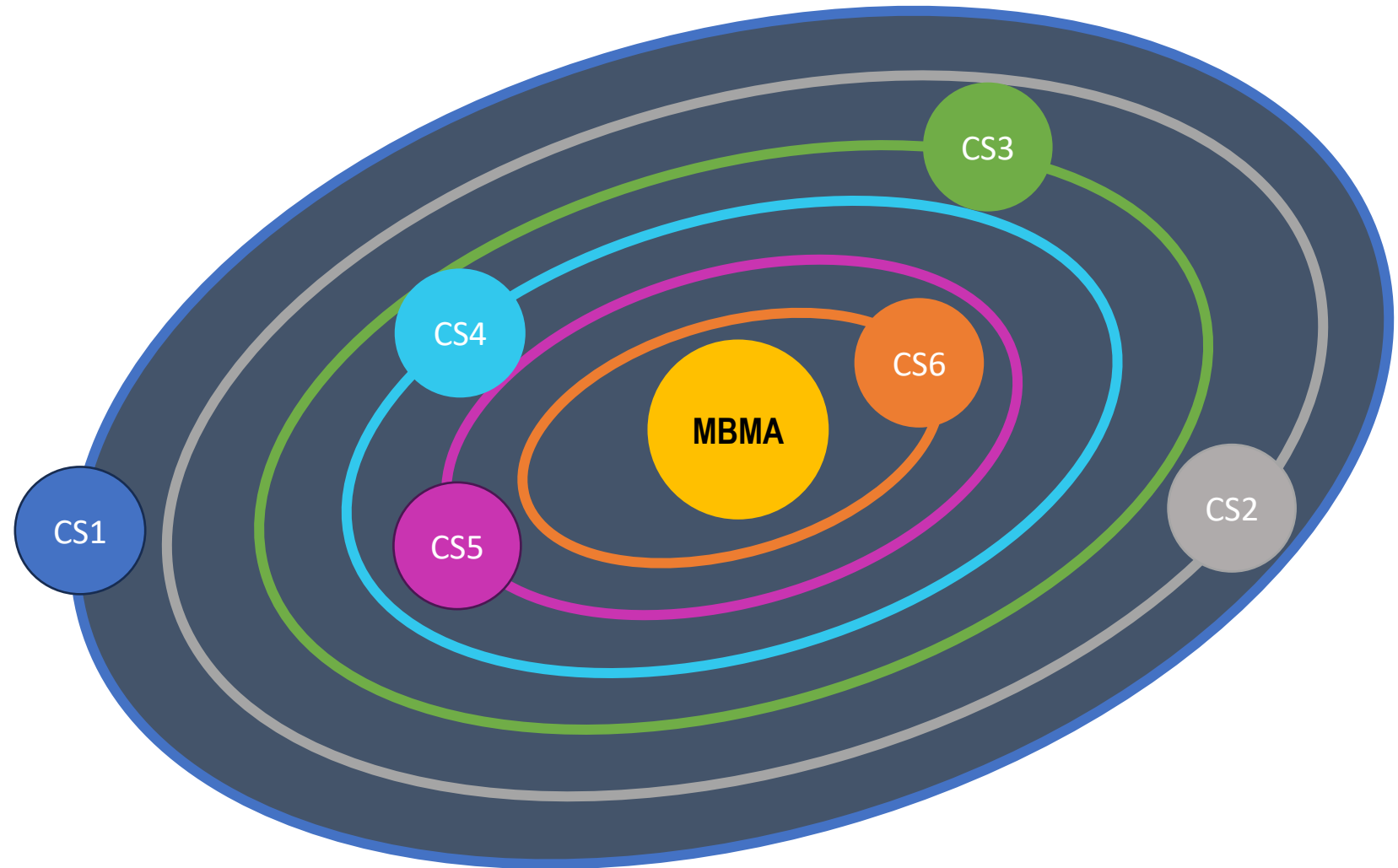
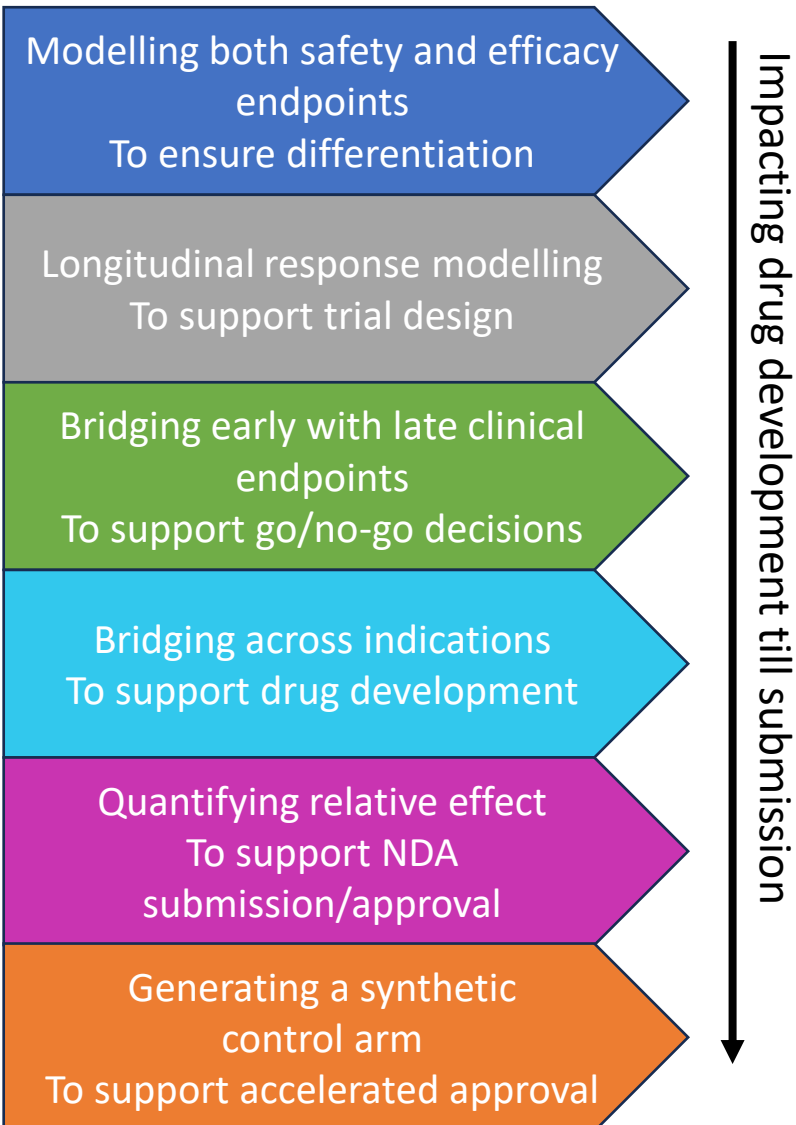
SPECIAL INTEREST GROUP



Supplementary Material



MBMA (What and Why): Case Studies



MBMA in VTE prevention to quantify the anticoagulant landscape and identify differentiation targets in both efficacy and safety

CS1

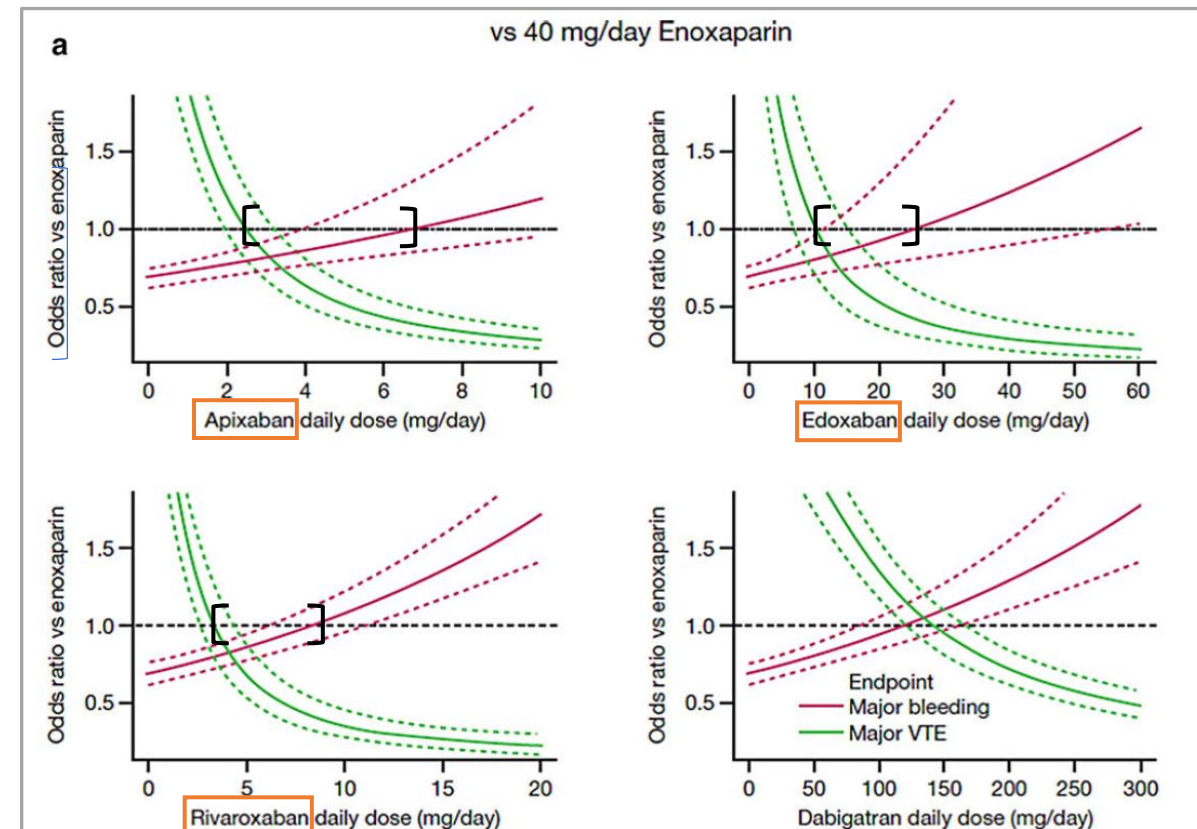
- A dose-response joint MBMA was developed using published Venous Thromboembolism (VTE) and bleeding results from 89 randomized controlled trials of 23 anticoagulants representing seven drug classes in orthopedic surgery patients (i.e. Total Hip/Knee Transplantation)

- Model:

$$P(event)_{kij} = f\{E_{0,ki} - g(Drug_{ij}, Dose_{ij}, X_{ij}, \theta_i)_k\}$$

- The therapeutic index was defined as the ratio of the model estimates of potency (i.e. bleeding (EDbld)/efficacy (ED50,vte)) for a particular drug.
- MBMA can be used in conjunction with emerging data from investigational agents to help inform dose selection and study design, which will ensure efficient clinical development and adequate differentiation from current therapy

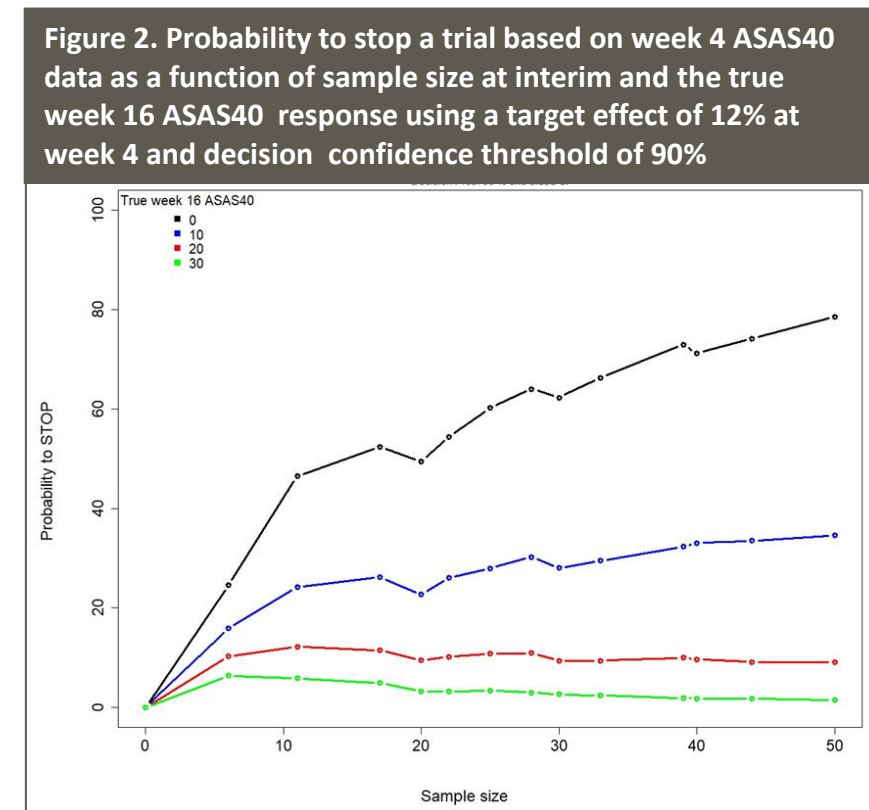
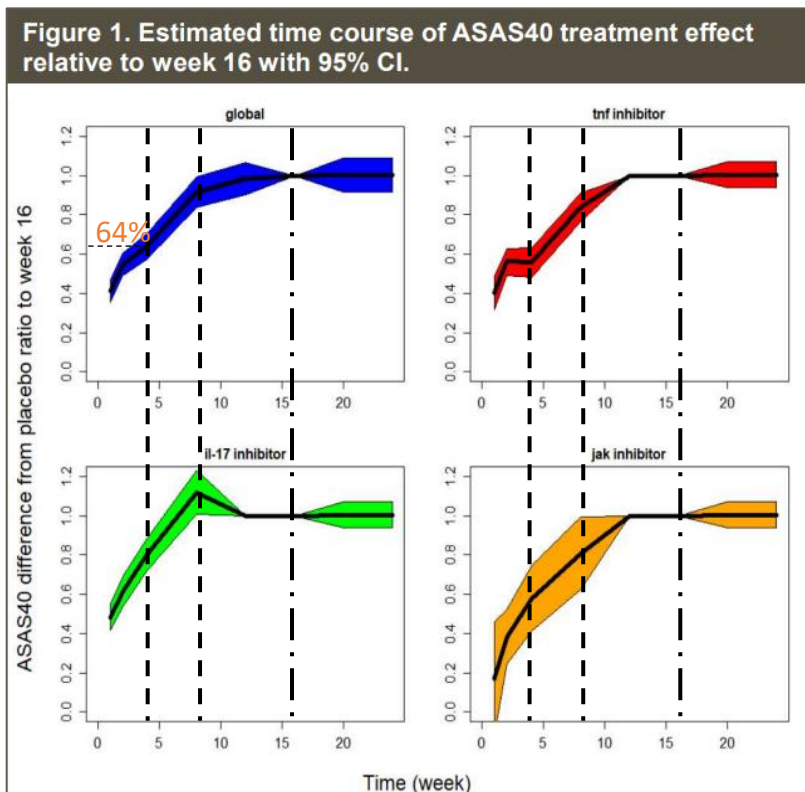
Direct Factor Xa (FXa) inhibitors have a wider therapeutic index than other classes → can improve both bleeding and efficacy



MBMA in Axial Spondyloarthritis (AxSpA) to characterize the longitudinal response for supporting trial design

MBMA based on AxSpA public domain data enables to quantify the onset of treatment effect in different drug classes. Furthermore, it offers a quantitative understanding of the performance of decision criteria based on early clinical trial responses.

- Quantify the relationship between the magnitude of early (e.g. week 4 or 8) treatment effect and at later time points (week 16), as compared to placebo across different mechanisms of action.
- Use the modelled trajectory of the treatment effect over time to inform the design of a randomised controlled trial (RCT) in AxSpA and benchmark the operating characteristics (OCs) of an early futility analysis



MBMA in Non-Small Cell Lung cancer (NSCLC) to Inform Development Decisions

$$\text{logit}(\text{ORR}_{ij}) = \text{Intercept} + \text{Covariate Terms}_{ij} + \eta$$

ORR model

$$\text{YS}_{j,k} = \text{SR}_k^{\text{HR}_j}$$

YS : modelled survival

$$\text{YP}_{j,k} = [\text{YS}_{j,k} - \text{YS}_{j,k+1}] / \text{YS}_{j,k}$$

YP : modelled conditional death probability

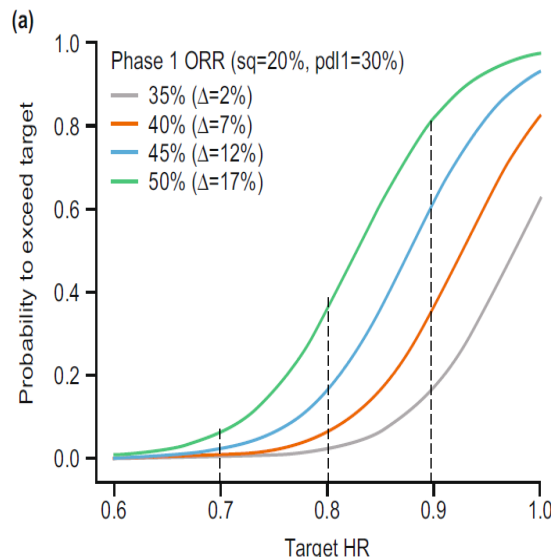
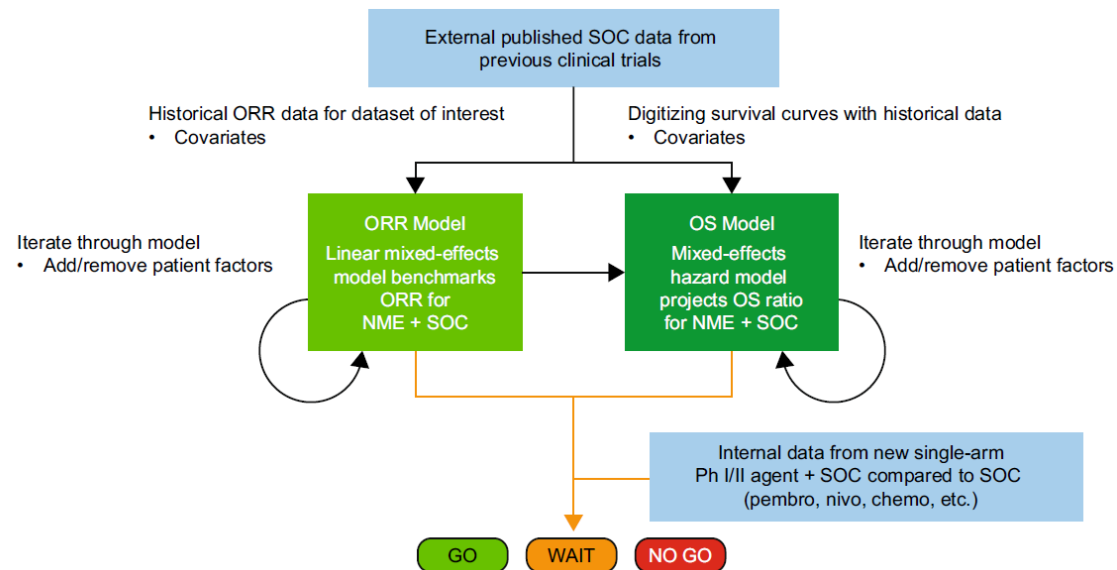
$$\log(\text{HR}_j) = \text{Slope} \times \text{ORR}_{ij} + \text{linear combination of covariates} + \eta_j$$

OS model

Model predicts probability to achieve OS HR targets based on different scenarios for observed ORR and population covariate values

Scenario	Observed NCE ORR	Comparator ORR [90% PI]	Likelihood $\Delta\text{ORR} > 10\%$	OS HR [90% PI]	Prob Target HR vs. PD-1		
					Pr70 (%)	Pr80 (%)	Pr90 (%)
Base case	0.3	0.33 [0.26-0.41]	3%	1.04 [0.90-1.20]	0	1	7
Base case	0.4	0.33 [0.26-0.41]	36%	0.92 [0.78-1.07]	1	6	36
Base case	0.5	0.33 [0.26-0.41]	82%	0.81 [0.68-0.95]	6	35	82
Low responders	0.3	0.28 [0.21-0.36]	11%	0.98 [0.85-1.12]	0	3	19
Low responders	0.4	0.28 [0.21-0.36]	60%	0.86 [0.73-1.00]	2	17	64
Low responders	0.5	0.28 [0.21-0.36]	94%	0.76 [0.63-0.90]	15	61	93
High responders	0.3	0.41 [0.33-0.49]	0%	1.15 [0.99-1.35]	0	0	1
High responders	0.4	0.41 [0.33-0.49]	9%	1.01 [0.86-1.18]	0	1	10
High responders	0.5	0.41 [0.33-0.49]	43%	0.9 [0.75-1.05]	1	10	48

Abbreviations: HR, hazard ratio relative to PD-1 inhibitor; NCE, new-chemical immuno-oncology entity; ORR, overall response rate; OS, overall survival; PI, prediction interval; Pr70, probability of achieving target 70% HR; Pr80, probability of achieving target 80% HR; Pr90, probability of achieving target 90% HR, ΔORR difference from PD-1 inhibitor, 10% was selected as an arbitrary cutoff.

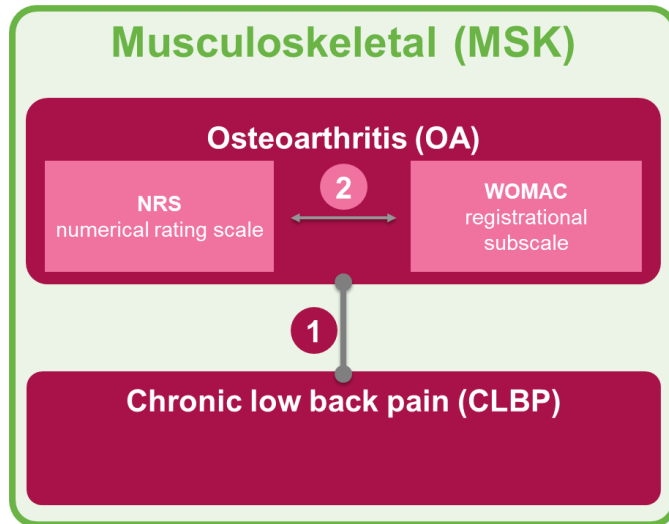
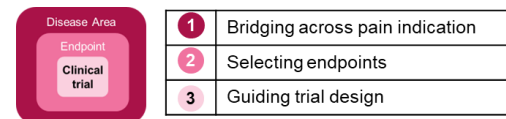


Improved Go/No-go decisions with a comprehensive MBMA framework to predict efficacy (ORR and OS) of PD-1 inhibitors (SOC) combined with novel agents (NME)

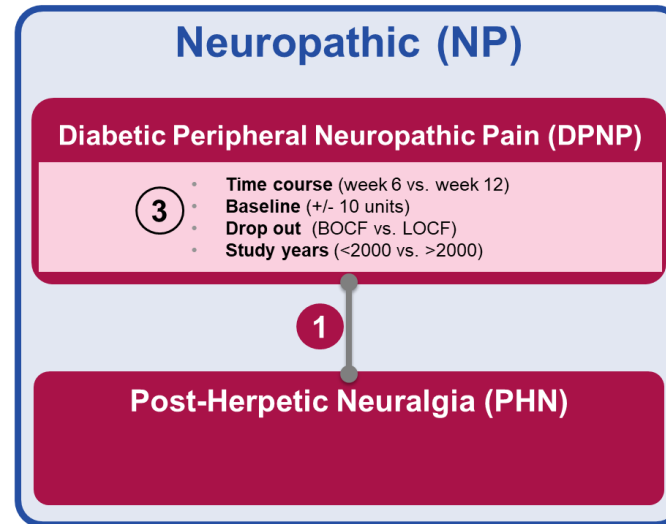
MBMA in Chronic Pain to Bridge across Indications to Guide Clinical Development

CS4

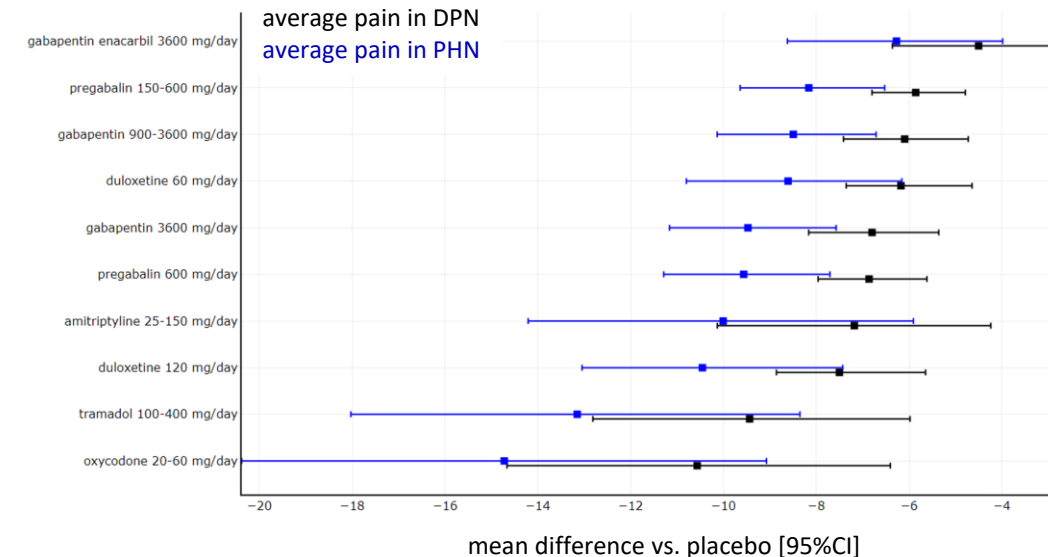
- Understanding the relative effects between different types of associated pain indications to inform the clinical development strategy within each broad category: (i.e. bridging relative effects within neuropathic pain (NP) indications as well as within musculoskeletal (MSK) pain indications to support phase 3 strategy)
 - NP: The landmark MBMA of change from baseline measures of average pain intensity (NRS or VAS by daily diary) showed a 43% greater treatment effect [15% to 71%] in PHN when compared to DPN.



Different pathophysiology



Estimated treatment effect (with 95% CI) at 12 weeks for selected treatments in DPN vs. PHN



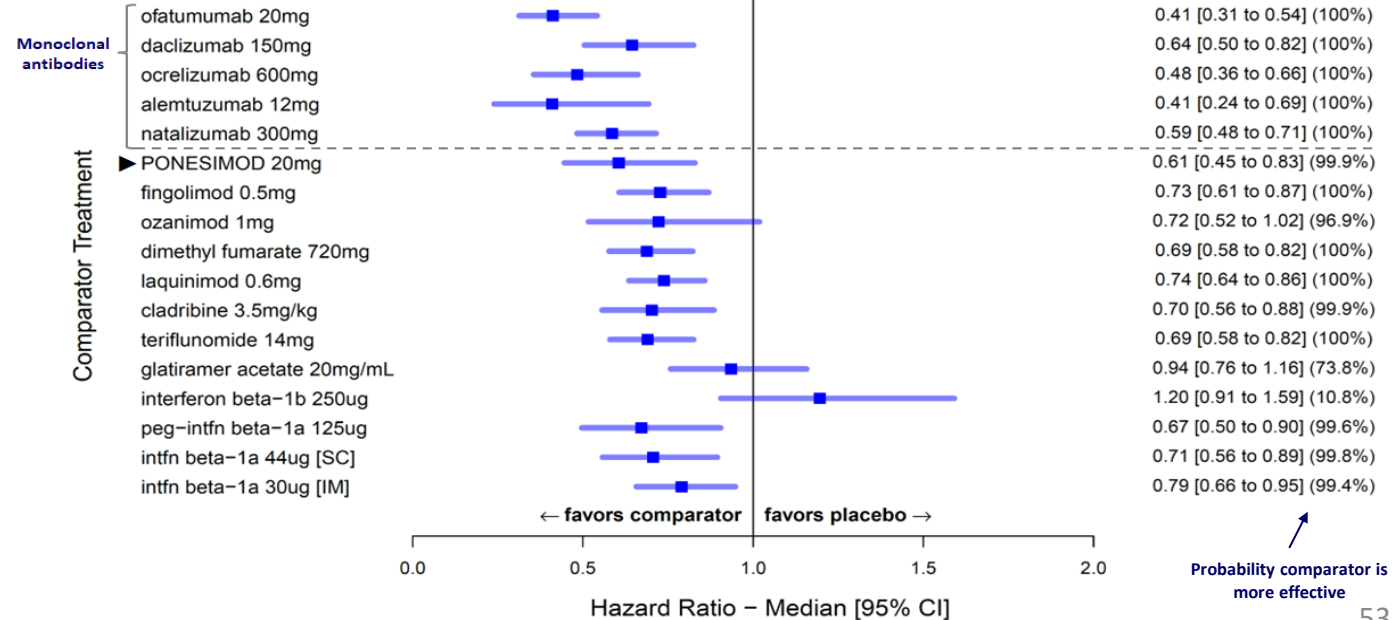
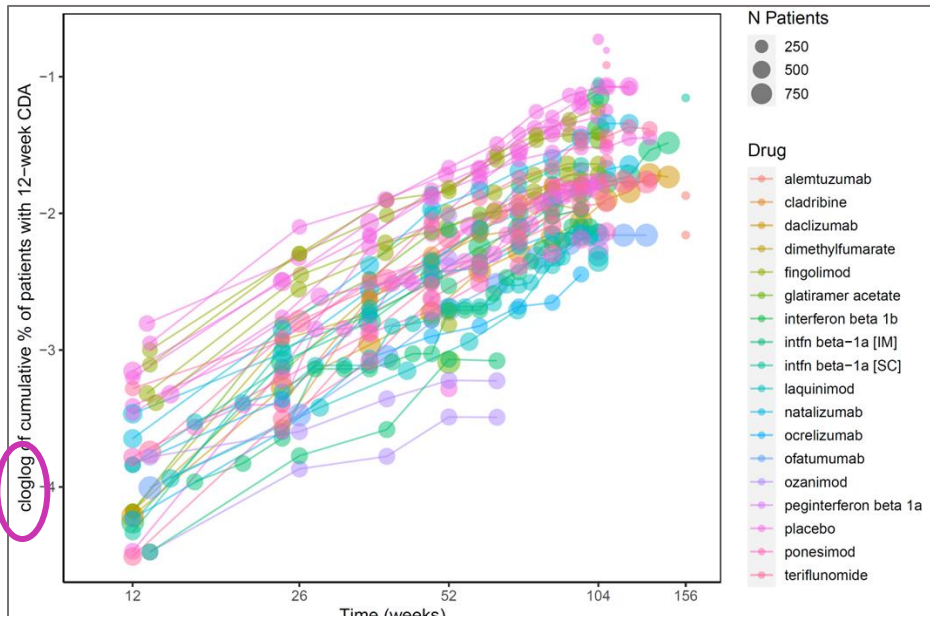
MBMA in Relapsing Multiple Sclerosis (RMS) to Assess Comparative Efficacy for Regulatory Support

- A longitudinal MBMA quantified the relative effects (HR) on 12-week Confirmed Disability Accumulation (CDA) for 17 unique treatments using published Kaplan-Meier data from 26 clinical trials treating patients with RMS
- linear (and parallel) relationship across treatment arms → proportional HR under Weibull distribution
- MBMA accounted for dose, time, and prior Disease Modifying Therapies (DMT) to compare CDA for all drugs in the proper context
- Results supported ponesimod NDA submission/approval; included in promotional materials

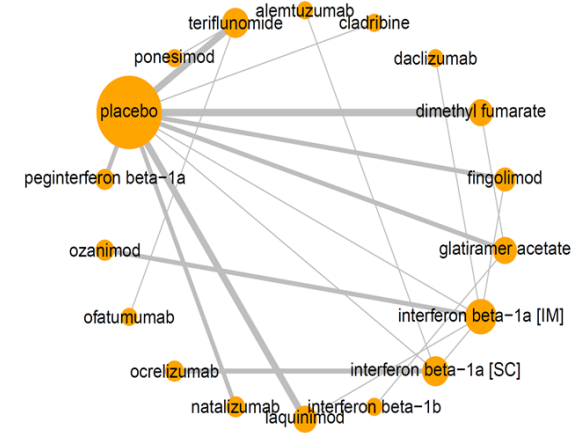
$$p(CDA)_{ijk} = \text{cloglog}^{-1}(pbo.\text{eff}_i + \gamma \cdot \log(t_k) + \text{drg}.\text{eff}_d(\text{dose}_{ijd}, \theta_{ij})) + w_{ijk} \cdot \varepsilon_{ijk}$$

$$\text{drg}.\text{eff}_d(\text{dose}_{ijd}, \theta_{ij}) = \log(HR_{\text{drg.pbo}})$$

Cumulative proportion of patients with 12-week CDA by drug



Trial Network



MBMA in Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) to create a synthetic control for Regulatory Support

CS6

- MBMA functioned as a **synthetic control arm to support accelerated approval** of blinatumomab in adult patients with R/R ALL based on **single arm trial** (MT103-211) with 185 patients
- Evaluated the expected relative effect (survival HR) of blinatumomab versus existing salvage therapies using meta-analysis models and **clinical trial simulations**
- Referenced by FDA and EMA for impact on approval process:

2.7.4. Conclusions on the clinical efficacy

Data from pivotal study MT103-211 showed a clinically significant response rate to blinatumomab in a high risk population of relapsed/refractory adult ALL patients for whom results obtained with conventional chemotherapy are usually unsatisfactory. These results are further supported by the high rates of negative MRD responses observed throughout all the clinical studies, and by the estimation of clinical responses obtained with conventional chemotherapy as provided by the historical comparator study 20120310 and by a model-based meta-analysis.

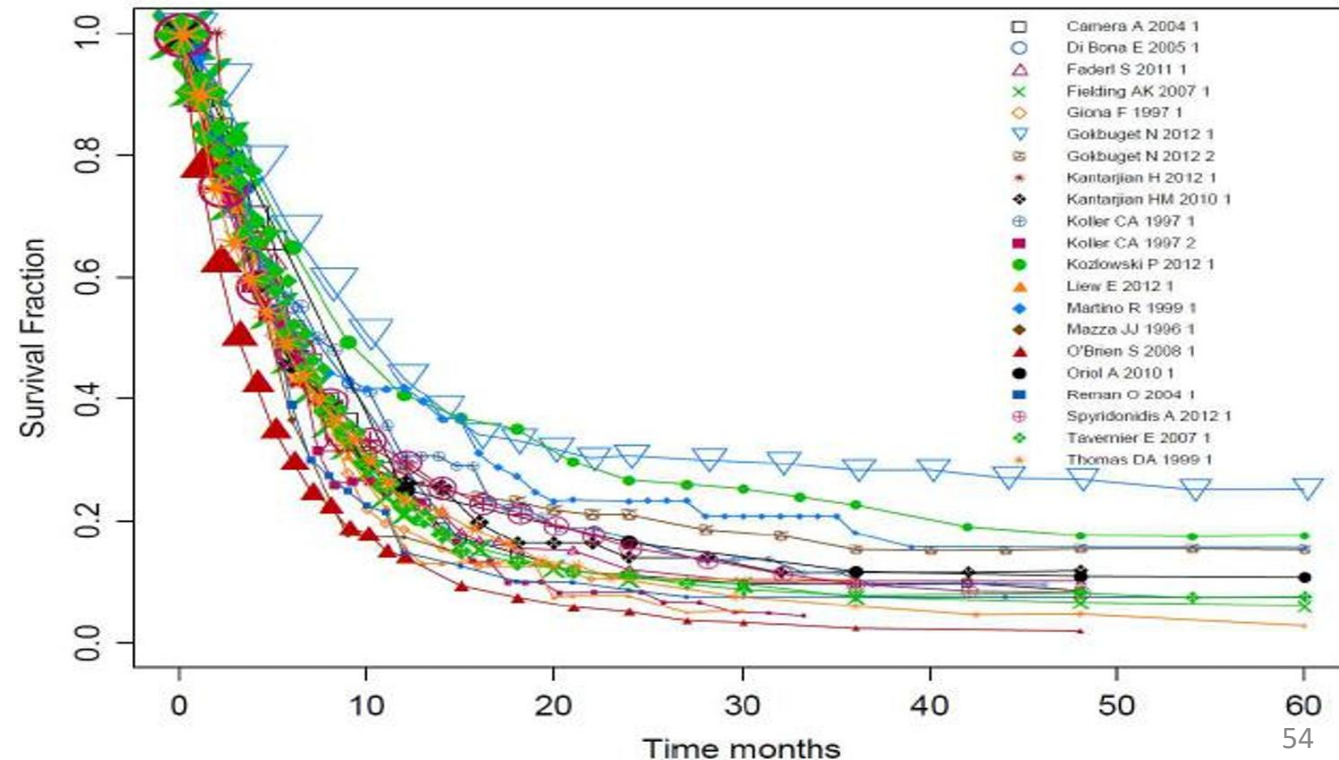
However efficacy results from direct comparison with chemotherapy regimens are needed in order to better quantify the magnitude of the effect.

- Accelerated FDA approval on Dec 3, 2014
- Full FDA approval granted on July 11, 2017, after confirmatory

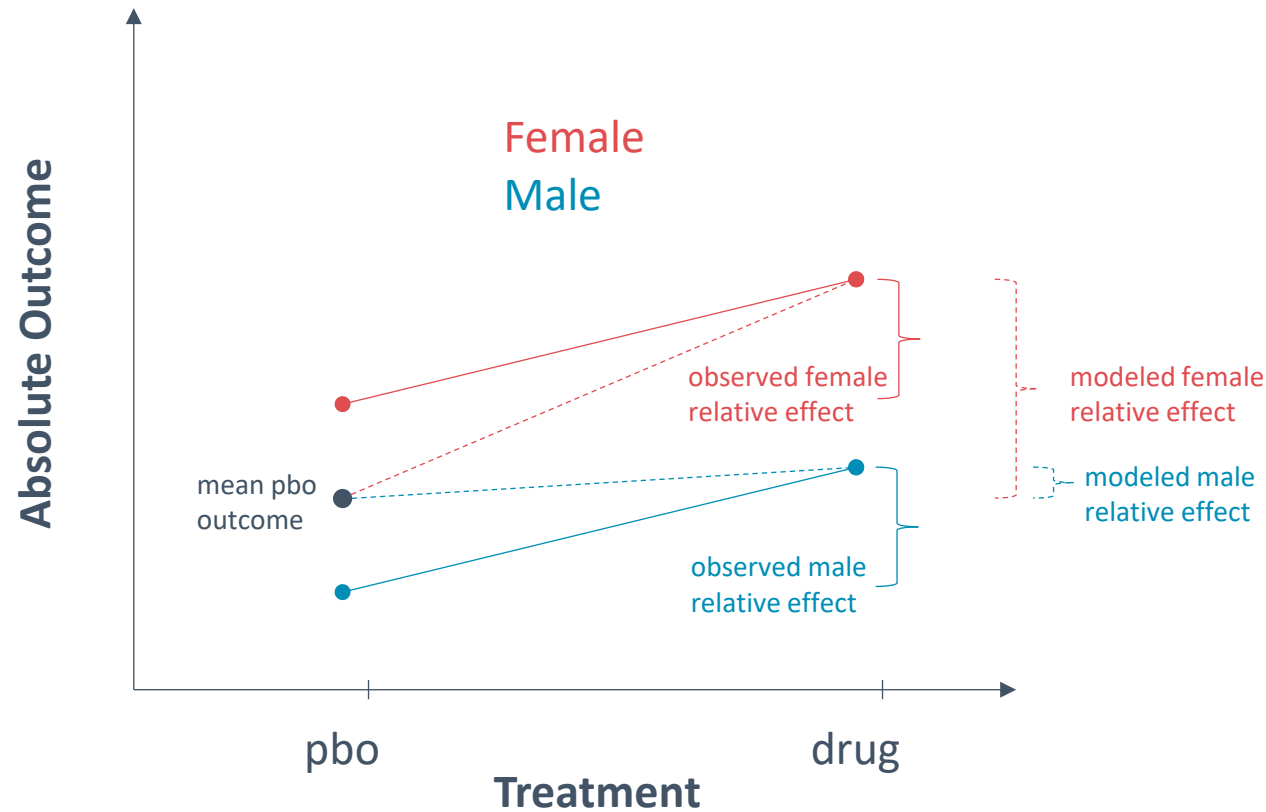
https://www.ema.europa.eu/en/documents/assessment-report/blincyto-epar-public-assessment-report_en.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125557Orig1s000StatR.pdf

Figure 1. Overall Survival Curves Across Included Studies with Salvage Therapies



Example: assigning a prognostic covariate as a predictive covariate

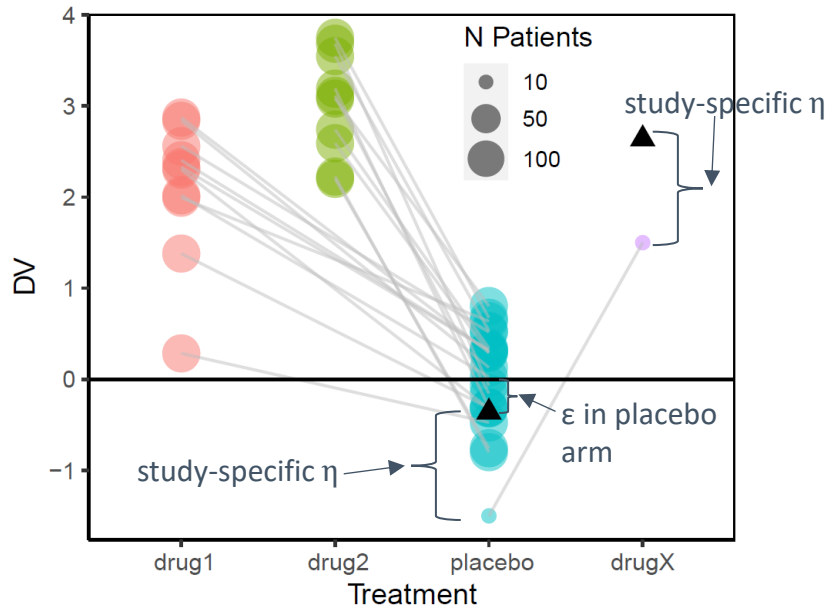


- Treating this prognostic covariate as a predictive covariate leads to very different conclusions, showing it is critical to understand prognostic covariates before exploring predictive covariates when using a placebo model approach with a relative effect focus
- The unstructured placebo approach implicitly accounts for all prognostic covariates, making predictive covariate exploration much easier

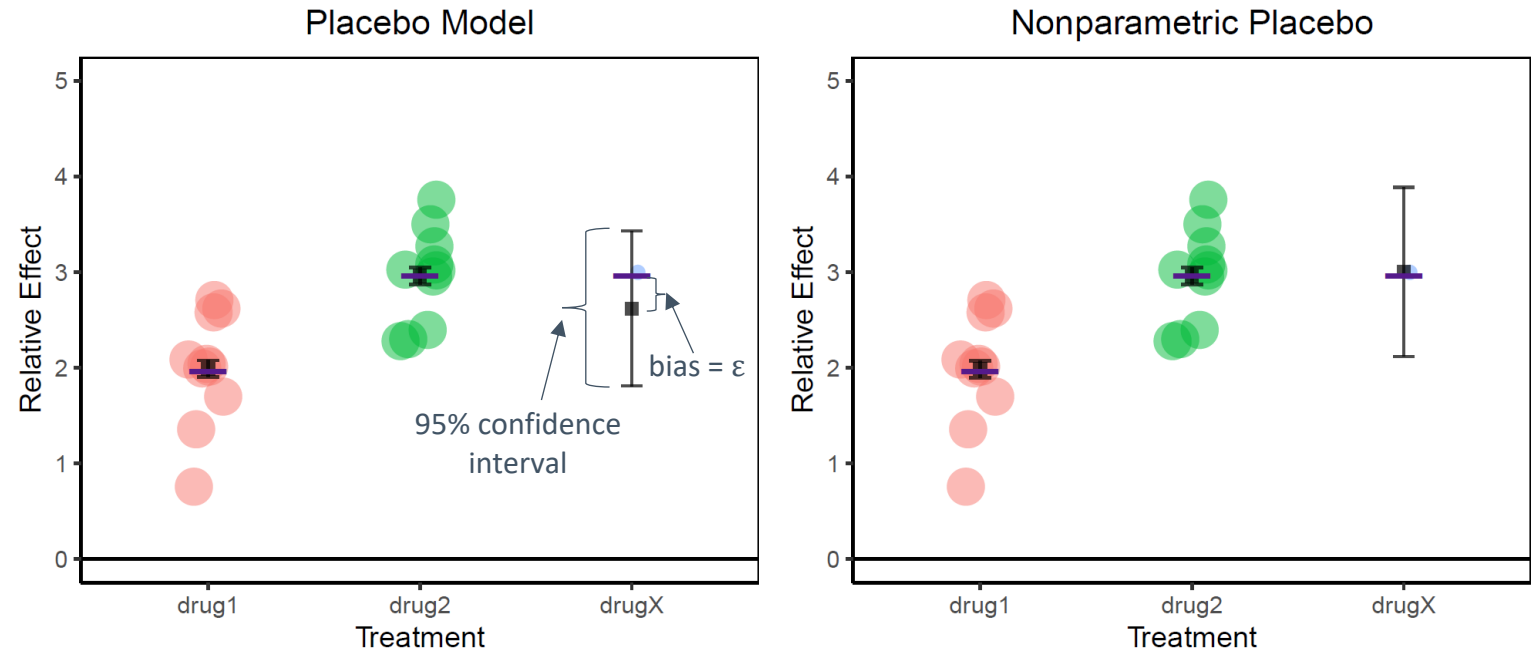
Explaining Potential Bias when Modeling Placebo Effect (part 1)

- This simulated example shows how a nonparametric placebo approach reduces the potential bias that can occur with a placebo model approach

Raw Data



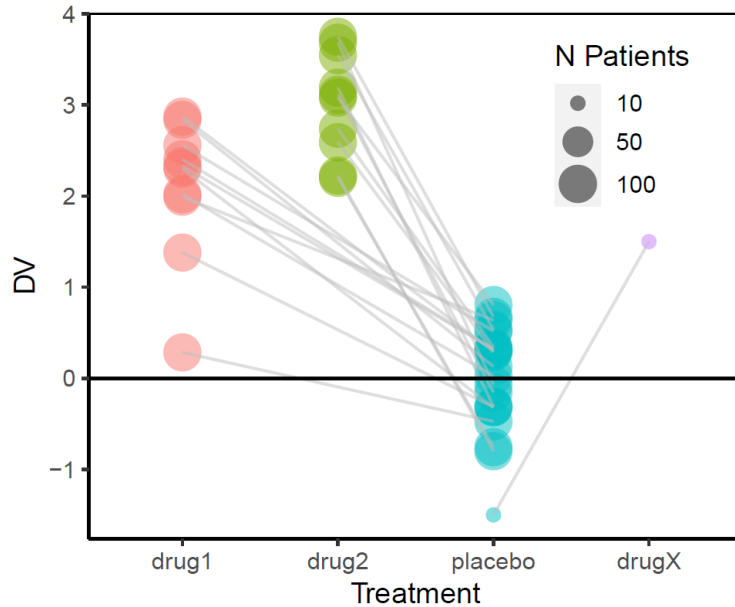
Relative Effect with Fixed Effect Model Prediction and Truth



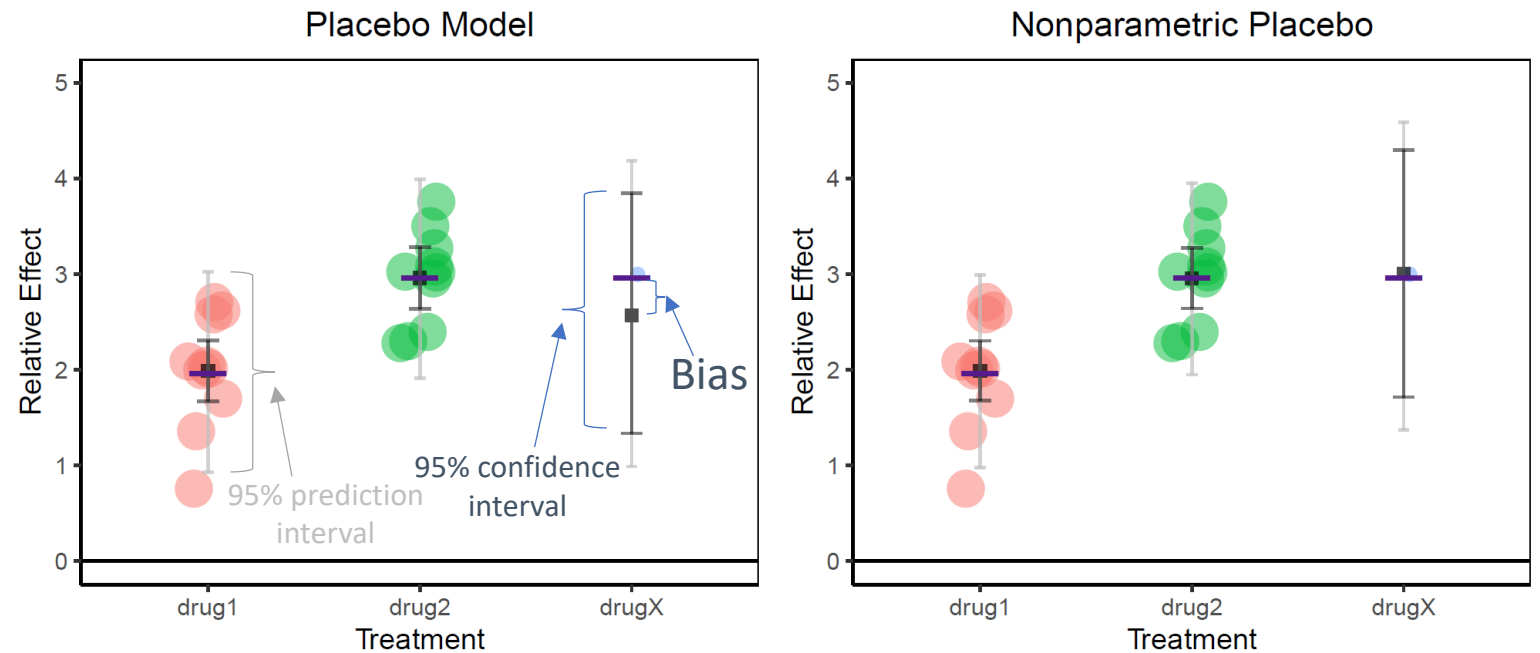
Explaining Potential Bias when Modeling Placebo Effect (part 2)

- Using the same simulation example, now with a random effect model, shows wider confidence/prediction intervals, as expected, but with same bias as before

Raw Data



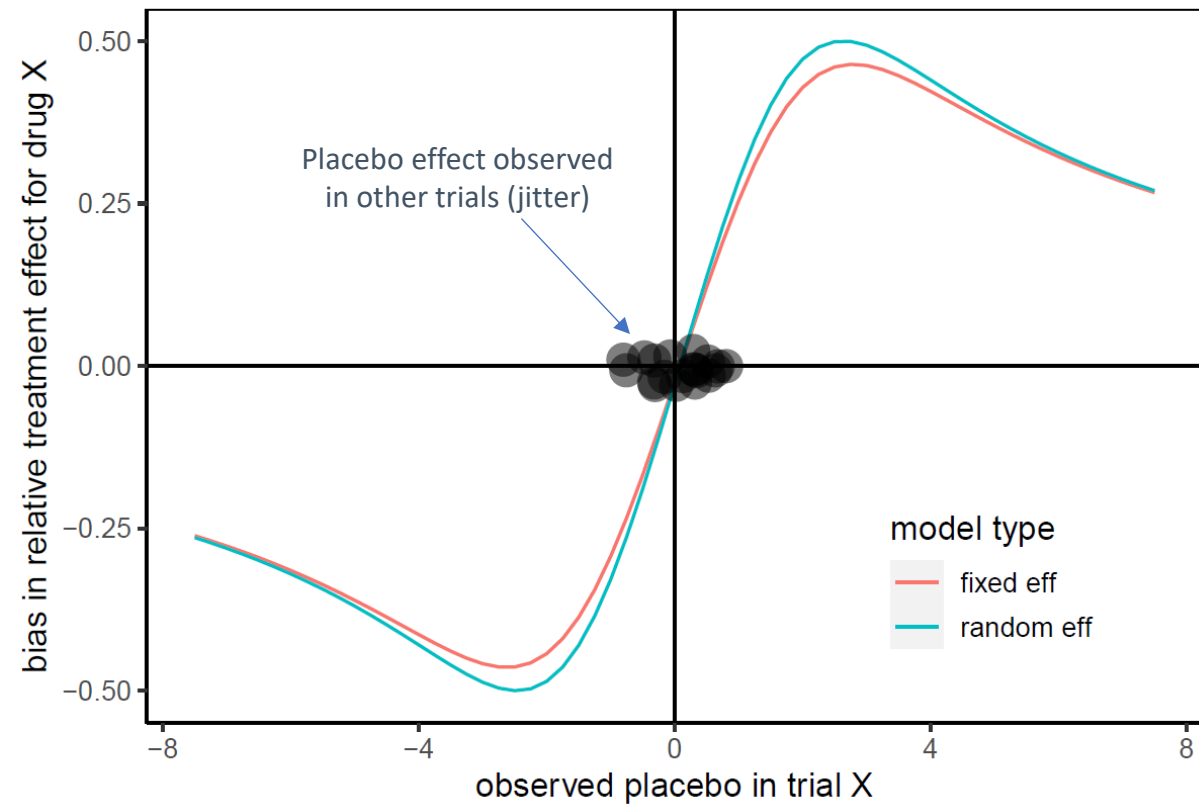
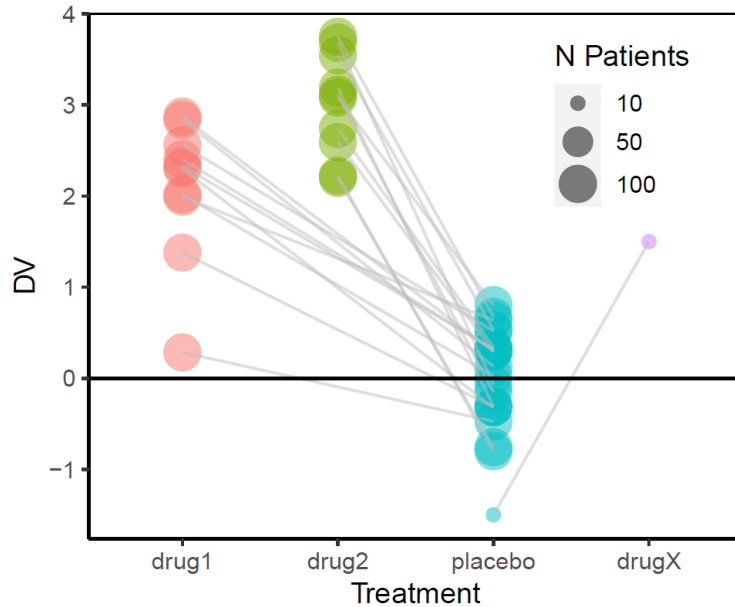
Relative Effect with Random Effect Model Prediction and Truth



Explaining Potential Bias when Modeling Placebo Effect (part 3)

- Bias from placebo model changes with of observed placebo effect
 - typical placebo effect = 0

Raw Data



Model Development Strategies in R

- For MBMA we use the `gnls()` and `nlme()` functions in R
 - The `gnls()` function is for fixed effect regression models and `nlme()` accommodates random effects
 - The `nlme()` function's minimization takes more time
- A recommended strategy
 - Start with `gnls()` and estimate an intercept for each study
 - These can be used as initials for the non-parametric placebo
 - Next, if supported by the data, build a model that accommodates dose-response by drug, but don't estimate ED50s initially
 - Start by estimating a simple effect for each drug without a dose response; i.e., fix all ED50s to a small number
 - Extend the model in small steps because `gnls()` can be sensitive to initial values
 - Try ED50 estimation, time courses, covariate effects
 - With each step assess model fit (`anova()` to compare AIC/BIC/LL) and the value and SE of estimates

R Packages

- For pairwise meta-analysis and meta-regression *meta*, *metafor*, and *rmeta* are key packages
- For network meta-analysis, *gemtc*, *netmeta*, and *pcnetmeta* provide the most common options
- For meta-analysis of diagnostic tests, *mada*, *HSROC*, and *metamisc* are good resources
- There is no package for model-based meta-analysis, we use *gnls* and *nlme* functions within the *nlme* package
- This website is a really good (and regularly updated) reference:
<https://cran.r-project.org/web/views/MetaAnalysis.html>

Additional support for unstructured placebo approach

From: Mawdsley D, et al. *Model-Based Network Meta-Analysis: A Framework for Evidence Synthesis of Clinical Trial Data*. CPT Pharmacometrics Syst Pharmacol. 2016 Aug;5(8):393-401.

- “There tend to be two approaches to fitting [placebo response]. One is to **assume the placebo response is different for each study** (modeling heterogeneity as independent, the nuisance parameter [or unstructured placebo] approach) while the other is to **fit with random effects** (hence, modeling heterogeneity as random but similar across studies). In this latter approach, the **principle of concurrent control is violated, which can lead to biased estimates of relative effect.**” [1]
- “Often the placebo effect is of interest in itself, making it attractive to put a random effects model on the placebo arm. This is **better achieved by a separate analysis of the placebo arms**, which delivers estimates of placebo effect, but **avoids introducing bias in the estimation of the relative effects.**”

[1] Senn, S. The many modes of meta. Ther. Innov. Regul. Sci. 34, 535–549 (2000).

Further supportive references:

[2] [Piepho HP and Madden LV. Res Synth Methods. 2022 Nov;13\(6\):821-828.](#)

[3] [Piepho HP, Madden LV, Williams ER. Res Synth Methods. 2024 Sep;15\(5\):747-750.](#)

A Brief Note on MBMA with Individual Patient Data

- Individual patient data (IPD) can be very helpful to better identify prognostic covariates (i.e., covariates on absolute outcomes)
- However, to properly assess relative effects (and predictive covariates), one needs to compare an outcome to an estimated **counterfactual**
 - A counterfactual is the outcome in the exact same population when given a different treatment
 - A well-designed RCT approximates this situation and aims to enable a proper relative effect assessment
 - Aggregating data is necessary to compare an observed treatment response to an observed control
- A relative effect-focused MBMA based on IPD will need to estimate the counterfactual (e.g., placebo effect) with a parametric model, violating the principle of concurrent control
- IPD may better inform predictive covariates by allowing the analyst to stratify results by covariate categories, thus maintaining an estimated counterfactual with concurrent control, but this is ultimately still an analysis of aggregate data (AD)

Some informative sources relative to MBMA with IPD:

- [Pham TN, et al. CPT Pharmacometrics Syst Pharmacol. 2026 Feb;15\(2\):e70159.](#)
- [French JL. 19th PAGE Meeting. Berlin, Germany. 8-11 June, 2010.](#)