A unified framework for synthesis of safety data in the presence of changing hazards

Work in Progress

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on behalf of the Safety Data Subgroup of the
EFSPI Integrated Data Analysis SIG

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Contributors

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  - Amy Xia, Amgen
  - Christy Chuang-Stein, formerly Pfizer

Contents

- Motivation
- Summer Intern Implementation Project –
  - Simulation of a programme of studies and model fitting
- Exploration
  - Focus on random treatment effects across studies or treatment effects increasing / decreasing over time
- Final Remarks
  - Some Learning So Far
  - Future Work

Why should we care?

- The impact of exposure duration is often effectively ignored when safety data are pooled based on planned study duration
- FDA held a public meeting in 2013 on meta-analysis, with emphasis on the availability and use of individual participant data (IPD) as opposed to study-level data
  http://www.fda.gov/Drugs/NewsEvents/ucm370686.htm
- Key opportunity when utilizing IPD is the ability to examine the impact of short and long term exposure

FDA Review – Tofacitinib Safety Rheumatoid Arthritis

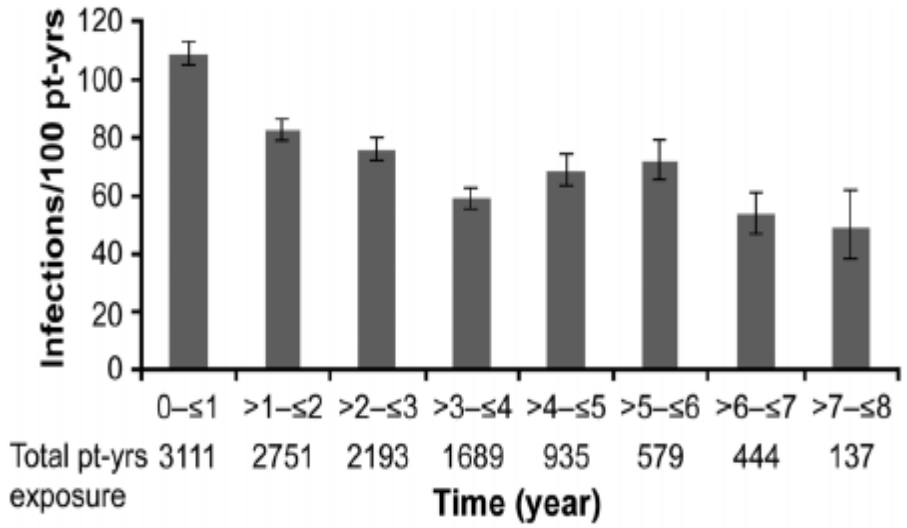
"concern that the **safety summaries … may not be adequate to make regulatory decision regarding safety** … the **results were summarized based on pooled data without controlling for differential study designs and patient populations**, … These issues made it **difficult for us to interpret the finding**. The applicant reported the results **primarily based on crude rates**. Given the complexity of the study design, we believed that **a model-based approach is more appropriate to summarize the safety data. …**

Poisson regression model stratified by study with an offset term given by the logarithm of time until first event or censoring"

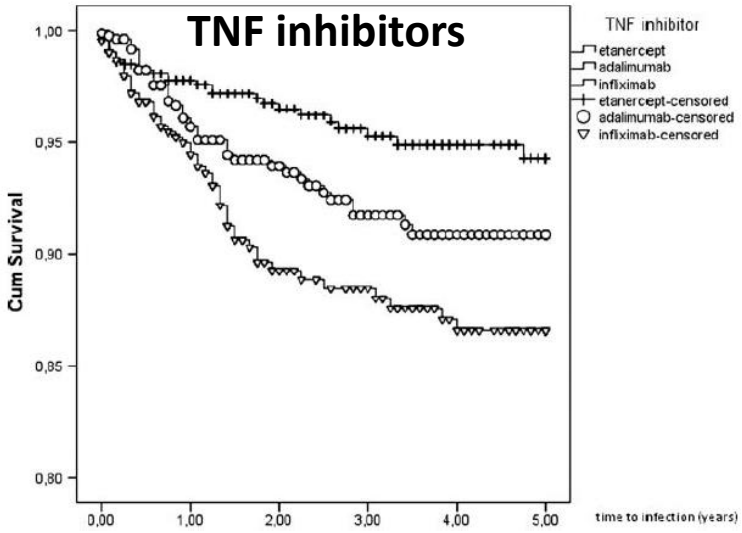
Why should we care?

Incidence rates of AEs may vary over time; we should characterize this for doctors and patients

Rituximab infection rates over time with 95% CI



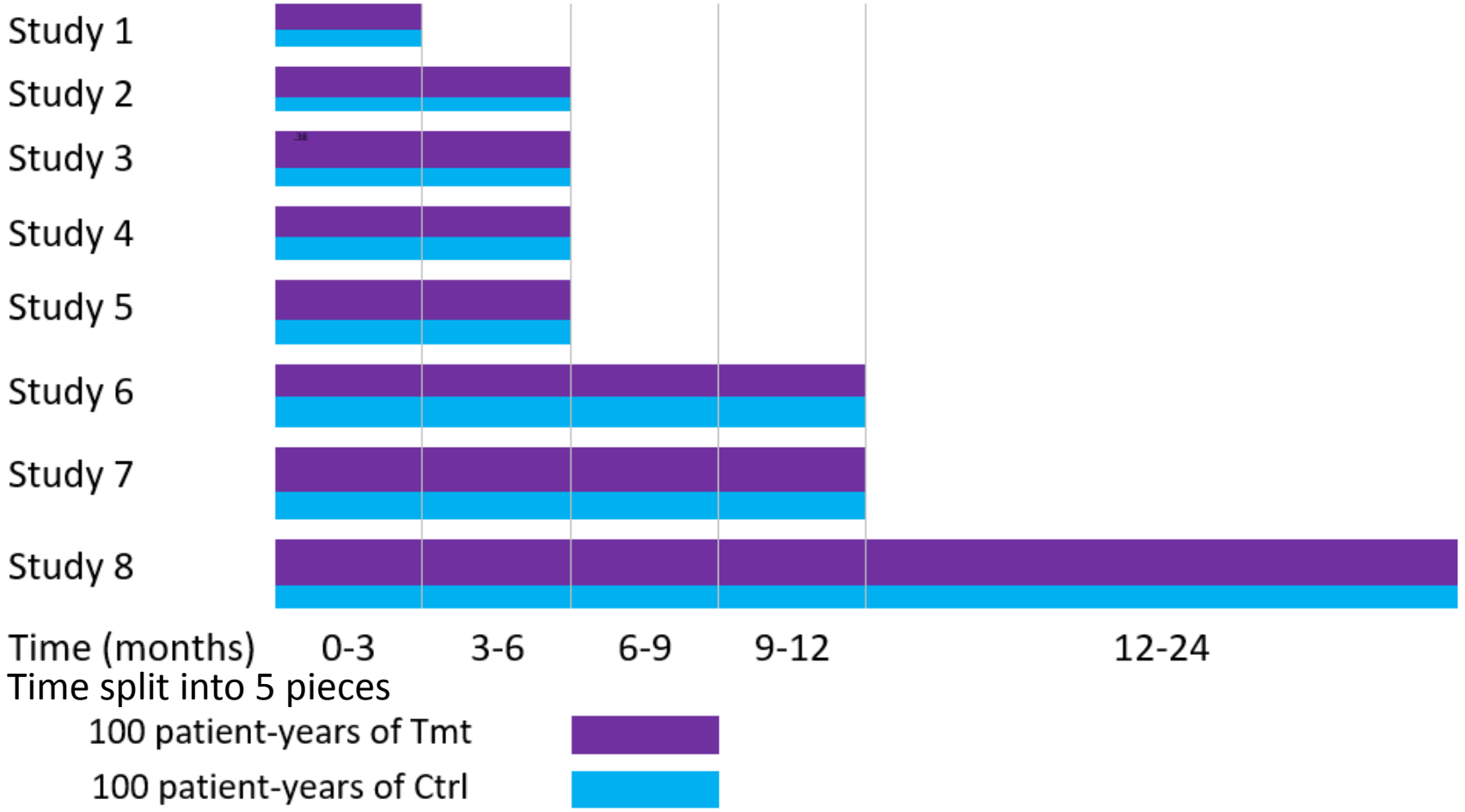
Time to first infection for TNF inhibitors



IMPLEMENTATION PROJECT

Programme of Studies Simulated
Based on Tofacitinib RA Program

8 phase 2 and phase 3 studies, N=280 to 800, ~4000 Patient Years



Scenarios Generated

- Base case
  - Control event rate 20% per year
  - Dropout rate 10% per year
  - Alternative hypothesis event risk ratio 1.8
- Multiple variations considered
  - E.g. risk or treatment effects varying across studies or across time

Models for Time to First Event

Non-proportional hazard across studies?	Variation in tmt effect across studies?	Variation in tmt effect across time?	Shape of control hazard	
			Piece-wise[a]	Flexible[b]
-	-	-	Logistic regression	
No	No	No	Poisson (constant ctrl hazard)	
No	No	No	PW1	Cox1
No	No	Piece-wise	PW2	Cox2
Yes	No	No	PW3	Cox3
No	Random	No	PW4	Cox4
Yes	Random	No	PW5	Cox5

a. Piece-wise exponential similar to Crowther et al. 2012
b. Cox proportional hazards regression similar to Smith et al. 2005

EXPLORATION

Scenarios Considered Here

Scenario	Alternative Hypothesis Tmt Effect (RR)
Base	1.8
Random effects across studies	mean 1.8 σ=0.125 [avg 1.51 to 2.14] σ=0.25 [avg 1.27 to 2.55]
Tmt effect increases / decreases across time pieces	~1.8 overall 1.63 to 2.16 1.97 to 1.49

All have ctrl event rate 0.2/year; drop-out 0.1/year

Models for Time to First Event

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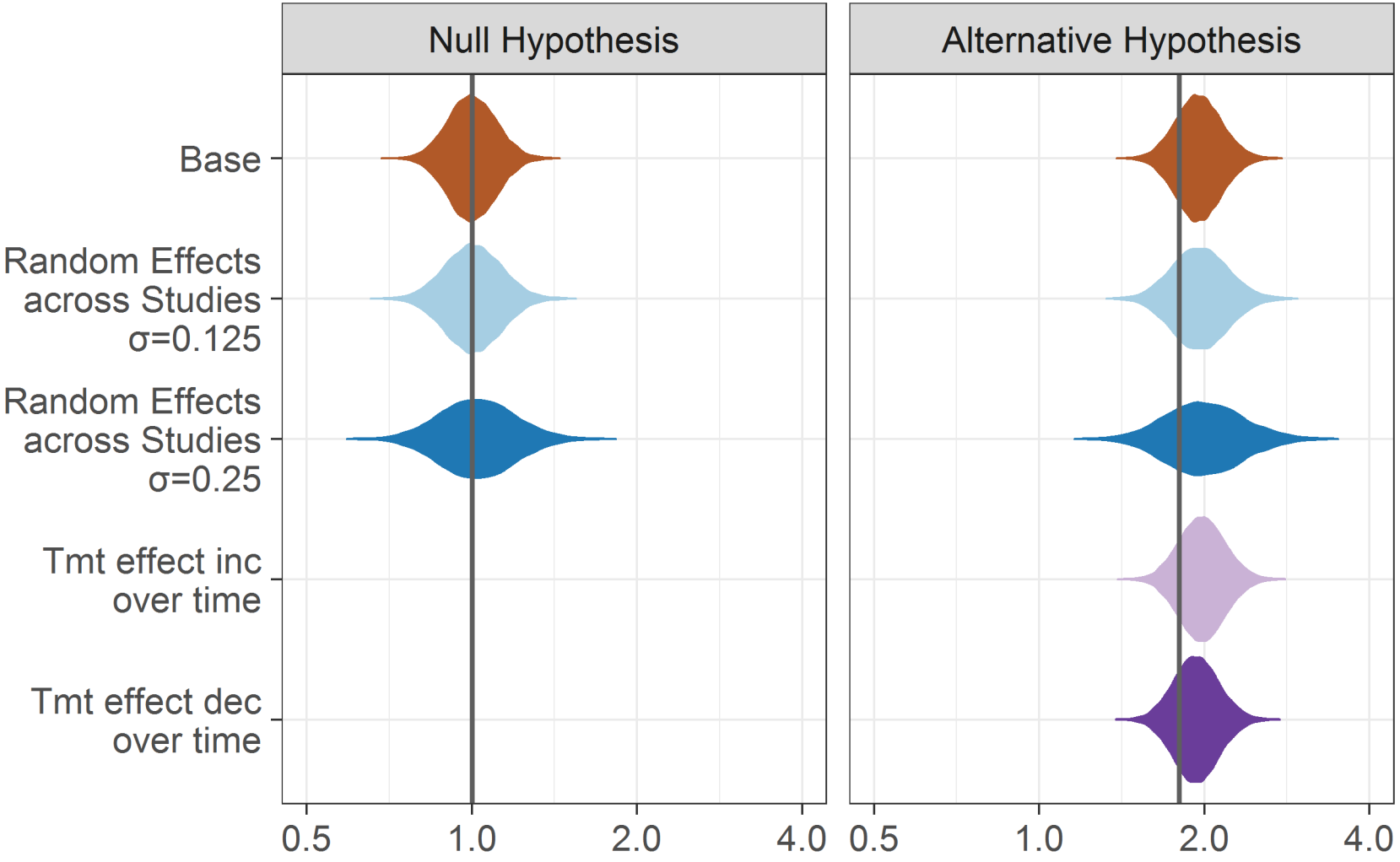
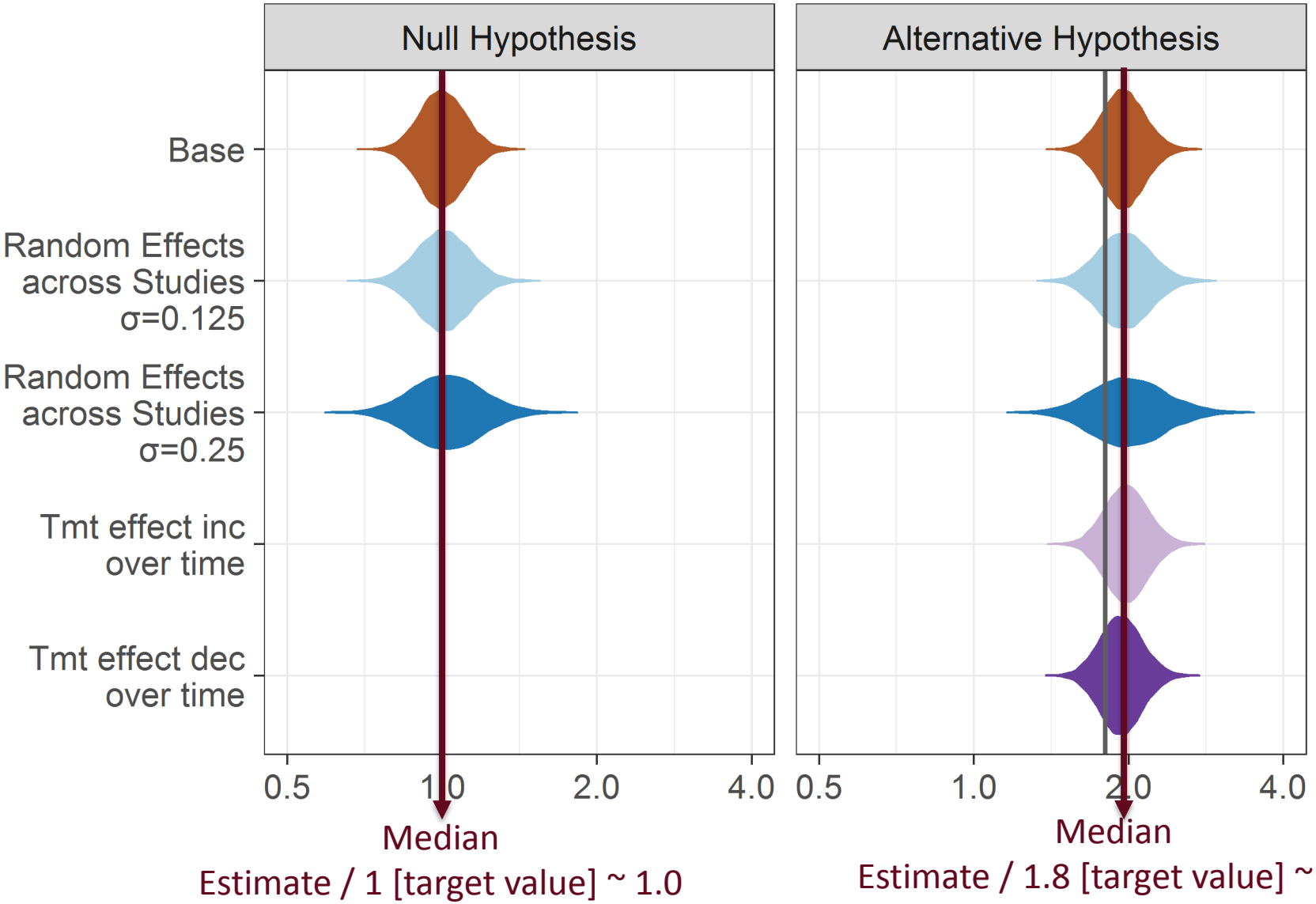
Logistic: Treatment Effect Estimates



10^4 simulations each scenario / hypothesis

Logistic: Treatment Effect Estimates



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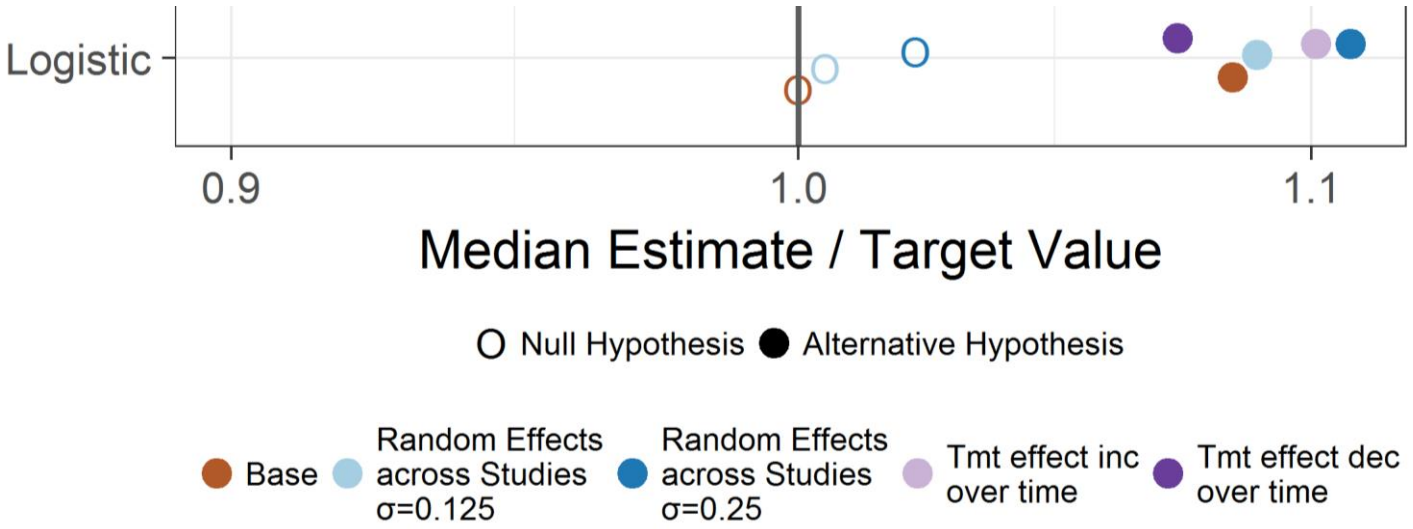
Median Treatment Effect Estimates



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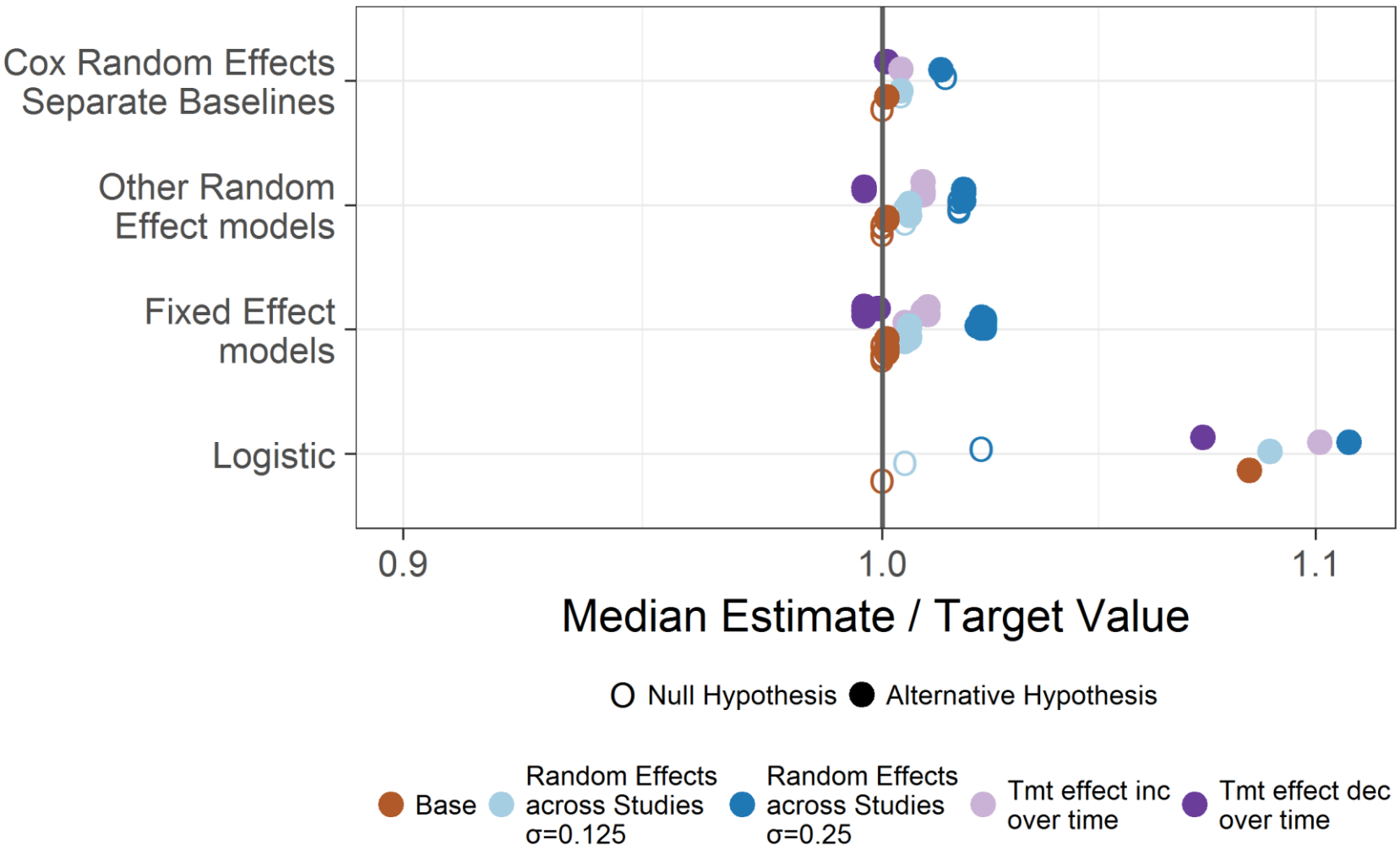

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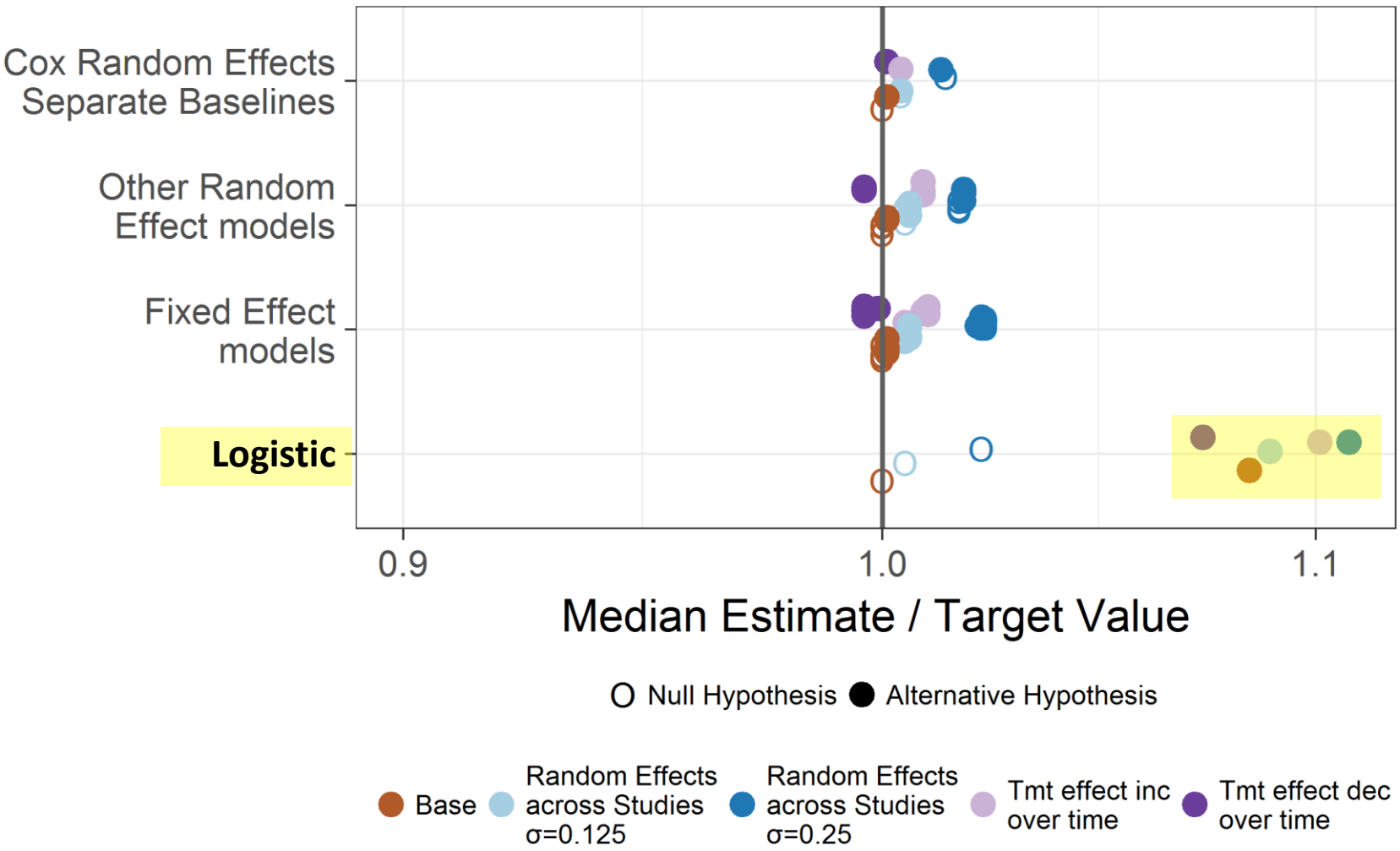
Bias - time at risk not accounted for



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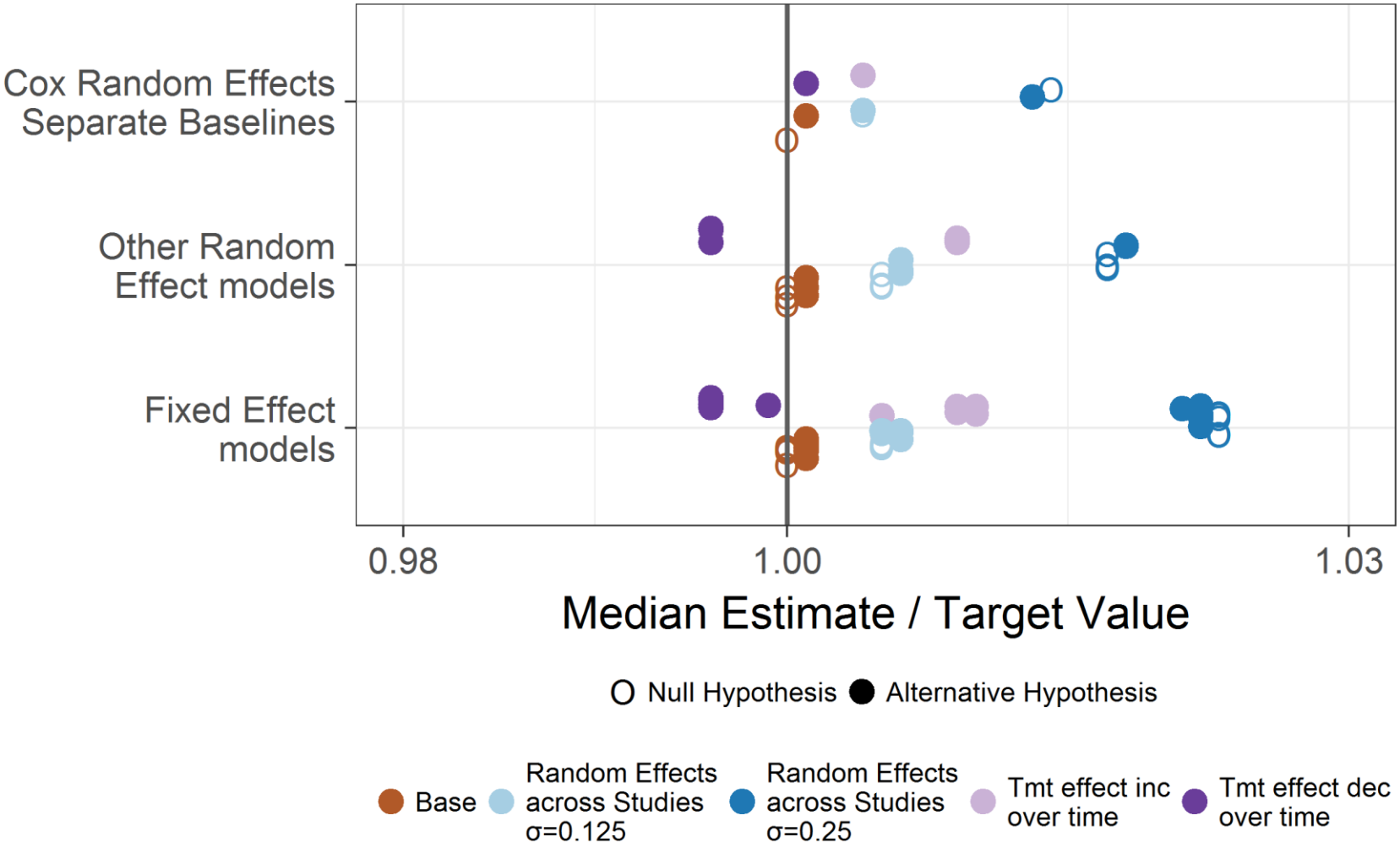
More complex models perform slightly better



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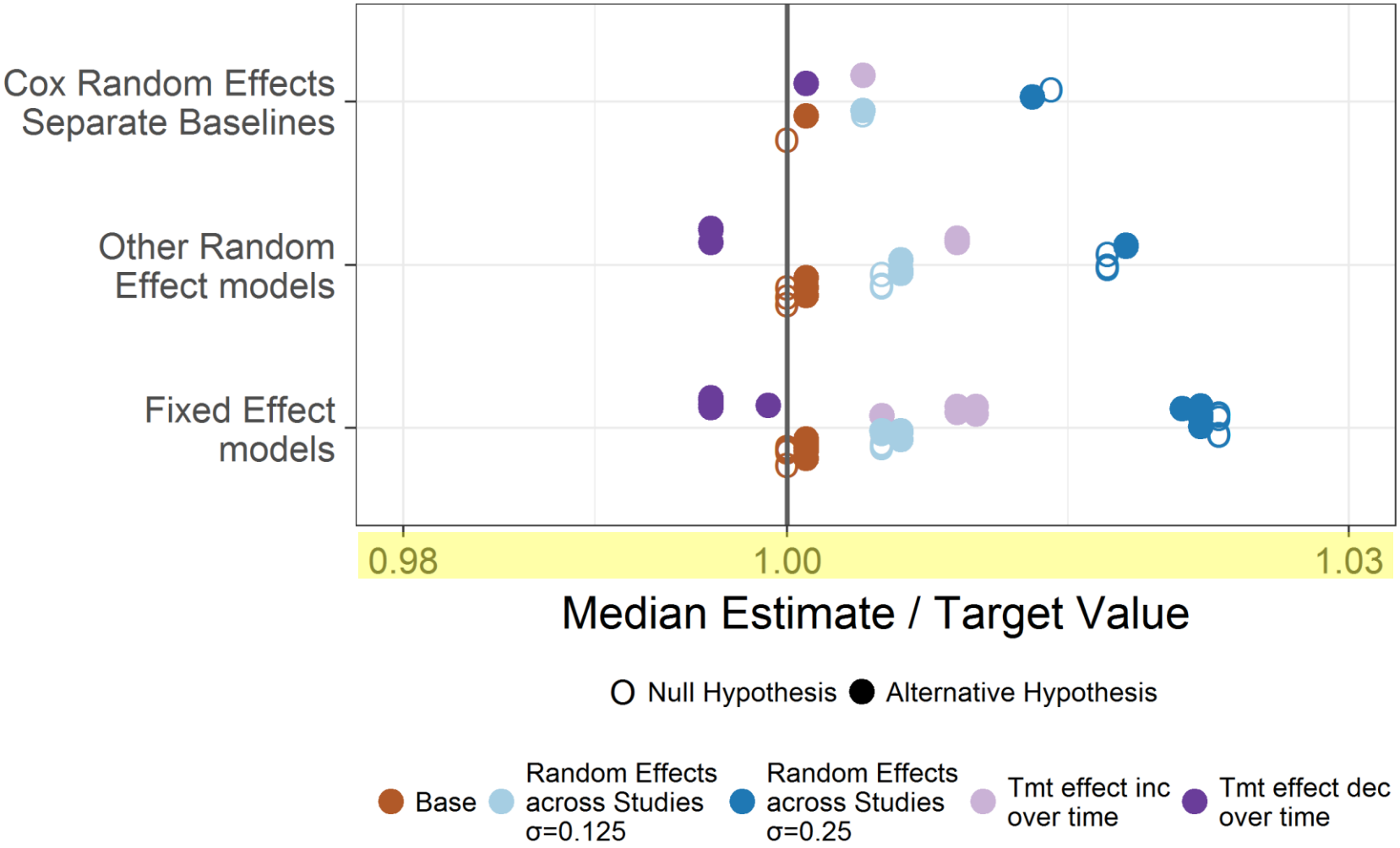

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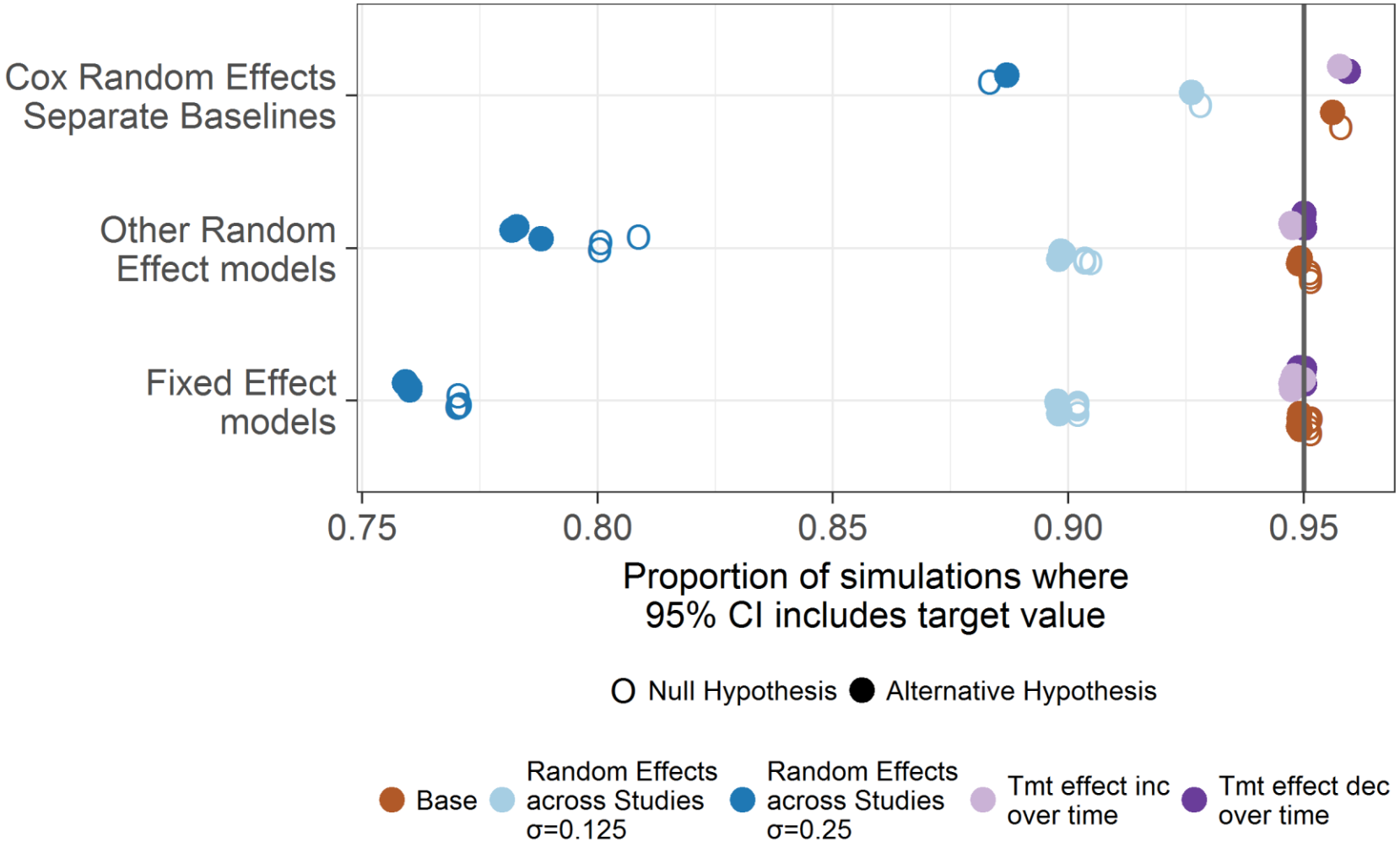
Coverage of 95% CI



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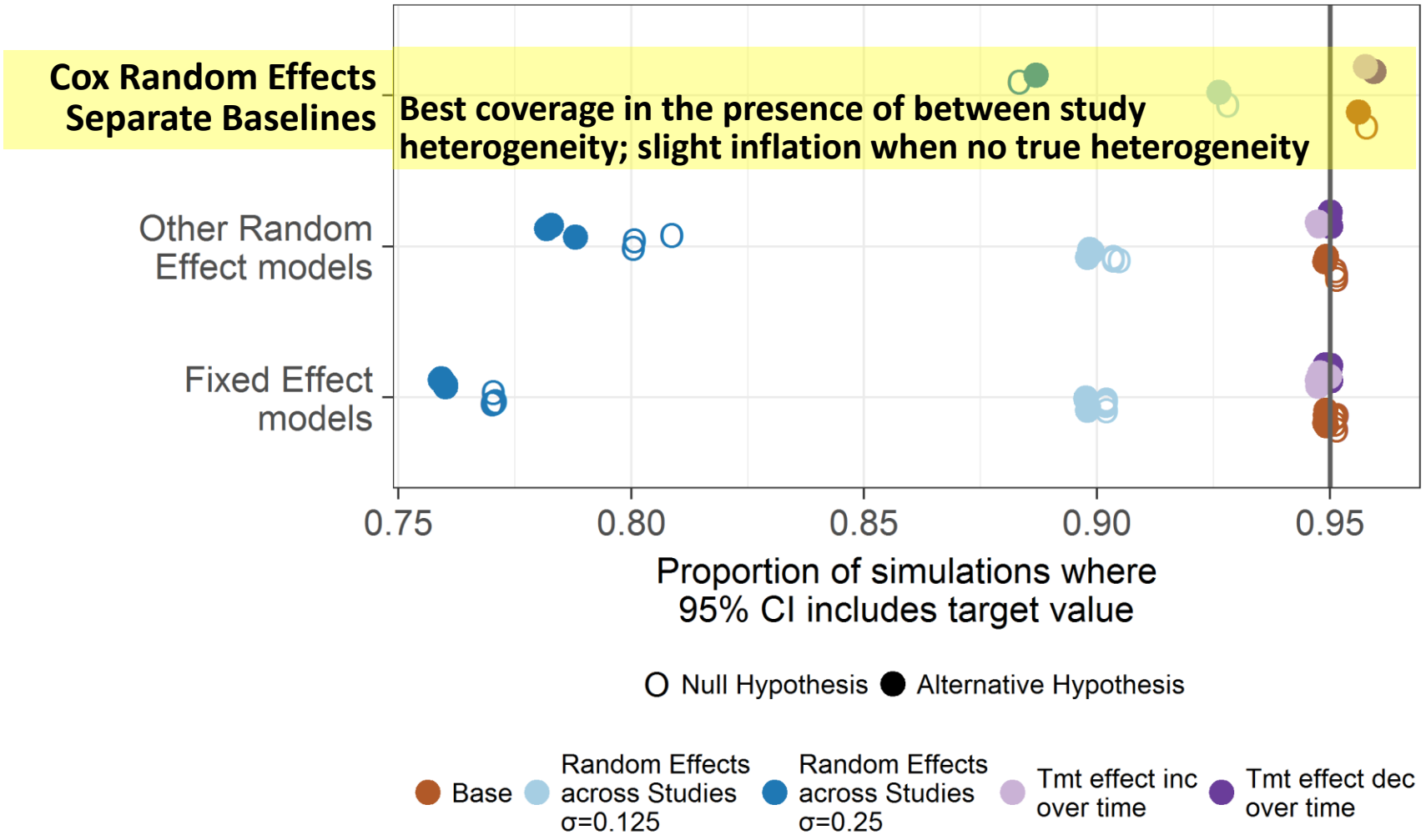
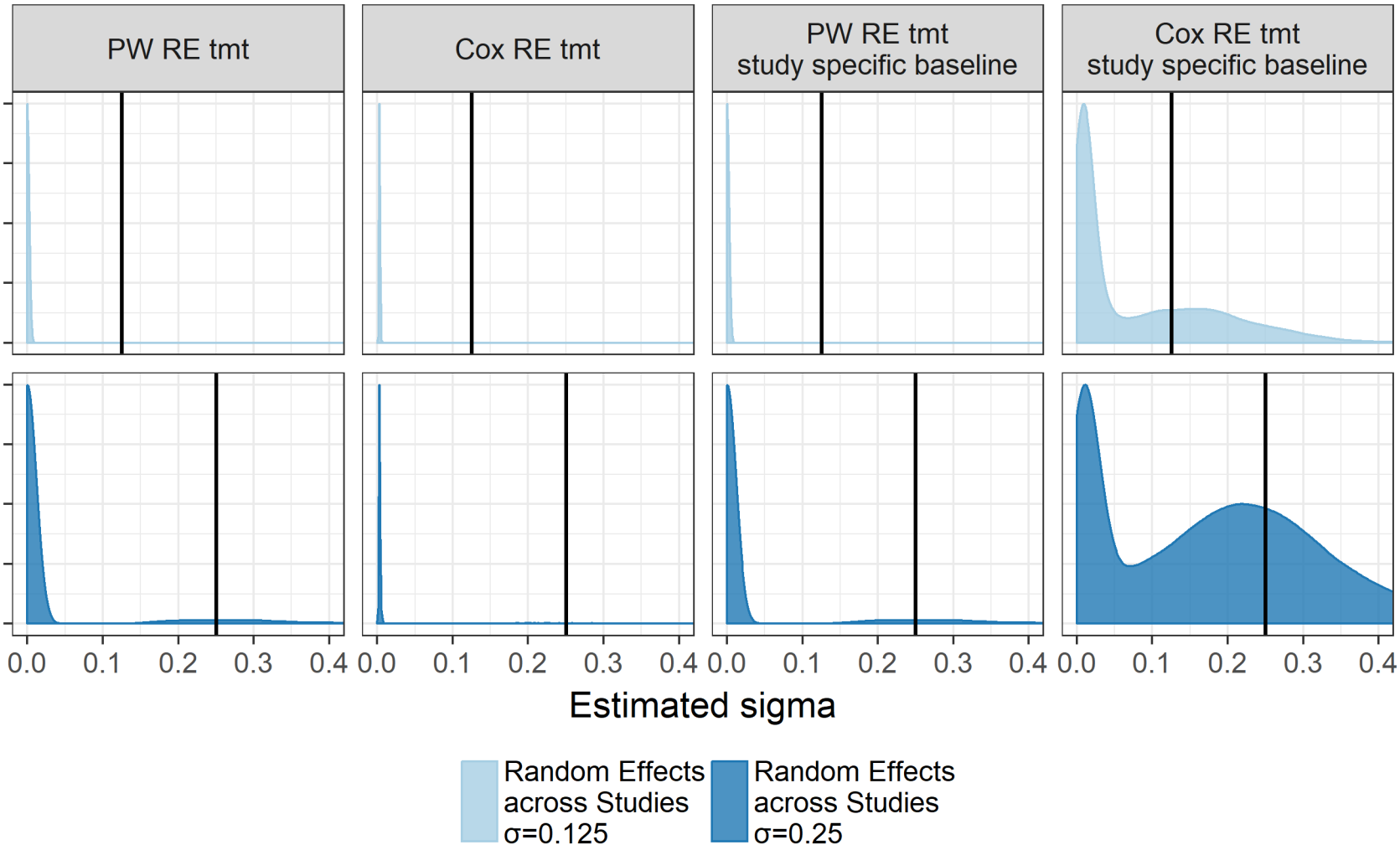
Cox random effects stratified by study performs well



10^4 simulations each scenario / hypothesis

Between study heterogeneity best estimated by Cox stratified by study



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a. Piece-wise exponential similar to Crowther et al. 2012
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FINAL REMARKS

Some Learning So Far

- Simulations ignore many real-life complexities
  - Ignored background therapy, multiple doses …
  - Consider implications of parameter choices, e.g. time-varying event rates and treatment effects
  - Confounding of study, time, clinical subgroups
- Models fit best when they match the data generation mechanism!
  - Look for robustness to misspecification
- Careful exploration of safety data will always be needed
  - Graphical techniques valuable to explore heterogeneity across studies and over time

SPERT / CIOMS VI (Crowe et al 2009) Recommendations still very relevant

- Data from RCTs most interpretable - tabulate separately from other safety information, e.g. open-label extension studies
- Combining across trials should be done with stratification, e.g. by clinical subgroup and study simultaneously
- Length of time each patient 'at risk' is important. Rates per person-time assumes a constant hazard rate over time.
- Goals of meta-analysis generally include the estimation of an average treatment effect, and the exploration of reasons for heterogeneity among study-specific effects

Future Direction

- In this complex situation, a lot of time would often be spent defining pools used to generate crude summaries. Instead, we aim to show how a model could used to allow for the complexities in the data structure and investigate the effect of the drug
- Plan to consider scenarios varying multiple factors, and with a low frequency adverse event
- Models to be extended to deal with time to recurrent events

Key References

- Crowe, B.J., Xia, A.J., Berlin, A.J. et al. (2009), Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clinical Trials, 6, 430–440

- Xia, A.J., Crowe, B.J., Schriver, R.C. et al. (2011) Planning and Core Analyses for Periodic Aggregate Safety Data Reviews. Clinical Trials, 8, 175–82.

- Smith, C.T., Williamson, P.R., Marson, A.G. (2005), Investigating heterogeneity in an individual patient data meta-analysis of time to event outcomes, Statistics in Medicine, 24, 1307–1319

- Crowther, M.J., Riley, R.D., Staessen, J.A., Wang, J., Gueyffier, F., Lambert, P.C. (2012), Individual patient data meta-analysis of survival data using Poisson regression models, BMC Medical Research Methodology, 12, 34

Further References

- Holford, T.R. (1980), The analysis of rates and survivorship using log-linear models, Biometrics, 36, 299-305

- Laird, N. and Oliver, D. (1981), Covariance analysis of censored survival data using log-linear analysis technique, Journal of the American Statistical Association, 76, 231-240

Models

- Random treatment effects
- $\beta_{j*} = \beta_{**} + b_j$
- $b_j \sim \mathrm{N}(0, \sigma^2)$
- Cox regression model stratified by study with random treatment effects
- $h_{ij}(t) = h_{0j}(t)\exp(\beta_{j*} i)$
- Piece-wise model with random treatment effects and separate baseline hazards for each study
- $\log(\mu_{ijk}) = \alpha_j + \beta_{j*} i + \log(\lambda_k) + \delta_{jk} + \log(t_{ijk})$

- Cox regression model with fixed study effect and treatment effects that change over time
- $h_{ijk}(t) = h_0(t)\exp(\alpha_j + \sum_{k=1}^{K} \beta_{*k} i_k)$
- Piece-wise model with fixed study effect and treatment effects that change over time
- $\log(\mu_{ijk}) = \alpha_j + \sum_{k=1}^{K} \beta_{*k} i_k + \log(\lambda_k) + \log(t_{ijk})$

Equivalence of PW Exponential and Poisson Regression

- Holford (1980) and Laird and Oliver (1981) noted independently in their papers that piece-wise exponential model is equivalent to Poisson regression with log of time at risk as offset
  - $d_{ijk} \sim \text{Poisson}(\mu_{ijk})$
  - t_{ijk} is time at risk
  - $\mu_{ijk} = t_{ijk} h_{ijk}(t)$
  - $\log(\mu_{ijk}) = \log(t_{ijk}) + \log(\lambda_k) + \boldsymbol{\beta X}_{ijk}$

Programme of Studies Simulated
Based on Tofacitinib RA Program

		Study 1	Study 2	Study 3
Phase II 3 studies	Duration	3 months	6 months	6 months
	N	280	350	500
	Randomisation Tmt : Ctrl	5 : 2	6 : 1	4 : 1
	Potential PY Exposure/100	0.5 : 0.2	1.5 : 0.2	2.0 : 0.5

		Study 4	Study 5	Study 6	Study 7	Study 8
Phase III 5 studies	Duration	6 months	6 months	1 year	1 year	2 years
	N	450	660	600	800	800
	Randomisation Tmt : Ctrl	2 : 1	8 : 3	1 : 1	3 : 1	4 : 1
	Potential PY Exposure/100	1.5 : 0.7	2.4 : 0.9	3.0 : 3.0	6.0 : 2.0	12.8 : 3.2

Models Fitted by Category

Logit	Meta-analysis based on logistic regression	glm(Event ~ Arm + factor(Study), data = record_1, family = binomial)
Poi	Meta-analysis based on Poisson regression with time at risk as offset	glm(Event ~ Arm + factor(Study), offset = log(Time), data = record_1, family = poisson)
Cox1	Cox regression model with fixed study effects and fixed treatment effect	coxph(Surv(Time, Event) ~ Arm + factor(Study), data = record_1)
Cox3	Cox regression model stratified by study with fixed treatment effect	coxph(Surv(Time, Event) ~ Arm + strata(Study), data = record_1)
PW1	Piece-wise model with fixed study effects and fixed treatment effect	glm(Event ~ Arm + factor(Study) + factor(Piece), offset = log(TaR), data = record_2, family = poisson)
PW3	Piece-wise model with fixed study effects and separate baseline hazards for each study	glm(Event ~ Arm + factor(Study) + factor(Piece) + factor(Piece) * factor(Study), offset = log(TaR), data = record_2, family = poisson)
Cox4	Cox regression model with fixed study effect and random treatment effects	coxme(Surv(Time, Event) ~ Arm + factor(Study) + (-1 + Arm | Study), data = record_1)
Cox5	Cox regression model stratified by study with random treatment effects	coxme(Surv(Time, Event) ~ Arm + strata(Study) + (-1 + Arm | Study), data = record_1)
PW4	Piece-wise model with fixed study effects and random treatment effects	glmer(y ~ Arm + factor(Piece) + factor(Study) + (-1 + Arm | Study), offset = log(E), data = record_2.sum, family = poisson, nAGQ = 20)
PW4.R	Piece-wise model with fixed study effects and random treatment effects using regularization	bglmer(y ~ Arm + factor(Piece) + factor(Study) + (-1 + Arm | Study), offset = log(E), data = record_2.sum, family = poisson, nAGQ = 20)
PW5	Piece-wise model with random treatment effects and separate baseline hazards for each study	glmer(y ~ Arm + factor(Piece) + factor(Study) + factor(Piece) * factor(Study) + (-1 + Arm | Study), offset = log(E), data = record_2.sum, family = poisson, nAGQ = 20)
PW5.R	Piece-wise model with random treatment effects and separate baseline hazards for each study using regularization	bglmer(y ~ Arm + factor(Piece) + factor(Study) + factor(Piece) * factor(Study) + (-1 + Arm | Study), offset = log(E), data = record_2.sum, family = poisson, nAGQ = 20)
Cox2	Cox regression model with fixed study effect and treatment effects that change over time	coxph(Surv(Time0, Time1, Event) ~ cluster(Patient) + Arm.P1 + Arm.P2 + Arm.P3 + Arm.P4 + Arm.P5 + factor(Study) , data = record_2)
PW2	Piece-wise model with fixed study effect and treatment effects that change over time	glm(Event ~ Arm.P1 + Arm.P2 + Arm.P3 + Arm.P4 + Arm.P5 + factor(Study) + factor(Piece) , offset = log(TaR), data = record_2, family = poisson)