Improving Strategic Decision-Making with Early Prediction of Survival Outcomes in Oncology Clinical Trials

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Collaborators

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With thanks to the patients and investigators who participated in these clinical trials.

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Early decision-making is a goal of all stakeholders

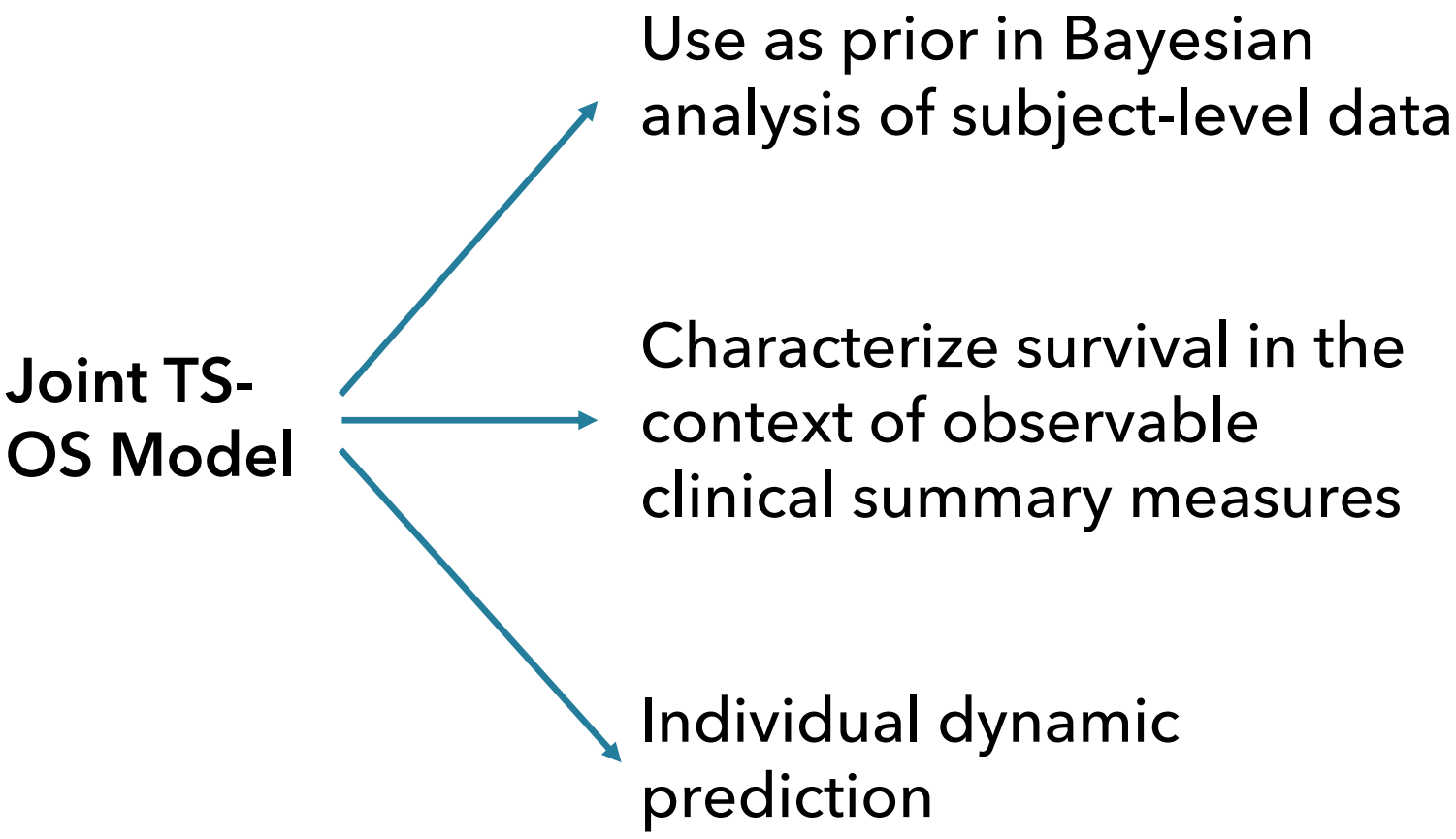
All stakeholders: get safe & effective treatments to patients quickly

Drug developers: stage investment of unpromising candidates

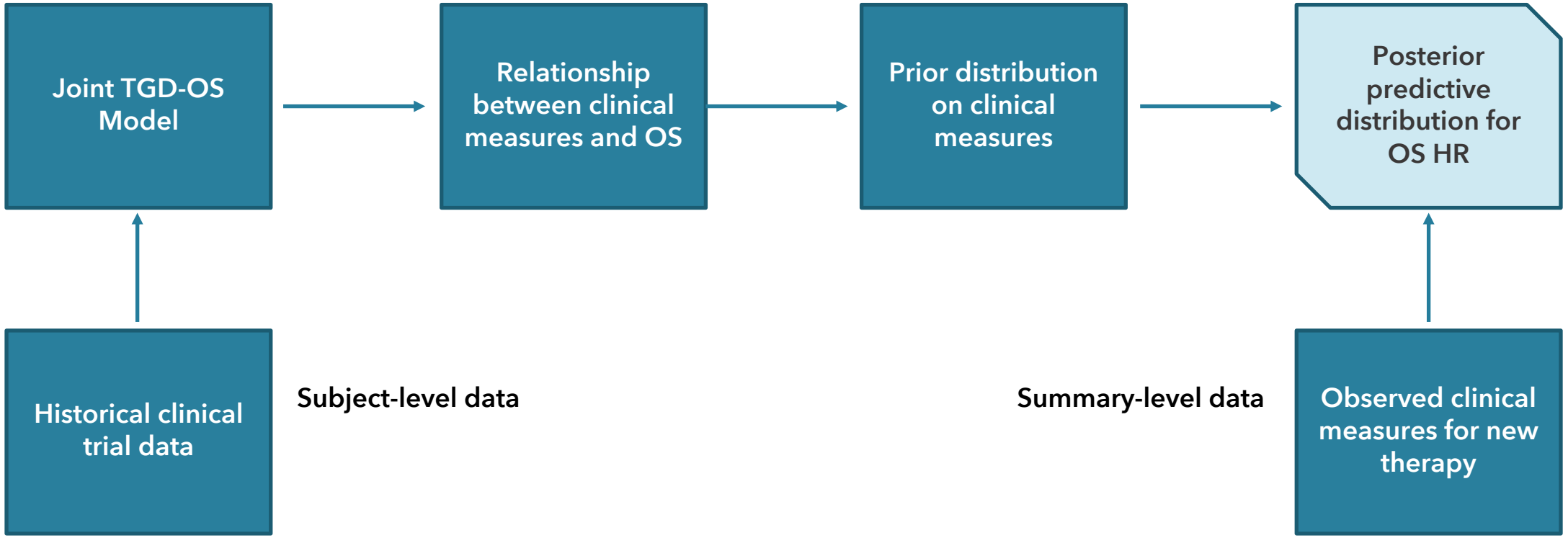
Use of modeling & simulation has grown substantially over the past 15 years

- Broad recognition of its utility (e.g., PDUFA VI)
- Impacting a variety of decisions (patient treatment, *drug development*, regulatory)

How do we leverage existing data to make decisions about new therapies?



Flow of proposed approach



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Joint model for tumor size and overall survival

- Data from 4 clinical trials of Pembrolizumab in NSCLC (N > 2500)
  - Chemotherapy (N=720; 28%)
  - Pembrolizumab (N=1324; 52%)
  - Pembrolizumab + Chemotherapy (N=497; 20%)

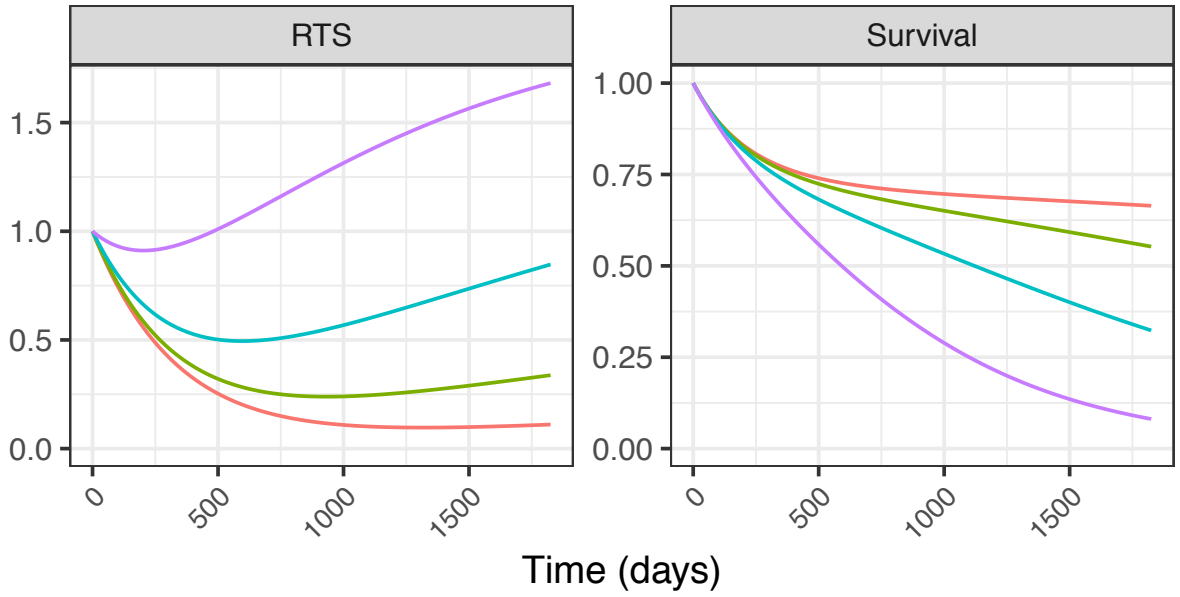
Moore model[1] for asymptotic tumor growth:

$$TS_i(t) = TS_{0,i}\left(5TS_{max,i}\right)\left(1 - e^{-k_{g,i}t}\right) + TS_{i,0}e^{-k_{d,i}t}$$

Hazard function with cure fraction:

$$h_i(t|X_i) = a(X_i)e^{\beta * \log(RTS_i(t))}e^{-\lambda t}\lambda$$

where $RTS(t) = \frac{TS(t)}{TS_0}$, α and λ are distributional parameters, and X_i is a vector of baseline predictive factors and effects.



1.Moore, H. A New Tumor Dynamics Mathematical Model. *American Conference on Pharmacometrics* (2016):Poster W–29.

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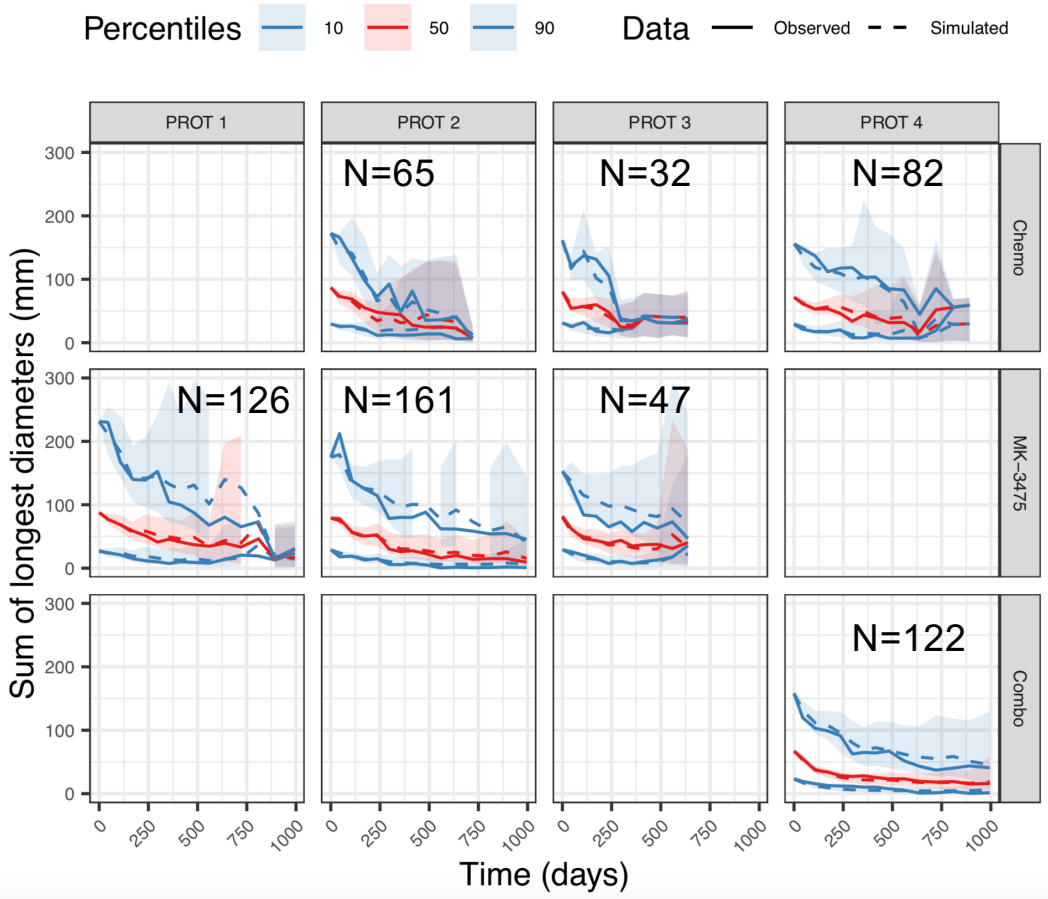
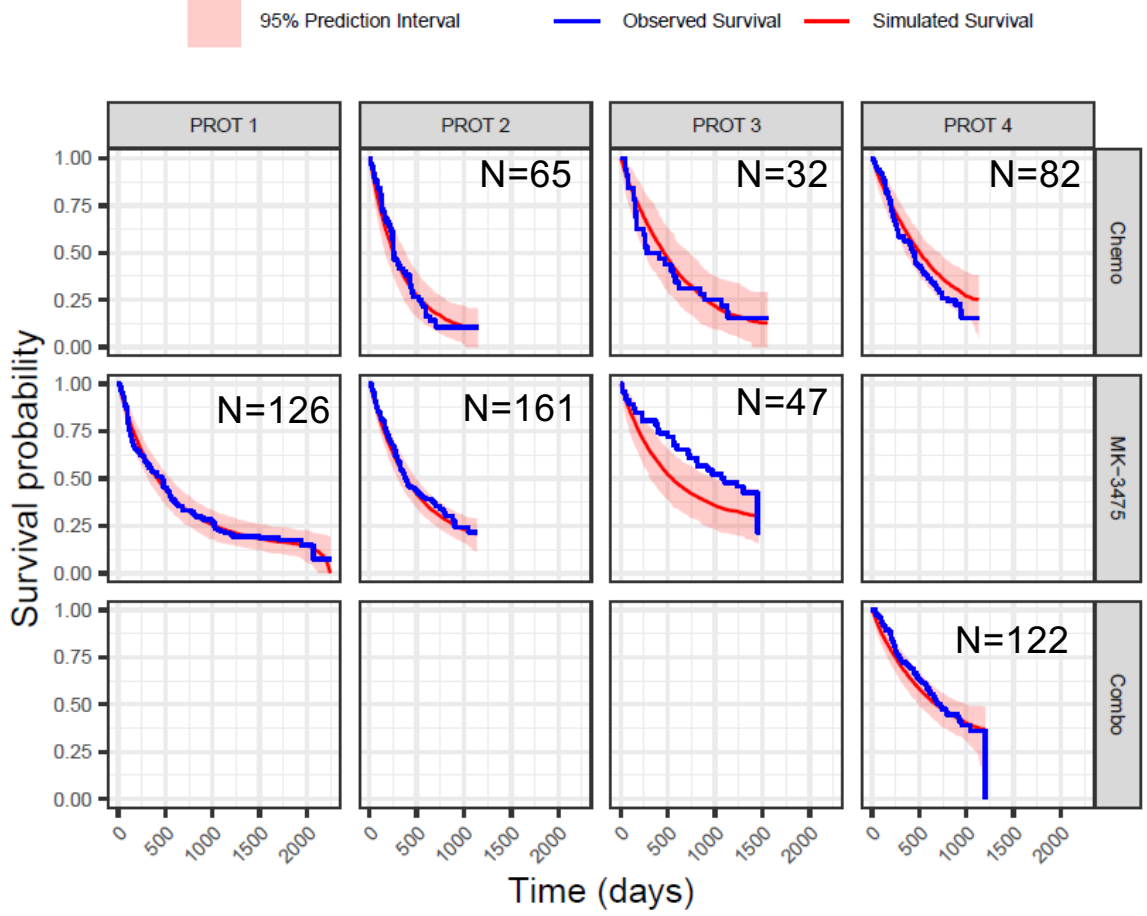
Joint model provides good out-of-sample prediction of tumor dynamics and OS

Joint TGD-OS Model

Historical clinical trial data





Validation Data (n= 635)

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Modulation of individual TS parameters highlights dynamic impact on OS outcomes.

Depth

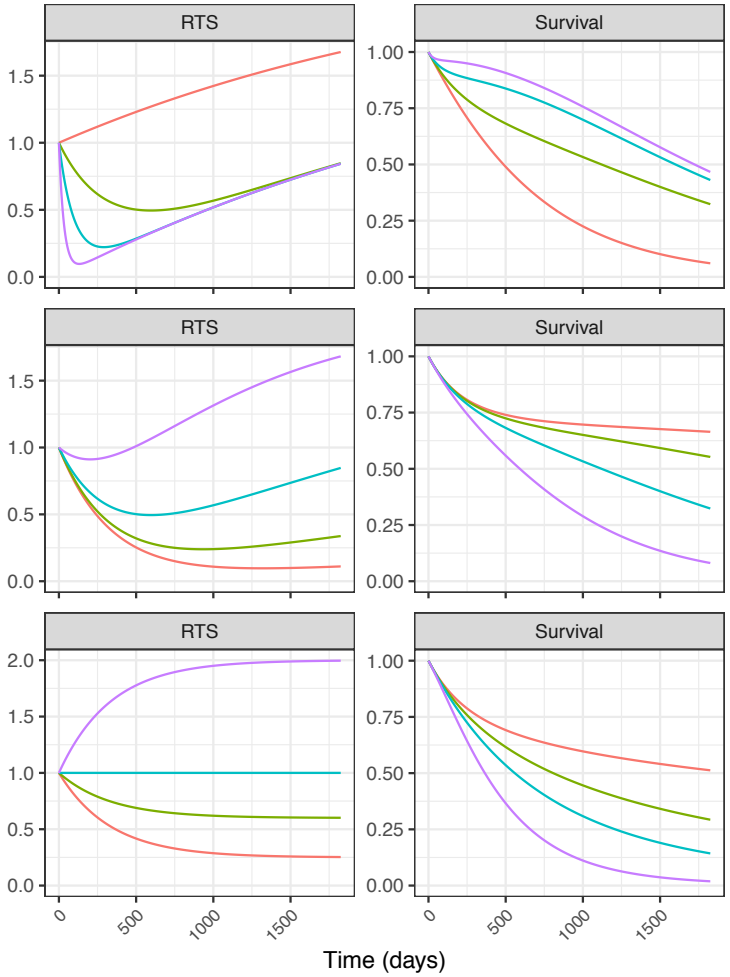
Modulate Kdying

Durability

Modulate Kgrow

Depth & Durability

Modulate Plateau



Difficult to predict how modulation of >1 parameter will impact OS.

Moore model[1] for asymptotic tumor growth:

$$TS_i(t) = TS_{i,0}\left(5TS_{i,max}\right)\left(1 - e^{-k_{i,g}t}\right) + TS_{i,0}e^{-k_{i,d}t}$$

Hazard function with cure fraction:

$$h_i(t|X_i) = a(X_i)e^{\beta * \log(RTS_i(t))}e^{-\lambda t}\lambda$$

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Multiple clinical measures could be used to describe tumor response

Effects on depth of response

- Difference in mean ***best relative change*** from baseline at t≤T.
- Difference in mean ***relative change from baseline at t=T***.
- Difference in ***proportion of patients with best change*** from baseline at t≤T of ≤ 0, 10, 30, 50%.

Effects on durability of response

- Hazard ratio for ***time-to-rebound*** (20% growth from nadir; "tPFS").

T=[18, 27, 36, 45, 54, 63, 72] weeks

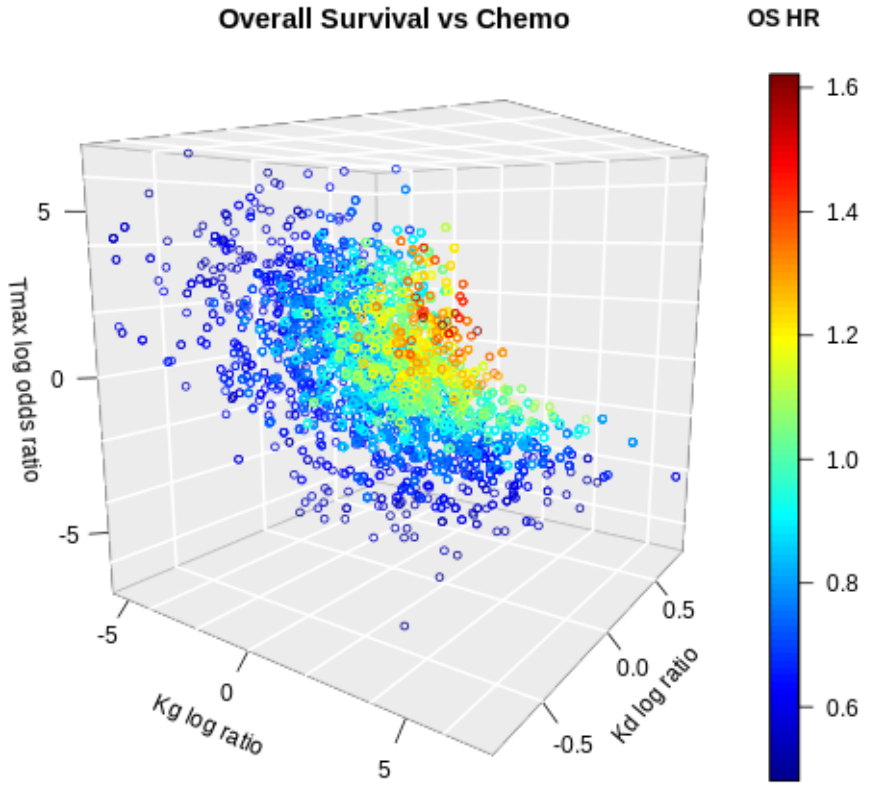
Prior distributions for new theoretical treatments

Using the reference model as a prior distribution for a new therapy, we constrain parameter space by the likely correlations between parameters observed previously

Derivation of Priors in THETA-space for simulation of novel therapies

	TS main effects	Other parameters
Chemo arm	Reference model standard error	Reference model standard error
New arm	Standard deviation = 1 “Pembro effect”	Reference model standard error

This gives ~16% probability that the novel therapy has an effect greater than Pembro.



OS is predicted to improve (HR<1 relative to chemo) when Kg and Tmax decrease, or Kd increases.

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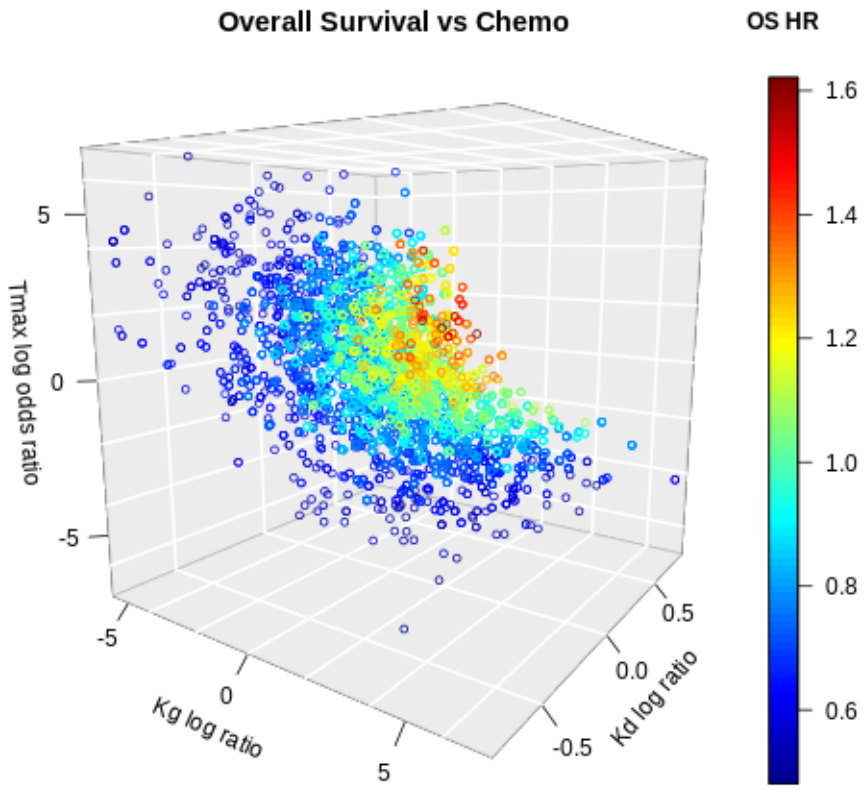
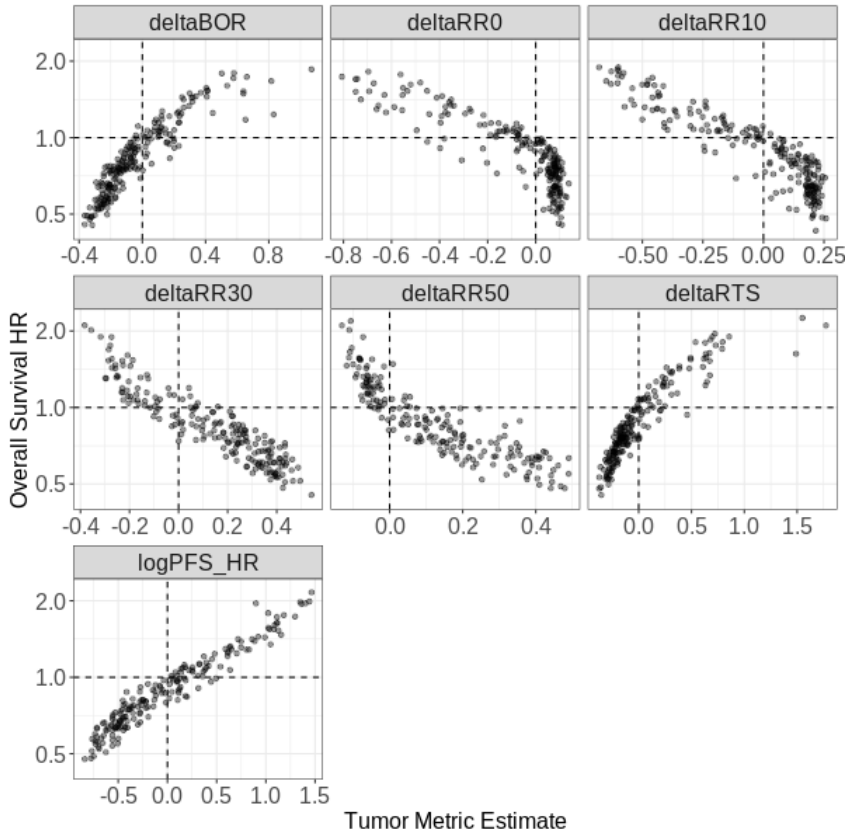
Converting THETA-space priors into clinical-space priors



Mapping via simulation



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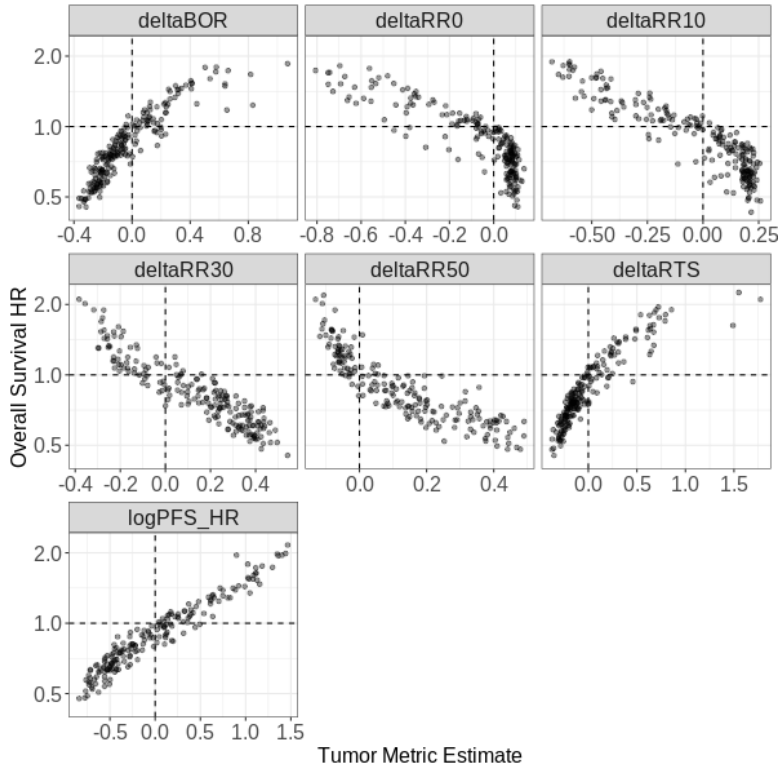
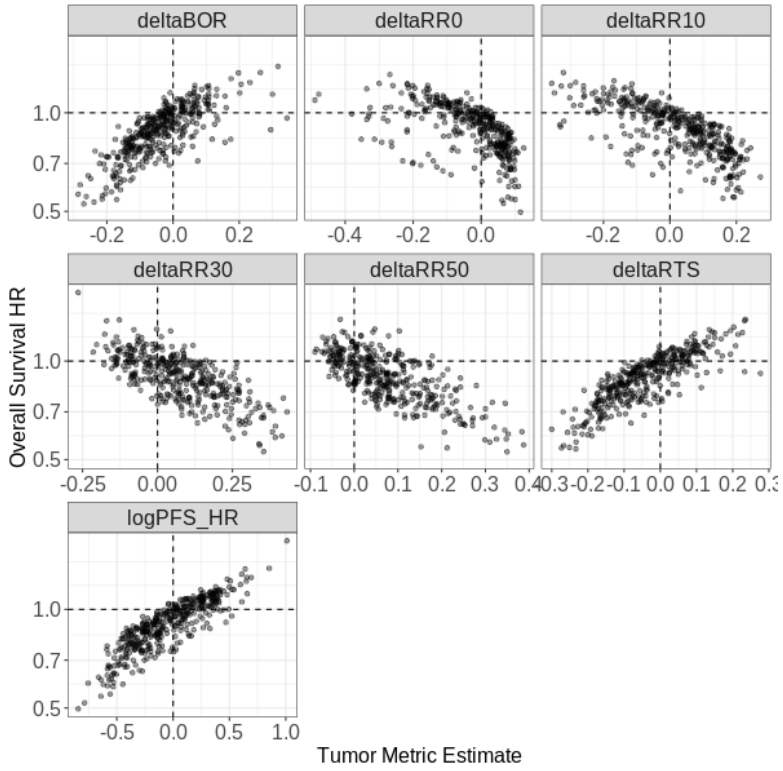
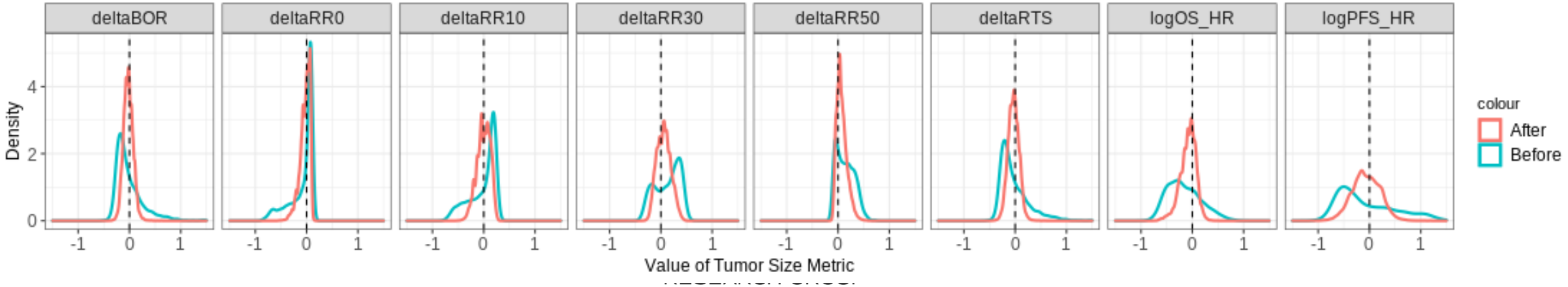
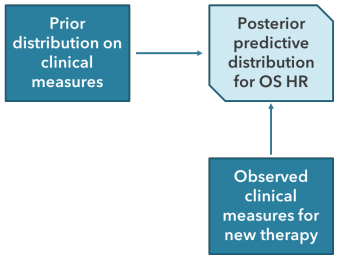
Modifying priors on clinical measures



Importance sampling

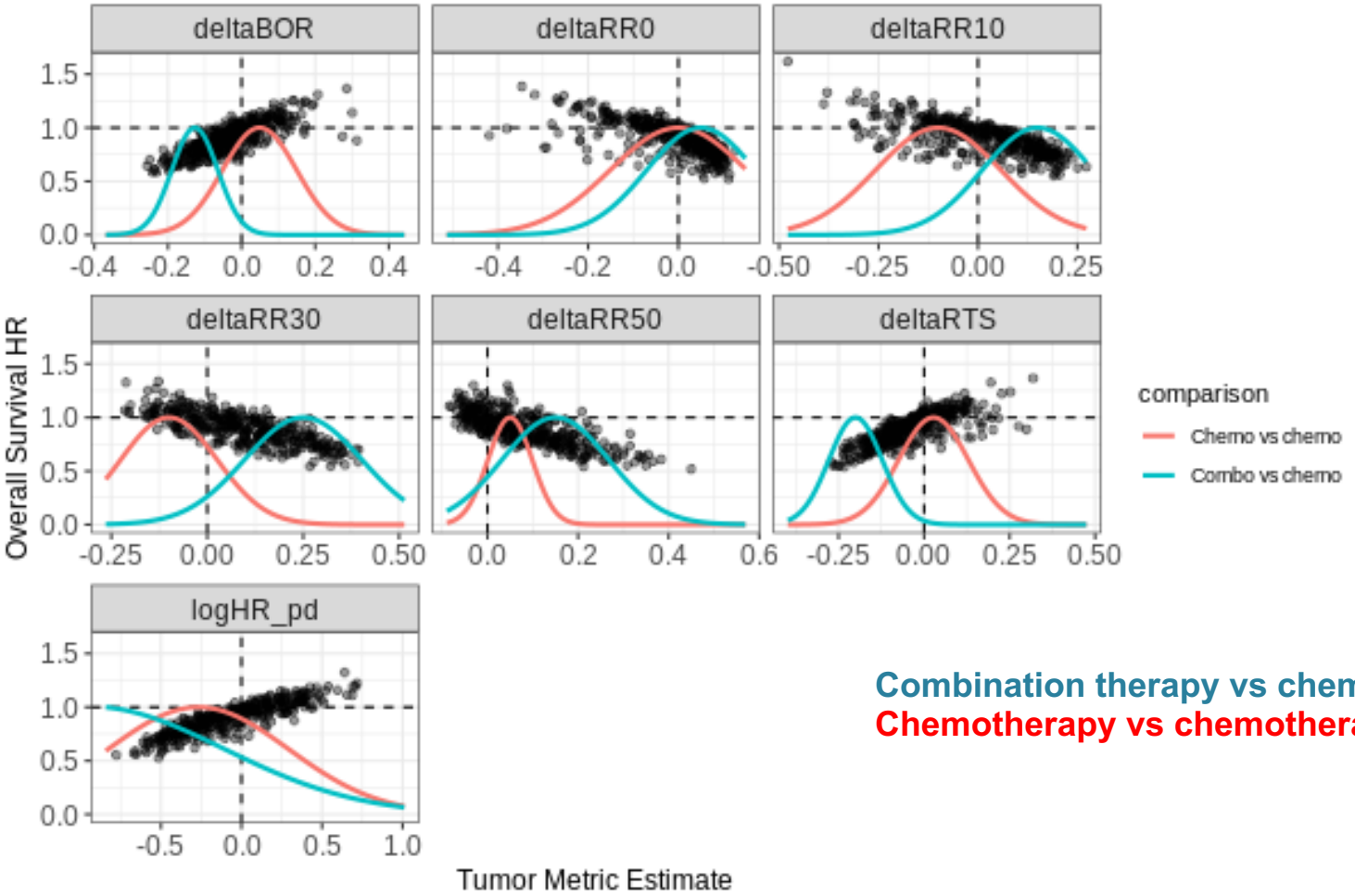






Application of model to two hypothetical therapies

Observed data at 18 weeks from randomly sampled data set of 20 patients/arm.



Combination therapy vs chemotherapy
Chemotherapy vs chemotherapy (Negative control)

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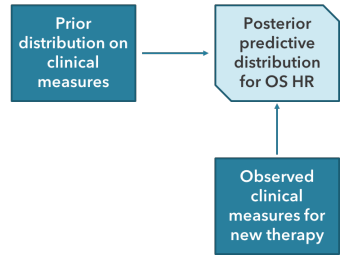
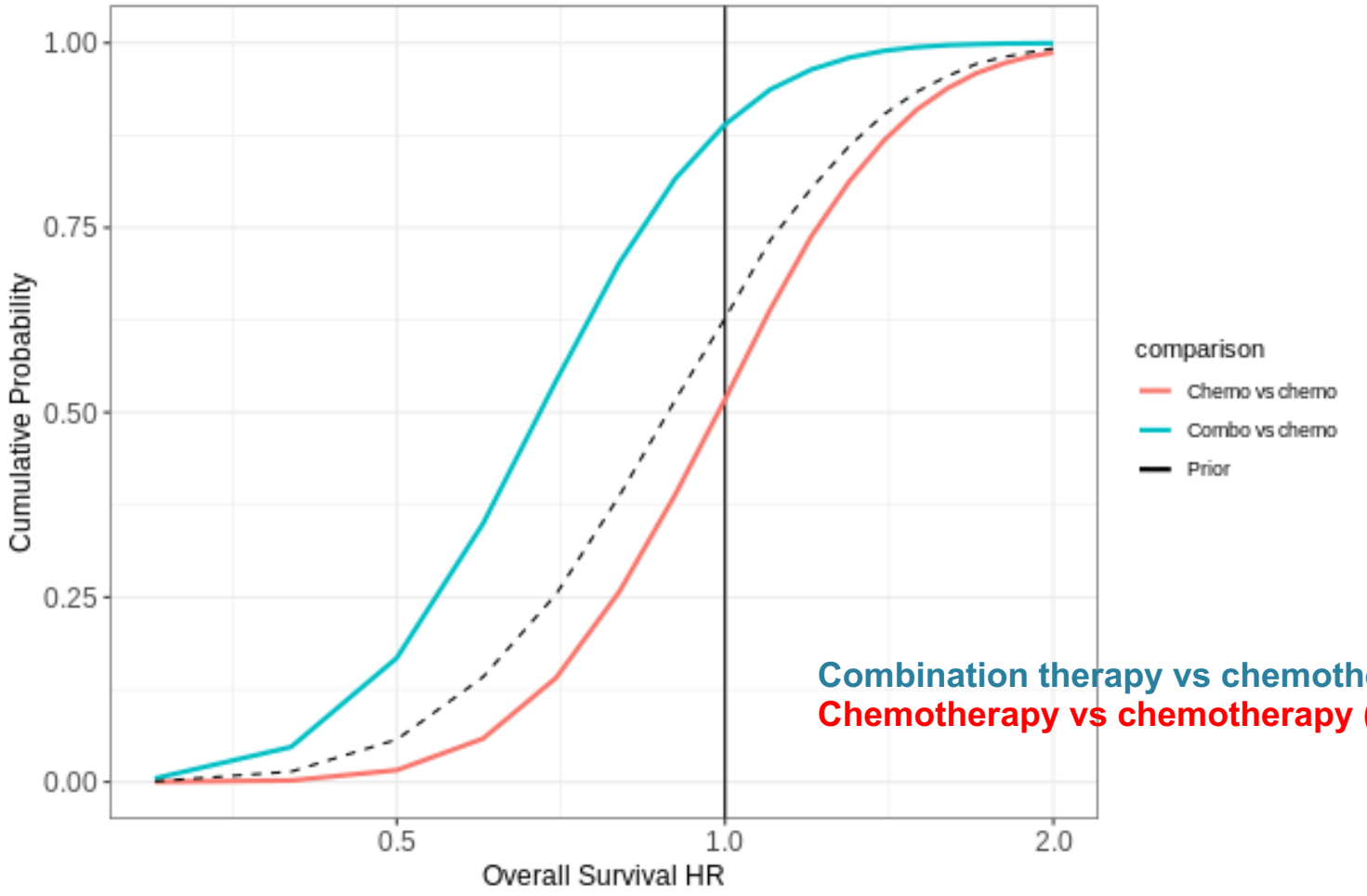
Application of model to two hypothetical therapies



80% power to predict survival benefit with summary data from 20 patients/arm at 18 weeks, even with very strong prior distribution.



Combination therapy vs chemotherapy
Chemotherapy vs chemotherapy (Negative control)

Conclusions

- M&S enables integration of information across a spectrum of clinical observations
- In non-linear models, prior distributions in parameter space don't result in normal priors in clinical space
- Importance sampling can be used to generate multi-dimensional normal priors.
- Summary level data from a small cohort of patients can be leveraged to simulate expected clinical benefit.
- Further work:
    - Use likelihood profiles to dissect the specific contribution of each metric to OS
    - Understand how the likelihoods of each TS metric change over time
    - Apply this approach in comparator analysis setting with summary level data from literature.