Dose-Finding in Early Phase II Trials When Targeting Two Response Rates with Several Models

Adrian Mander

MRC Biostatistics Unit Hub for Trials Methodology Research, Cambridge, UK.

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The Diabetes Interleukin-2 (IL-2) trial

PIs: Frank Waldron-Lynch, Linda Wicker, John Todd (JDRF/Wellcome Trust)
Statistcian: Simon Bond (CCTU)

- Single Doses are injected SC to each newly diagnosed participant
  - any concentrations can be delivered within the target dose range
- A biological response expected and measured by T-regulatory cell concentrations
  - (max) Treg % change from baseline over 5 days (used in literature)
- Find two ultra-low doses of Proleukin (contains IL-2)
  - Minimal T-reg response and a Therapeutic T-reg response.
- Needed a response adaptive design

Frank Waldron-Lynch et al. Rationale and study design of the Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D): a non-randomised, open label, adaptive dose finding trial *BMJ open* 4(6) e005559

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Models considered

As this study was entirely novel we had no idea of the shape of the dose-response curve (or whether there would be a response!).

Model	# params	$y = f(d, \theta)$
Linear	2	$\theta_0 + \theta_1 * d$
Quadratic	3	$\theta_0 + \theta_1 * d + \theta_2 * d^2$
Emax	3	$\theta_0 + \frac{\theta_1}{\theta_2 + d}$
Emax4	4	$\theta_0 + \frac{\theta_1}{\theta_2 + d^{\theta_3}}$
Logistic	4	$\theta_0 + \frac{\theta_1}{1 + exp(\theta_2 * d - \theta_3)}$
Cubic	4	$\theta_0 + \theta_1 * d + \theta_2 * d^2 + \theta_3 * d^3$

F Bretz, J C Pinheiro, and M Branson.Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*, 61(3):738–48, 2005.

Learning phase - based on simulations

Study started with a learning phase of 10 patients out of the potential 40 patients

- pairs of patients were put on the doses 0.04, 0.16, 0.6, 1 and 1.5 ($IUx10^6/m^2$)

Then a meeting was used to have a reality check on the design (were simulation parameters in the right area?)

- After the learning phase the clinicians choose to target 10% and 20% responses
- need to use the inverse function $f^{-1}(y, \theta) = d$
- e.g. for 20% response the dose $d_{0.2} = f^{-1}(0.2, \theta) = \mathbf{g}(\mathbf{0.2}, \theta)$.

Interest is in both $d_{0.1}$ and $d_{0.2}$ and want sufficient numbers of patients near these doses.

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Method for selecting the next two doses

Theoretically recruit 2 patients at a time so after k patients

- Estimate information given model parameters $\theta^{(k)}$
- Select two future doses d^* and d^{**} that minimise
  - Trace — $Var(d_{0.2}|\theta^{(k)}) + Var(d_{0.1}|\theta^{(k)})$
  - or Determinant $|Var(d_{0.1}, d_{0.2}|\theta^{(k)})|$
- In reality need to consider any cohort size due to recruitment (actually recruited up to 4 a time)

Minimising the variance of dose is less well used but mixes patient and variance gains.

Information

Need to calculate the **observed information matrix** after k patients for the design is defined as

$$\begin{aligned} M_k(\theta) &= \sum_{i=1}^{k} \frac{\partial f(d_i,\theta)}{\partial \theta} \frac{\partial f^T(d_i,\theta)}{\partial \theta} - (y_i - f(d_i,\theta)) \frac{\partial^2 f(d_i,\theta)}{\partial \theta^2} \\ Var_k(\theta) &\approx \sigma_e^2 M_k^{-1}(\theta) \end{aligned}$$

Efron and Hinkley (1978) *Biometrika* 65(3): 457-87.

The algorithm

Using the delta method

$$Var_k(d_{0.1}, d_{0.2}|\theta) \approx \left[\frac{\partial g(0.1,\theta)}{\partial\theta}, \frac{\partial g(0.2,\theta)}{\partial\theta}\right]^T Var_k(\theta) \left[\frac{\partial g(0.1,\theta)}{\partial\theta}, \frac{\partial g(0.2,\theta)}{\partial\theta}\right] \quad (1)$$

Now need to pick (d^*,d^{**}) and recalculate the above two equations

$$Var^*_{k+2}(\theta|d^*, d^{**}) = \sigma_e^2 \left(M_k(\theta) + \frac{\partial f(d^*,\theta)}{\partial\theta}\frac{\partial f^T(d^*,\theta)}{\partial\theta} + \frac{\partial f(d^{**},\theta)}{\partial\theta}\frac{\partial f^T(d^{**},\theta)}{\partial\theta} \right)^{-1}$$

- Set θ to be $\hat{\theta}^{(k)}$
- Then plug $Var^*_{k+2}(\hat{\theta}^{(k)}|d^*, d^{**})$ into equation (1)
- use optimization to find doses

Trial set up

- Attempt to fit each non-linear model to obtain $\hat{\theta}$
- Ignore the models that do not converge
- For each model repeat the optimisation to find two doses.
    - Ignore doses that have predicted values outside the dosing range
- Assess the predicted gain in precision by using each dose for each model

Repeat the steps until we have 40 patients with evaluable data

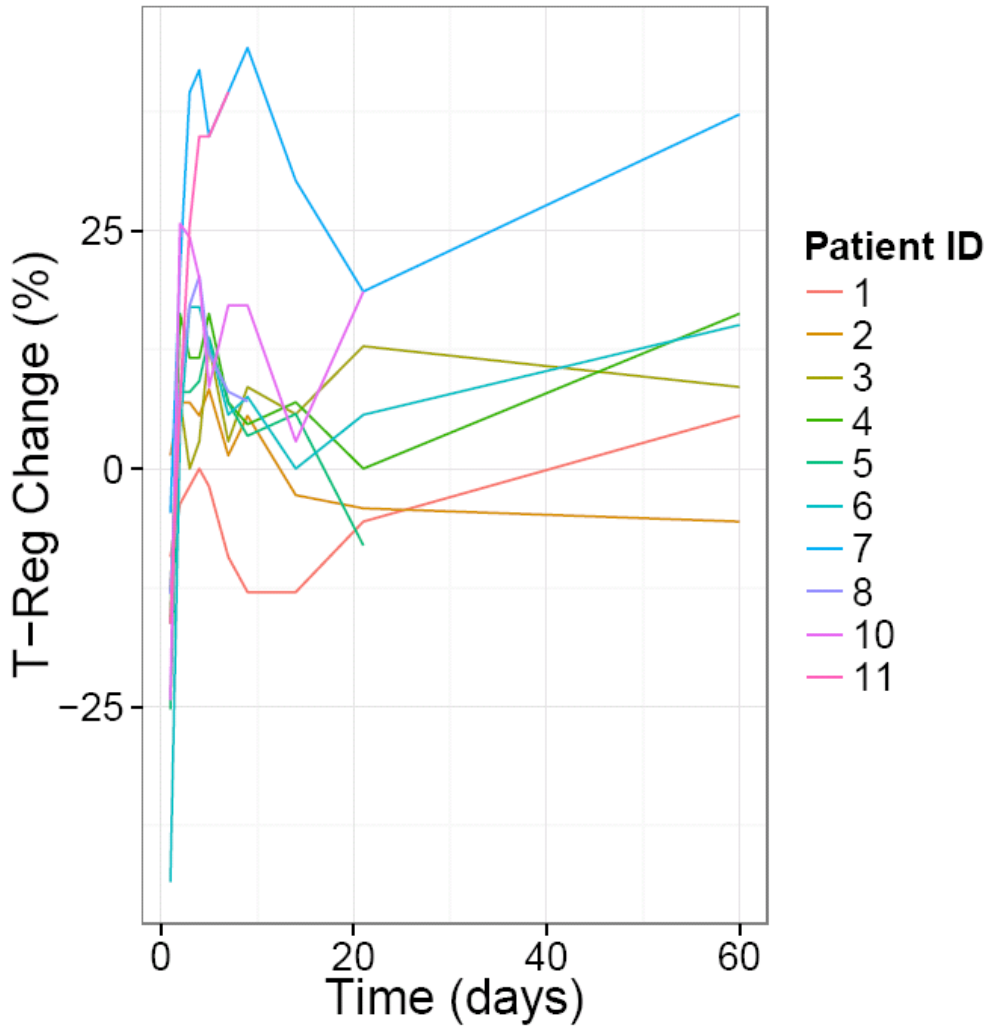
That was the theory....

A Dose Determining Committee was set up, consisting of 3 groups: Statisticians, Biologists and Clinicians.

- Each group had a single vote on which dose should be taken forward
- Had a strong DDC chair
- A Charter was set up that laid out the procedure

Interim Analysis Report after learning phase

Produced by Simon Bond using Rsweave.



Interim Analysis Report

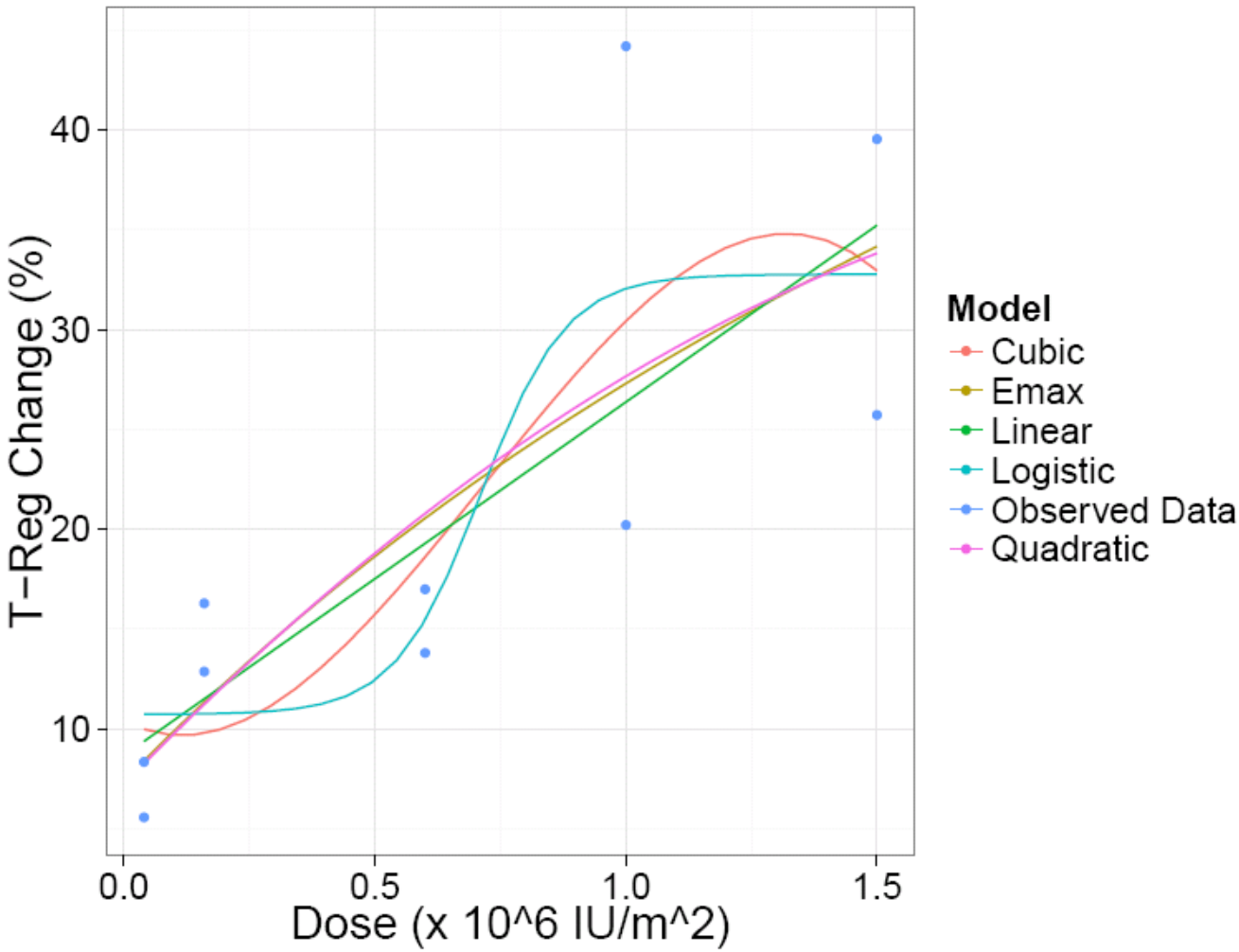


Table of estimated target doses and model fit

Model	**Target 1**		**Target 2**			
	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Deviance	AIC
Linear	0.076 (0.216)	-0.35, 0.50	0.641 (0.147)	0.353, 0.928	0.0540	-17.8
Quadratic	0.110 (0.168)	-0.22, 0.44	0.560 (0.217)	0.136, 0.985	0.0526	-16.1
Emax	0.105 (0.171)	-0.23, 0.44	0.571 (0.234)	0.112, 1.03	0.0529	-16.0
Cubic	0.197 (0.618)	-1.02, 1.41	0.646 (0.172)	0.309, 0.983	0.0489	-14.8
Logistic	NaN (NaN)	NaN, NaN	0.683 (0.228)	0.236, 1.13	0.0456	-15.5

Patient 11 recommendation

Model	Recommended Doses
Linear	1.5 (Max)
Quadratic	0.749
Emax	0.622
Cubic	0.42
Logistic	1.5

Emax model chosen and 0.622 dose given. A good fitting middle model and no desire to dose at highest (signs of site reactions at higher doses).

Interim Analysis Report — 11 Patients

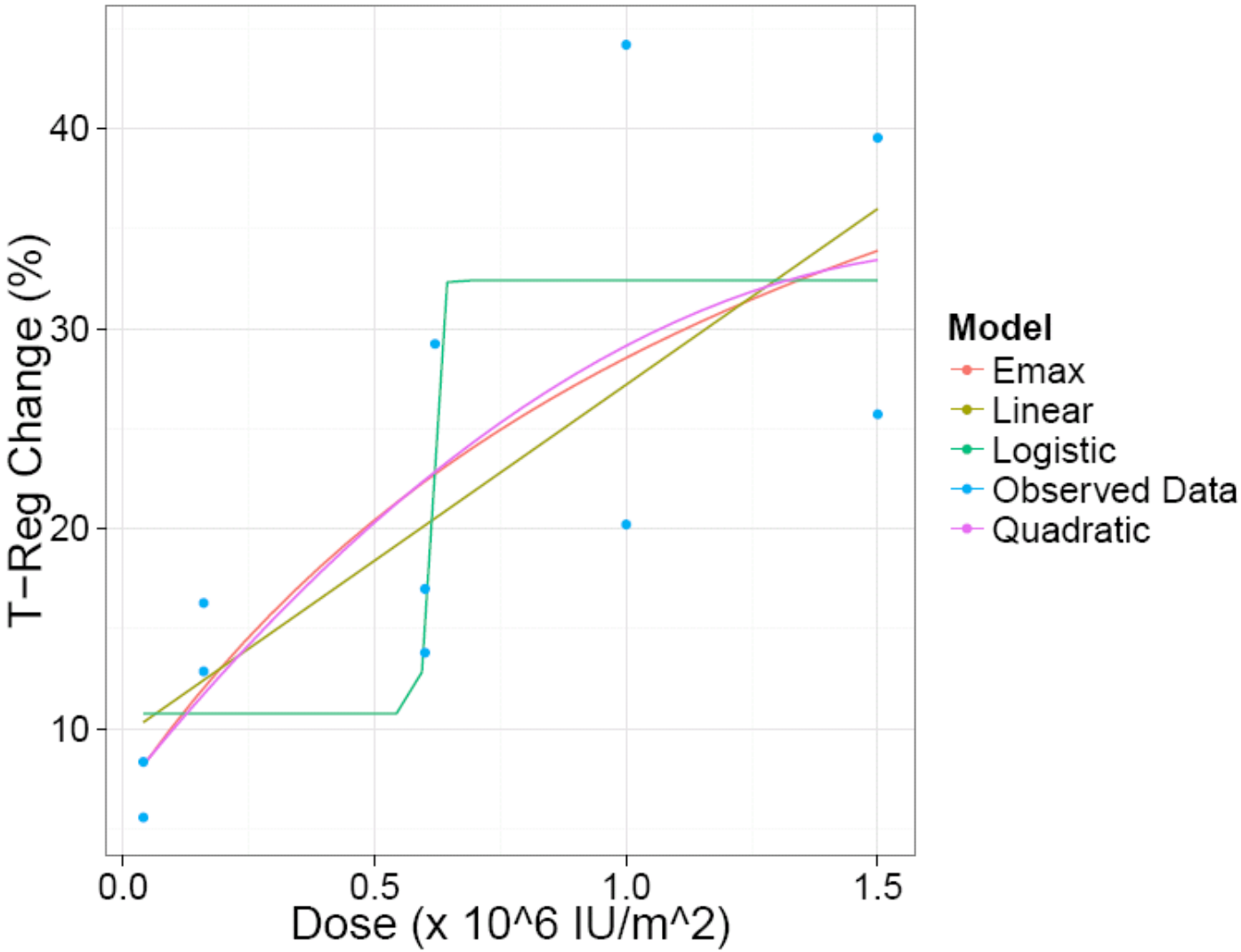
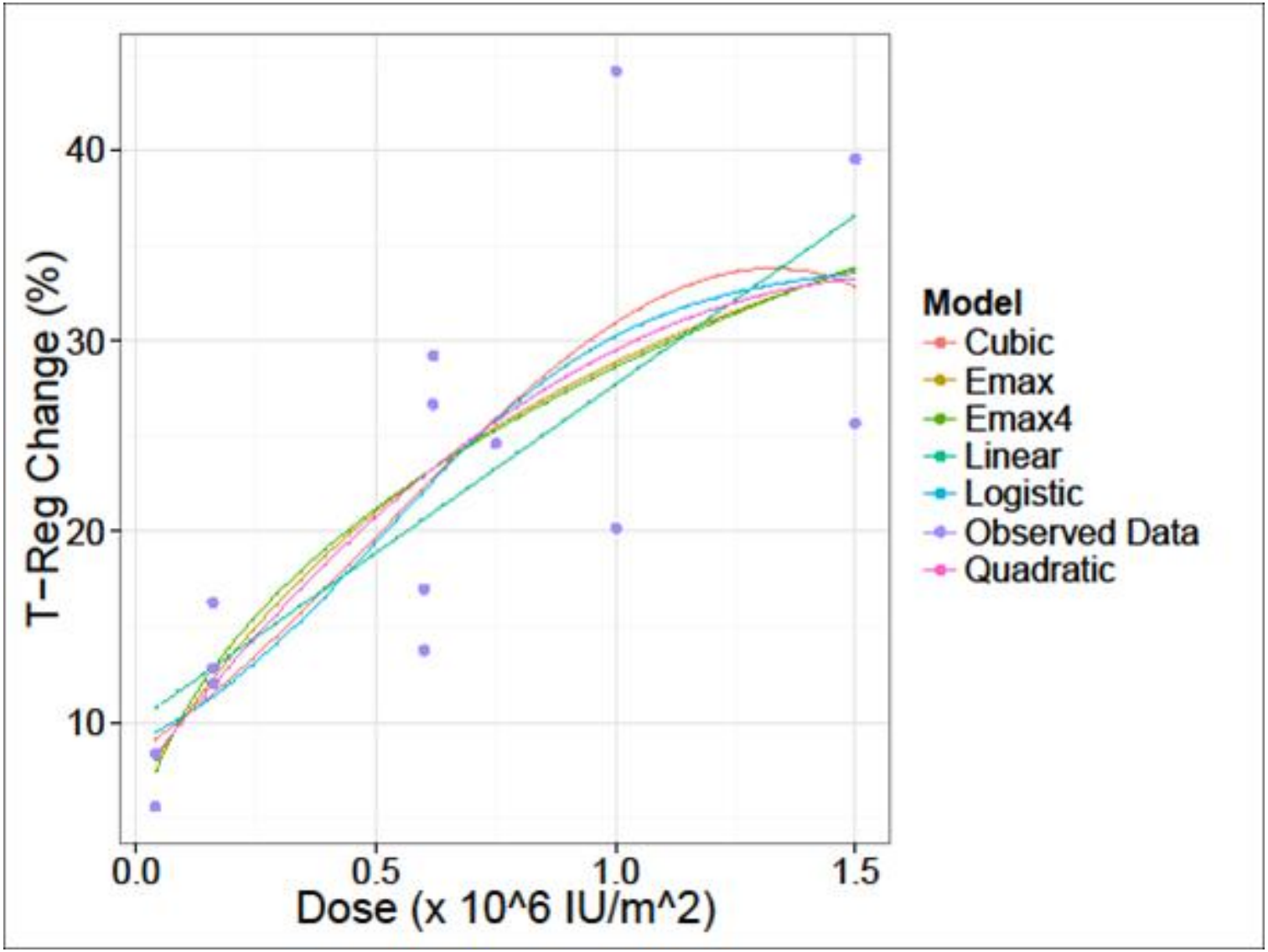


Table of estimated target doses and model fit

Model	**Target 1**		**Target 2**			
	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Deviance	AIC
Linear	0.022 (0.226)	-0.42, 0.47	0.591 (0.144)	0.309, 0.873	0.0624	-19.7
Quadratic	0.16 (0.129)	-0.09, 0.41	0.486 (0.158)	0.177, 0.795	0.0577	-18.5
Emax	0.095 (0.128)	-0.16, 0.35	0.479 (0.201)	0.085, 0.874	0.0583	-18.4
Logistic	NaN (NaN)	NaN, NaN	0.607 (0.01)	0.588, 0.625	0.0456	-19.1

Model	**Recommended Doses**		**Decrease in CR area (%)**		
			Linear	Quadratic	Emax
Linear	1.5	1.5	22.6	1.2	1.5
Quadratic	0.16	0.753	11.6	16.8	14.9
Emax	0.485	0.485	8.8	13.9	17.9
Logistic	NA	NA	-	-	-

Interim Analyses



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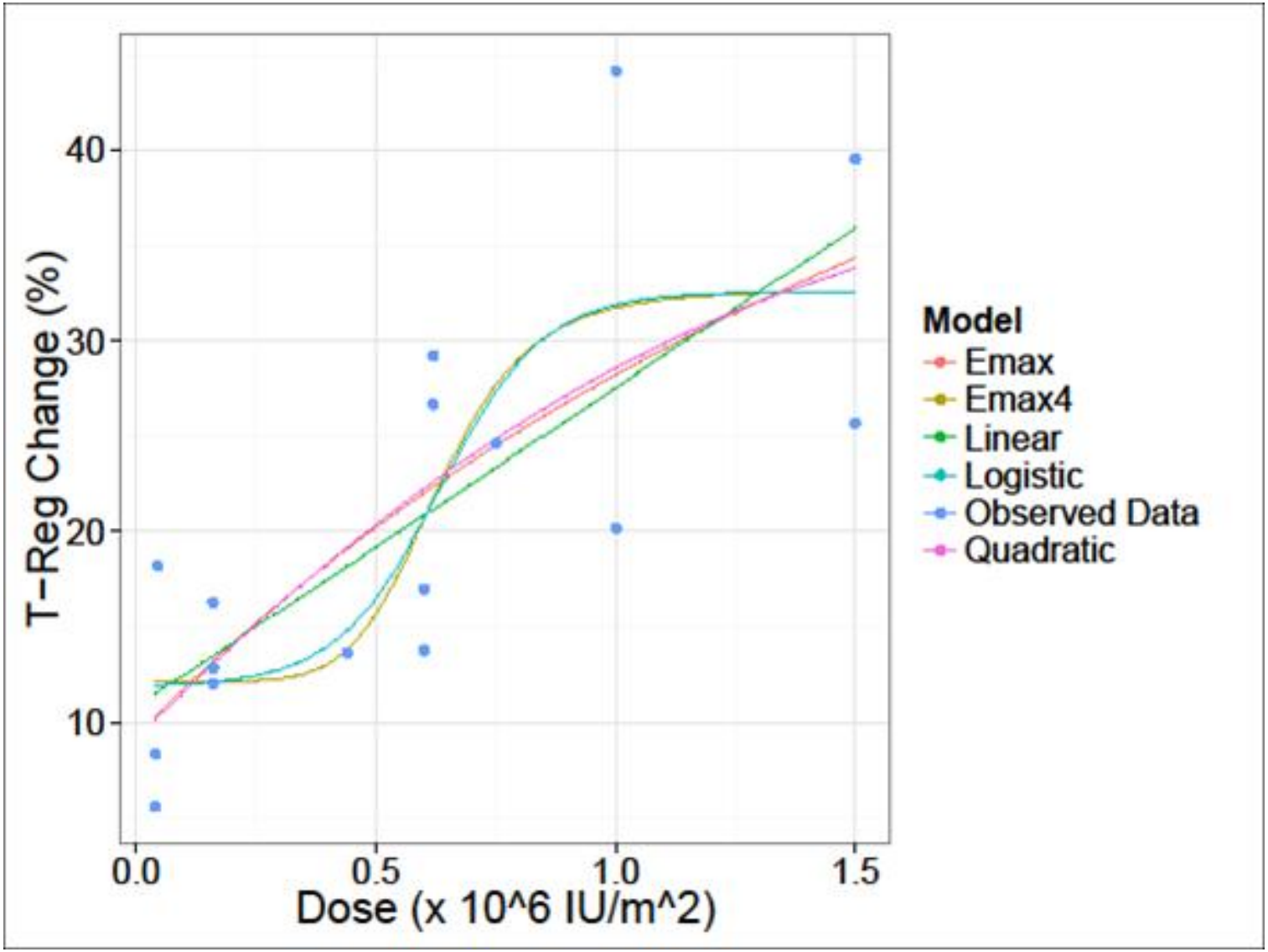

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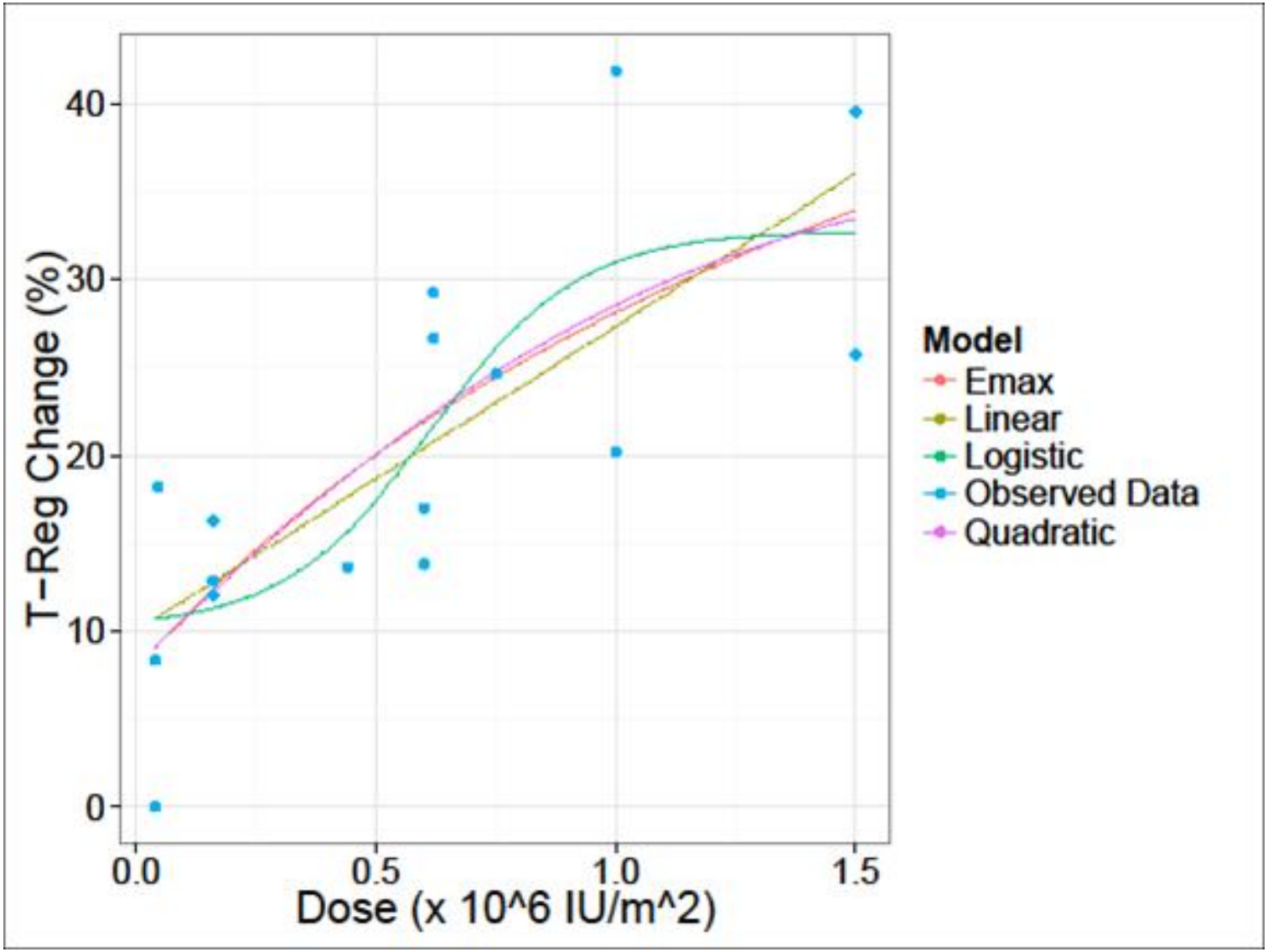

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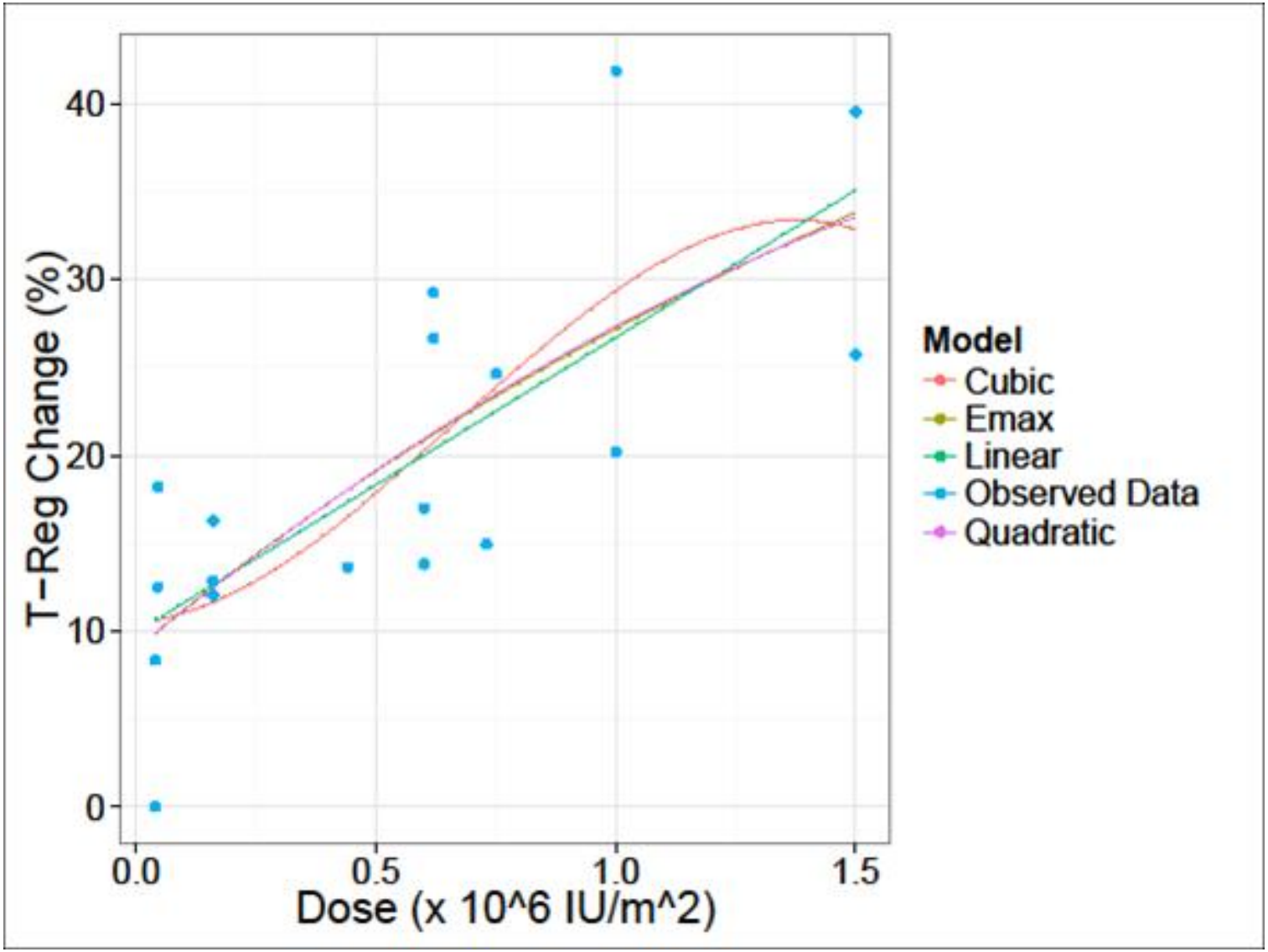

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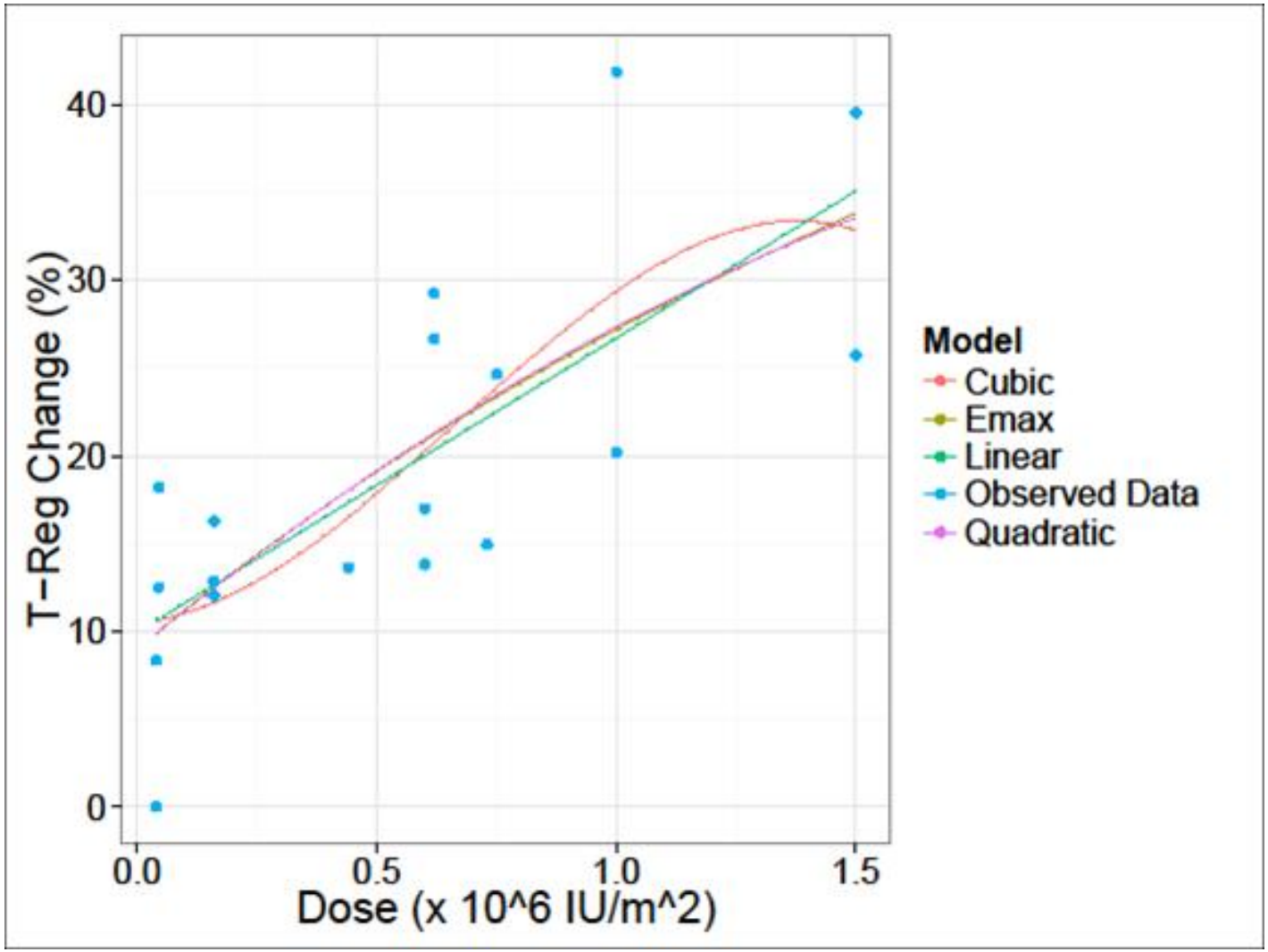

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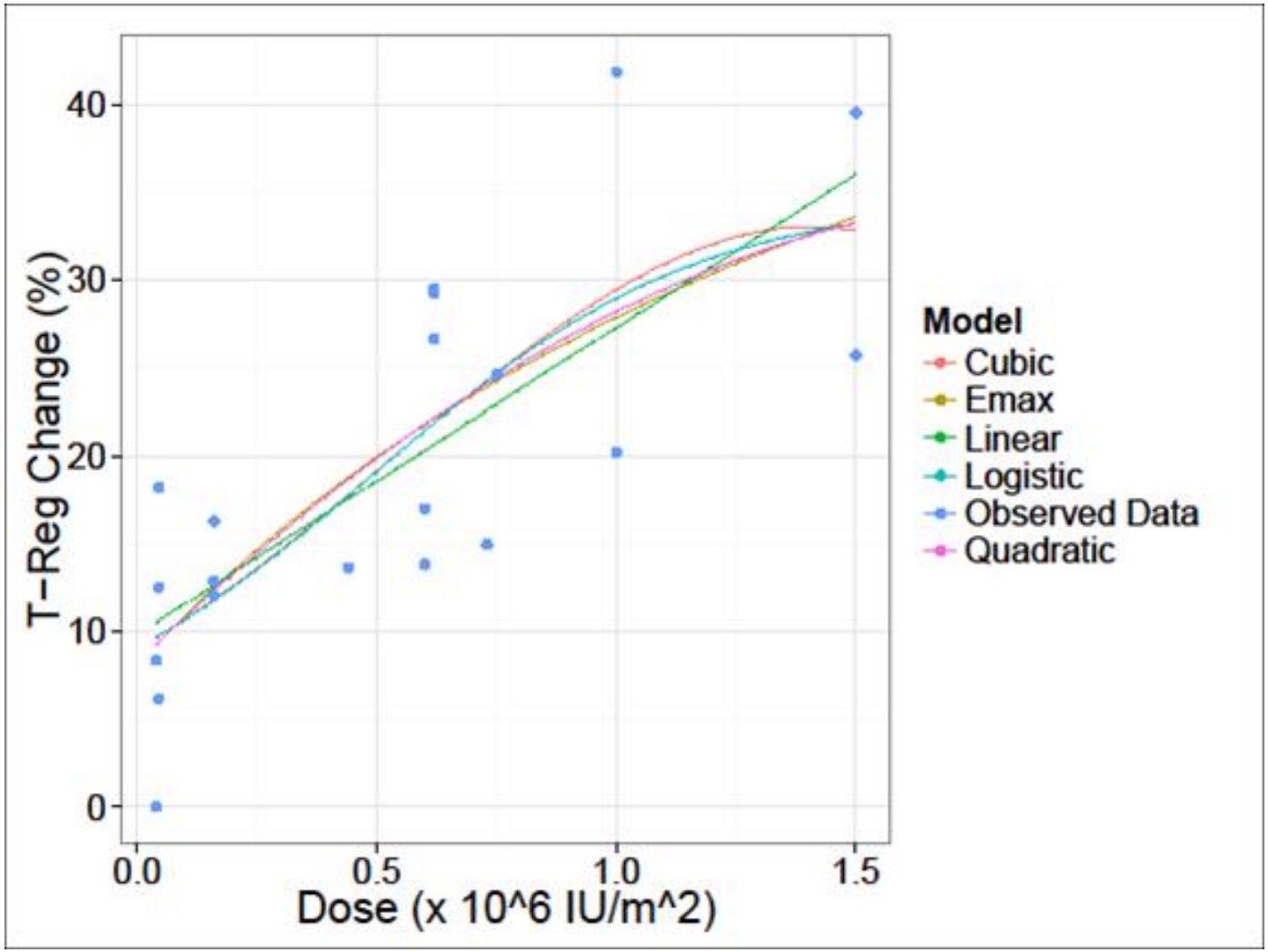

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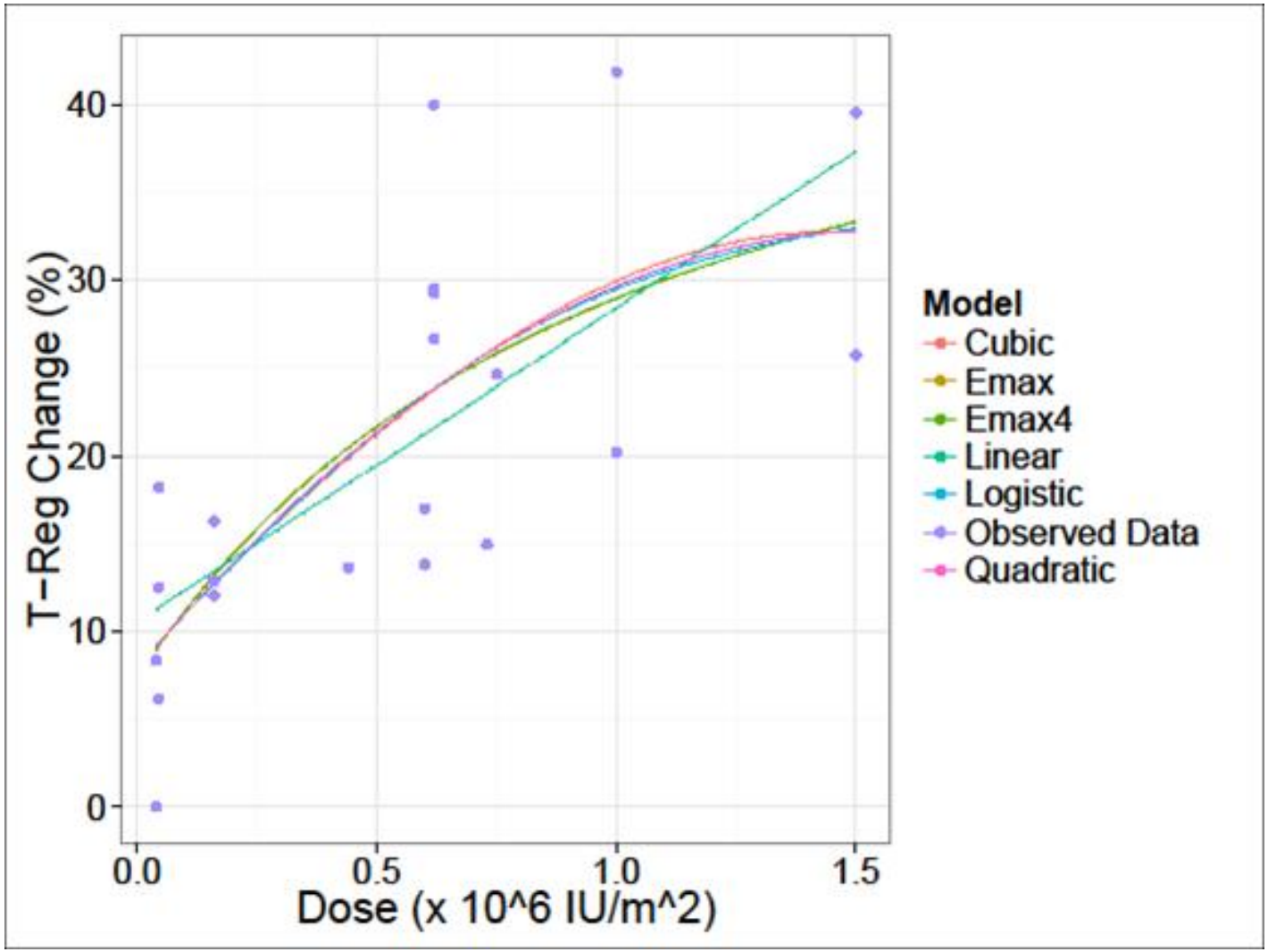

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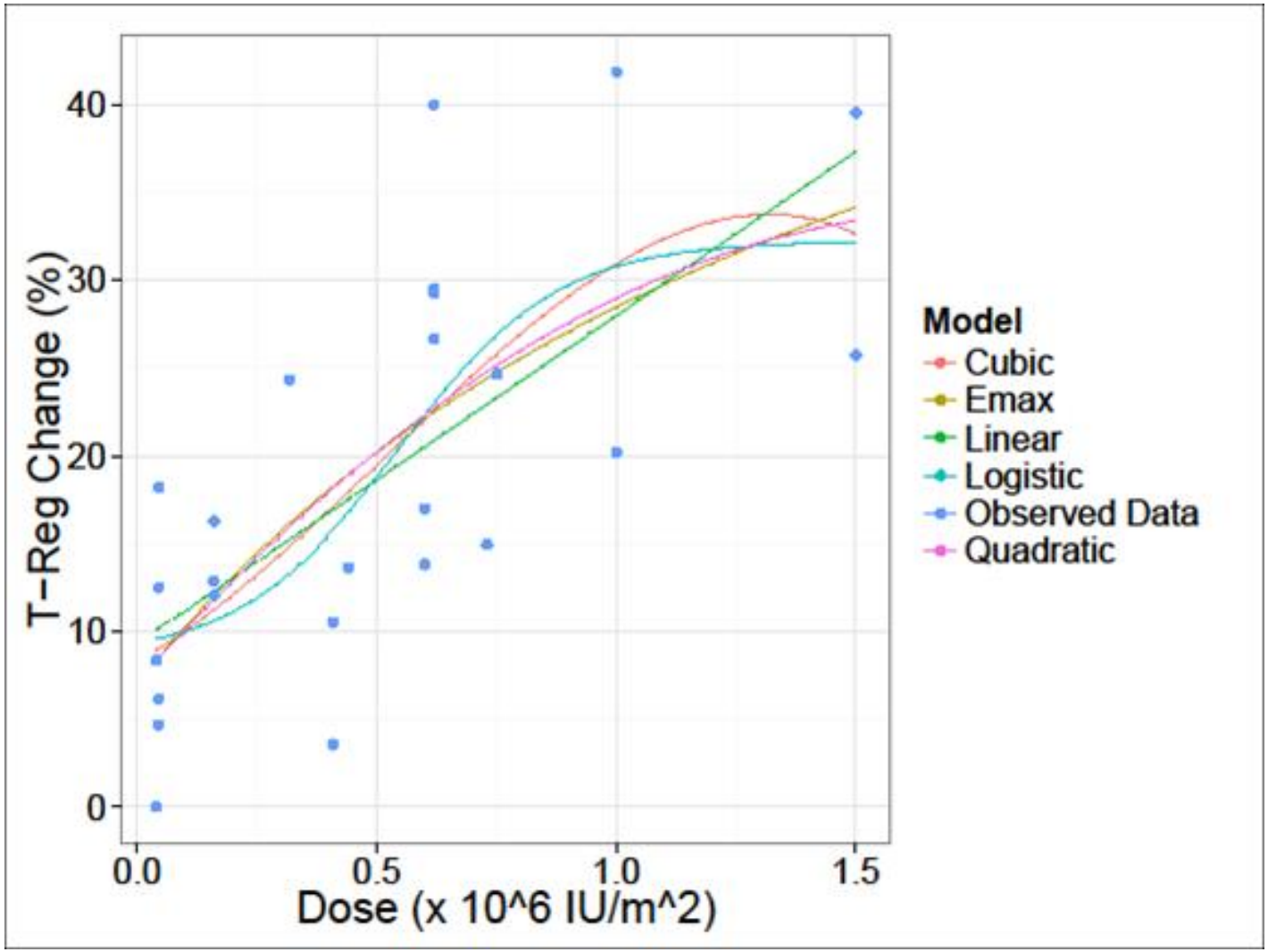

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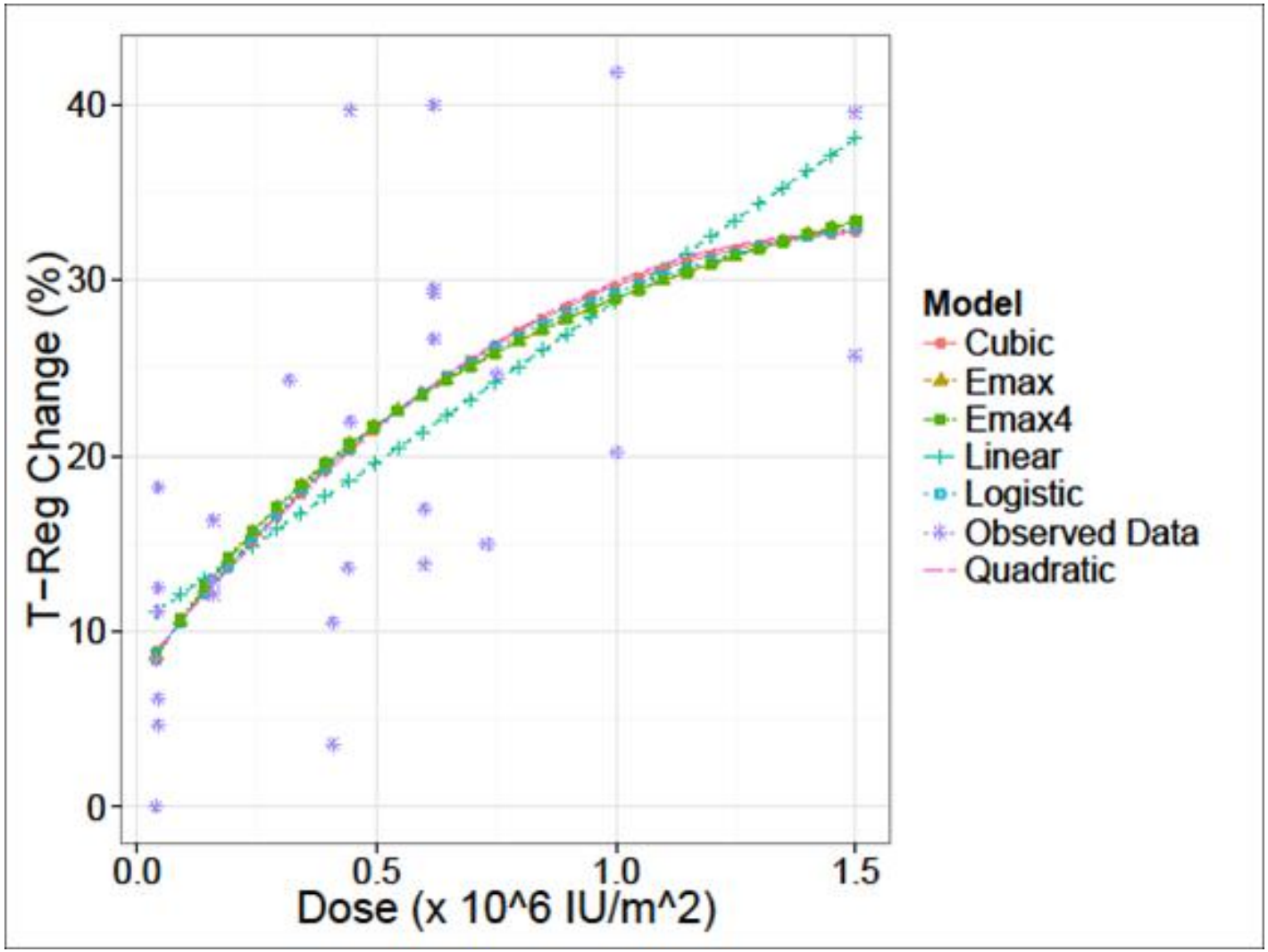

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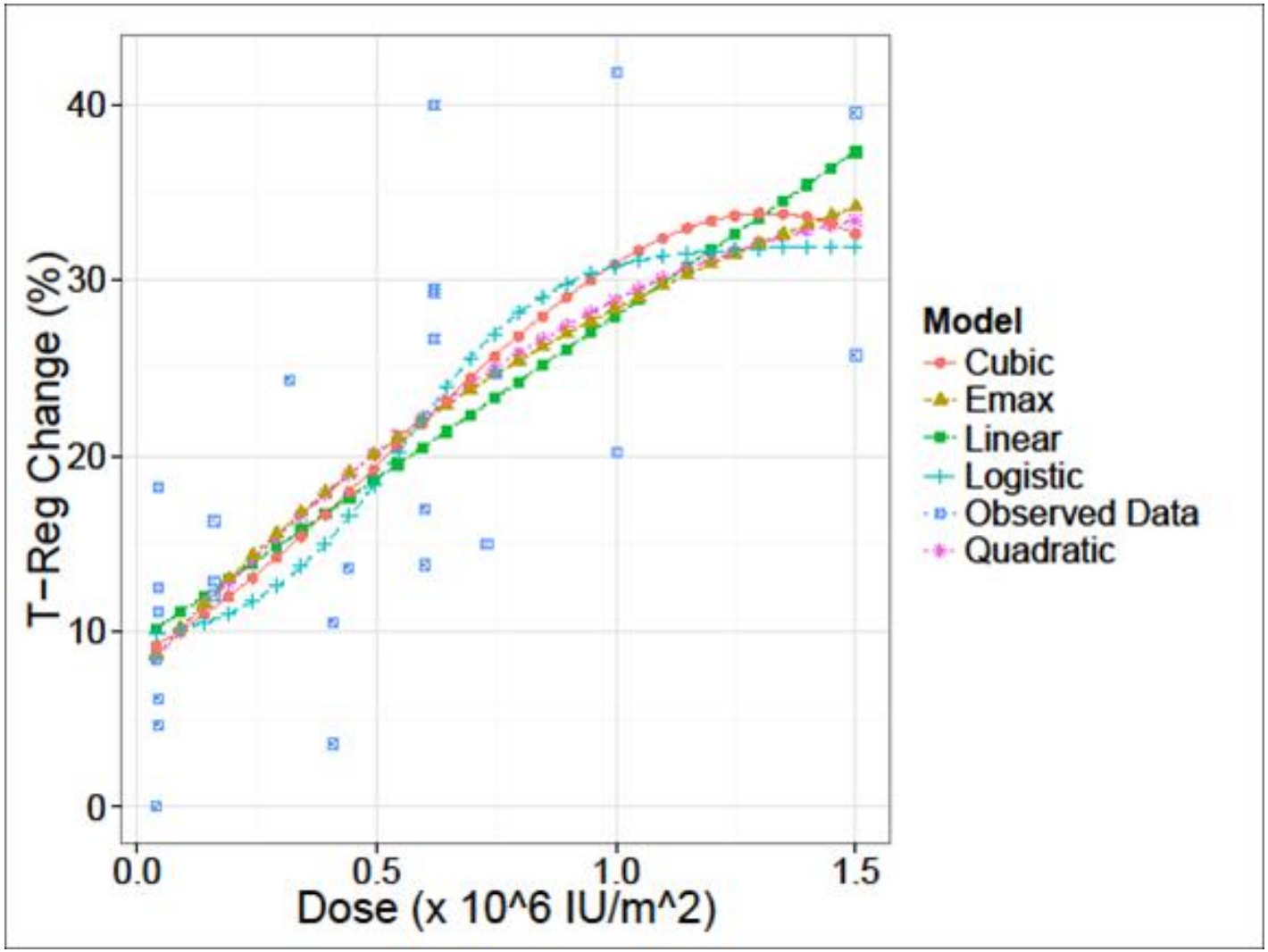

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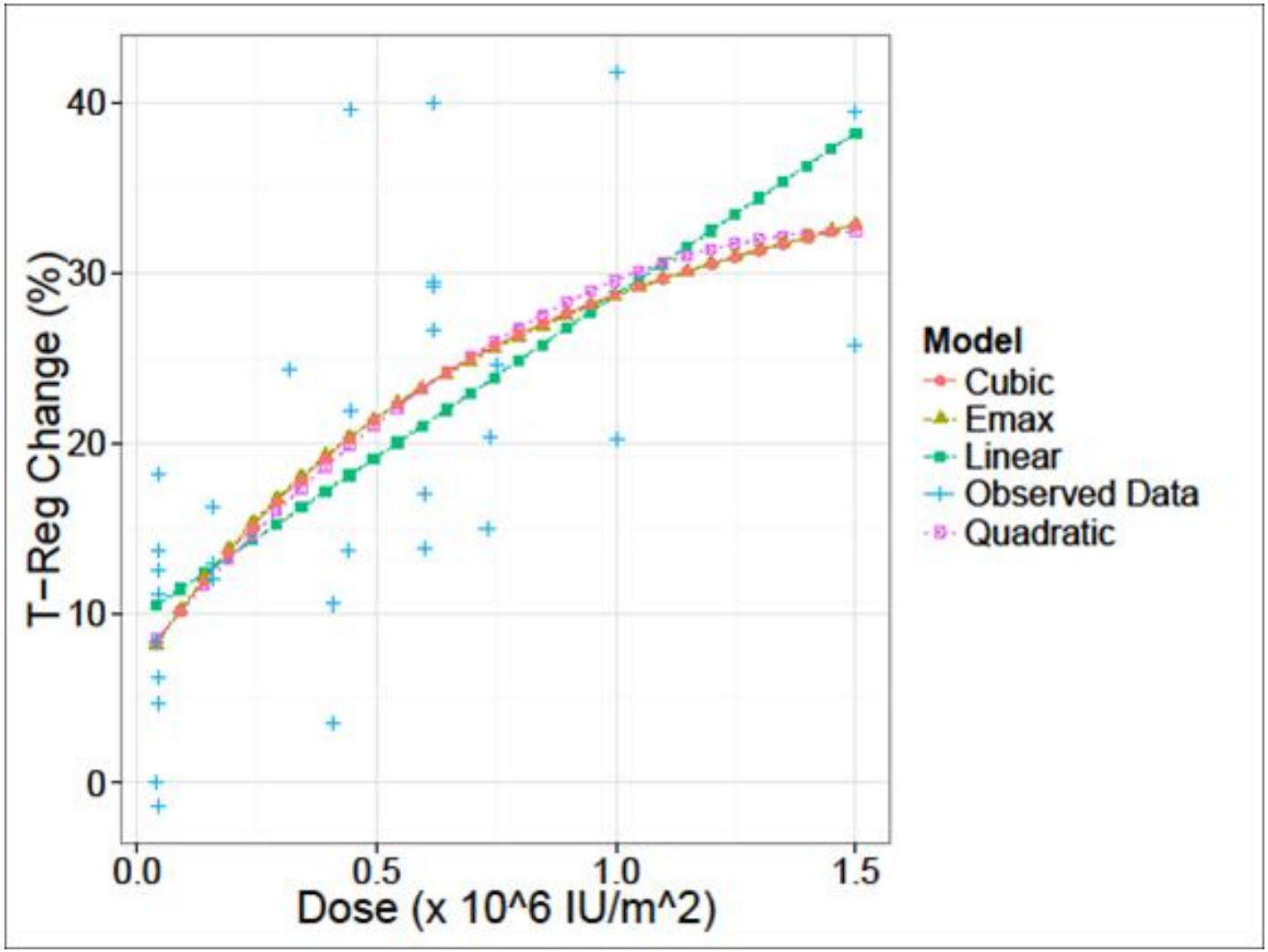

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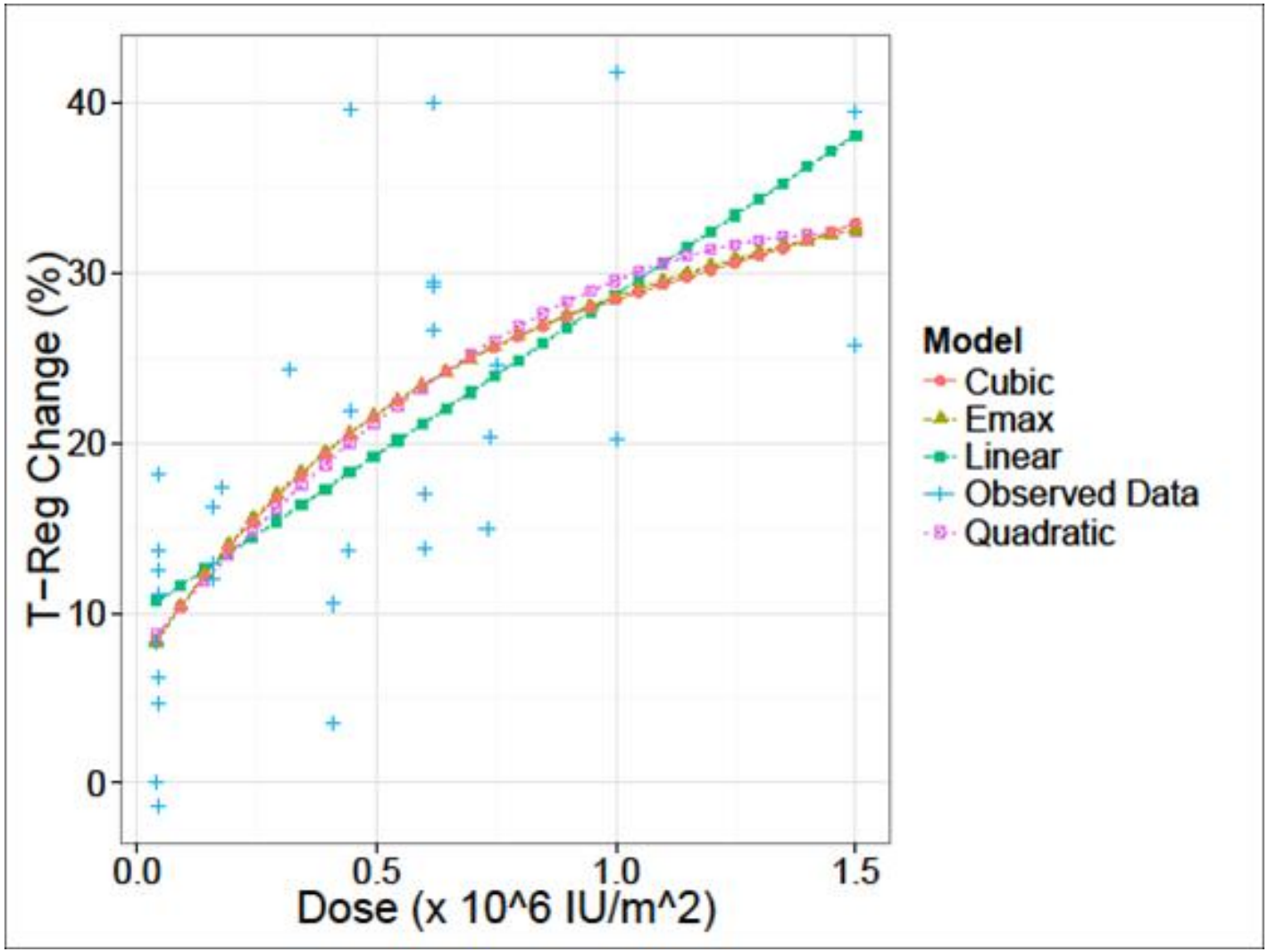

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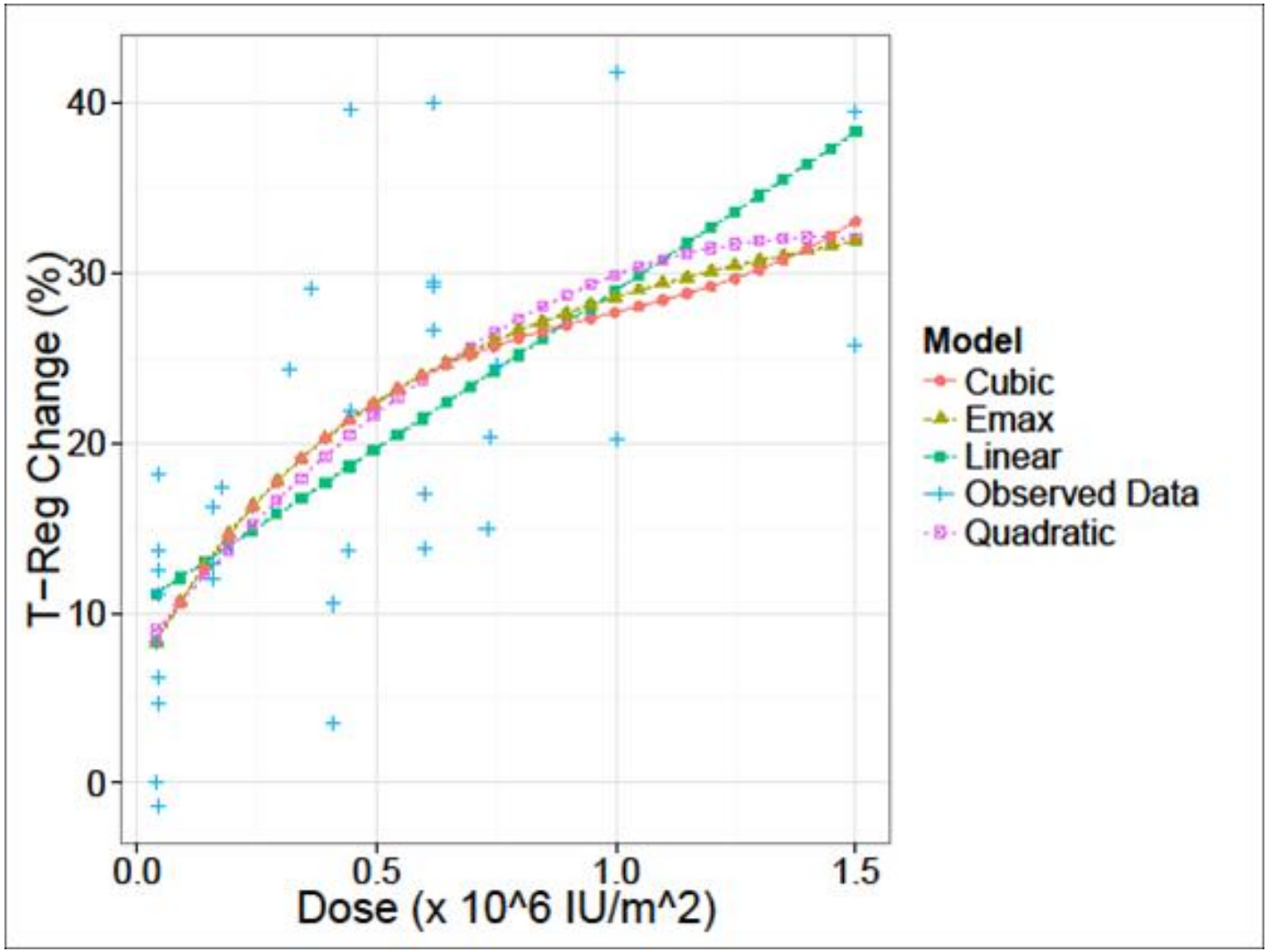

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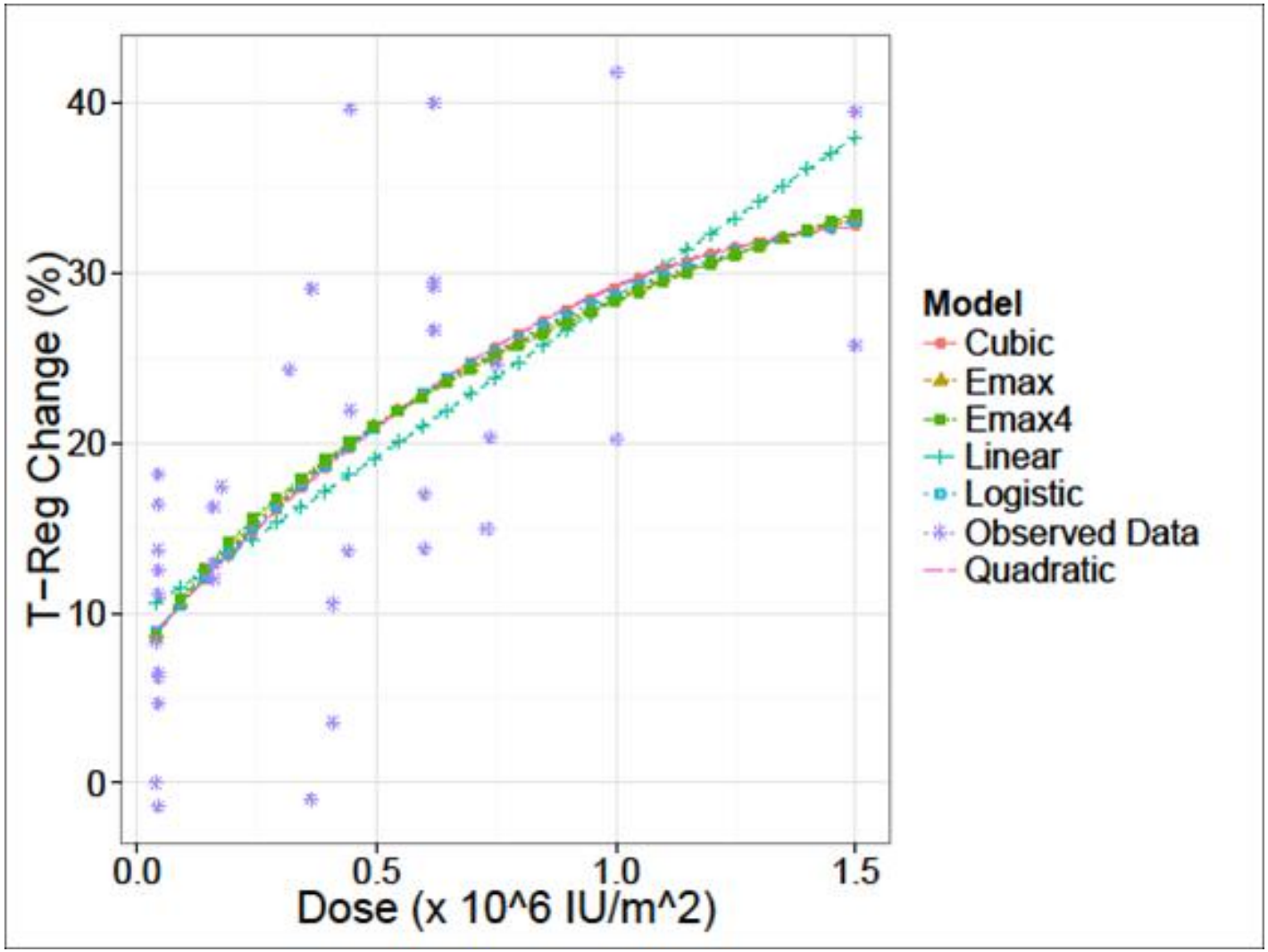

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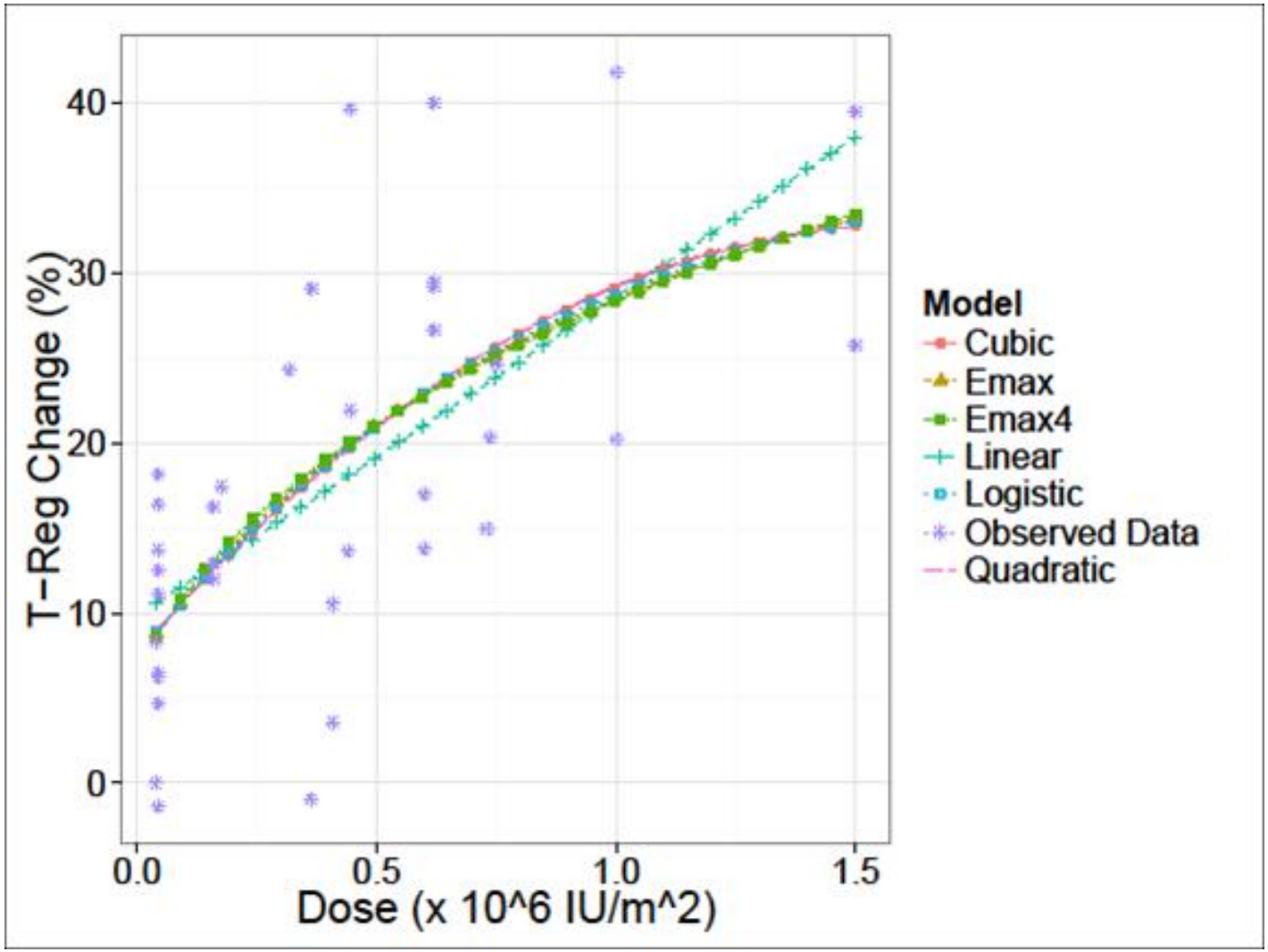

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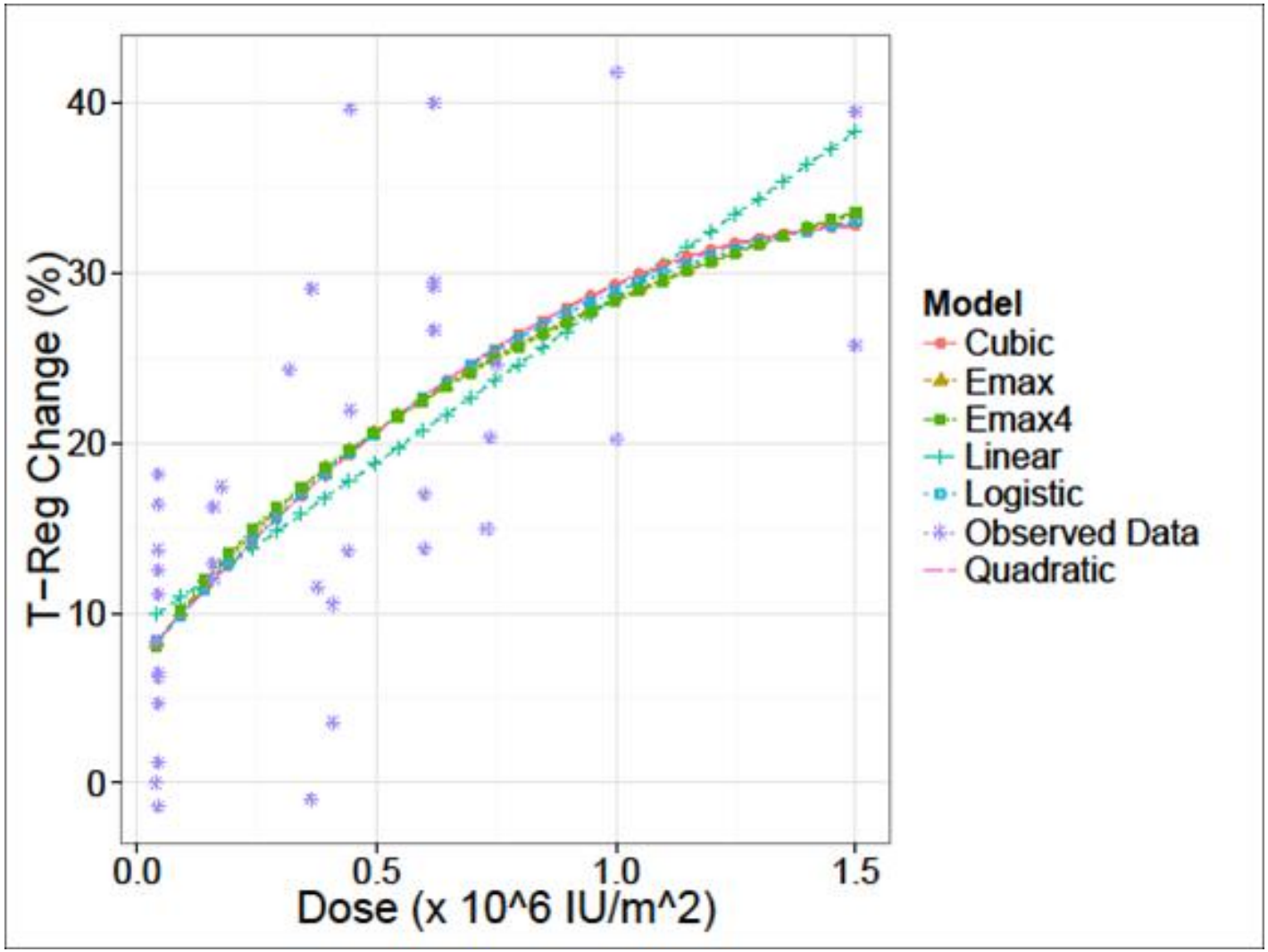

FINAL — Table of estimated target doses and model fit

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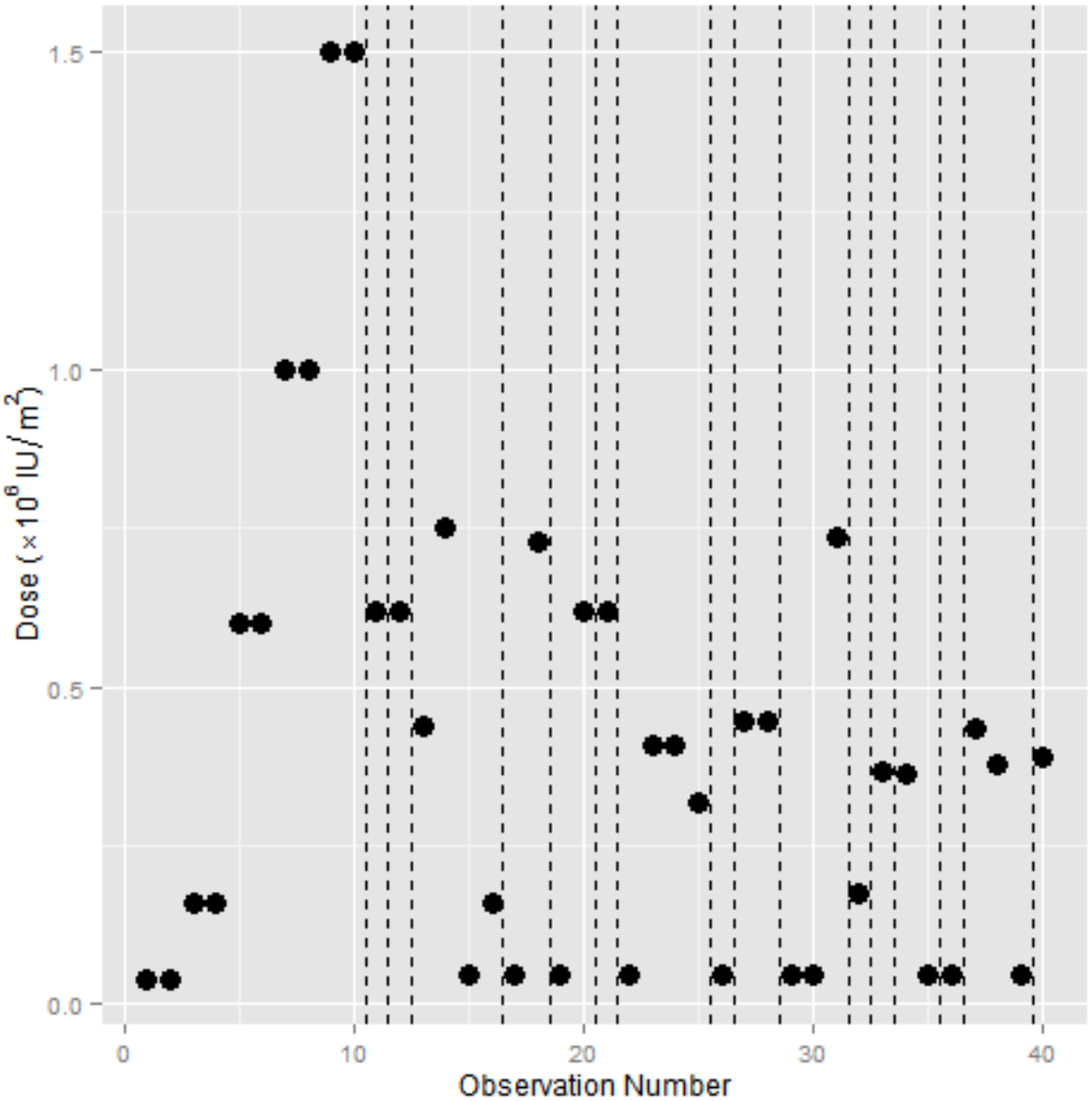
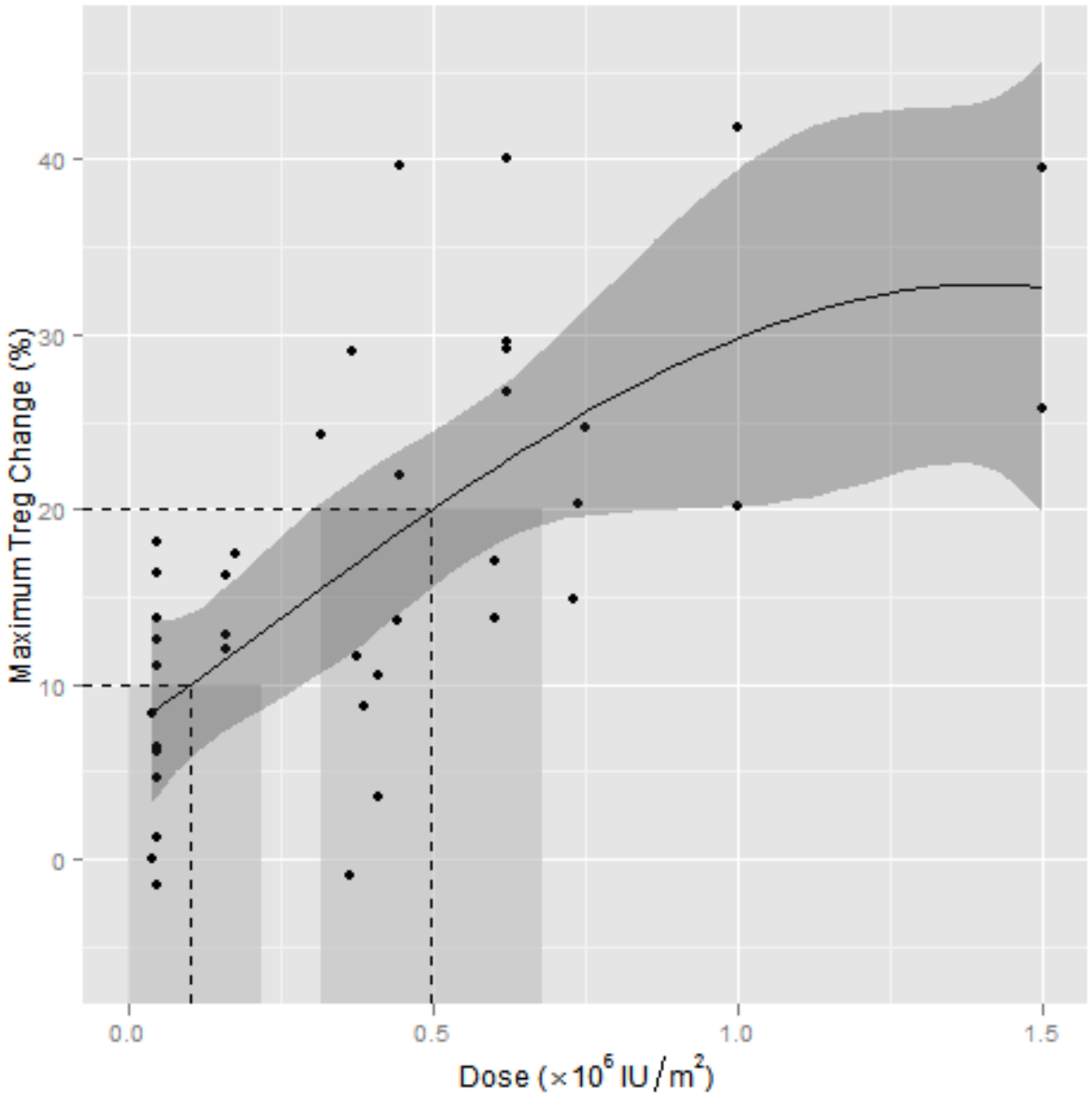
Linear	0.043 (0.10)	-0.16, 0.25	0.557 (0.080)	0.400, 0.714	0.290	-71.4
Quadratic	0.094 (0.067)	-0.04, 0.22	0.471 (0.085)	0.305, 0.636	0.276	-71.3
Emax	0.091 (0.058)	-0.02, 0.20	0.463 (0.100)	0.266, 0.659	0.277	-71.2
Cubic	0.094 (0.069)	-0.04, 0.23	0.472 (0.101)	0.275, 0.670	0.276	-69.3
Logistic	0.094 (0.070)	-0.04, 0.23	0.468 (0.103)	0.266, 0.670	0.277	-69.2
Emax4	0.086 (0.074)	-0.06, 0.23	0.461 (0.107)	0.252, 0.670	0.277	-69.2

Model	Recommended Doses		Decrease in CR Area (%)					
			Linear	Quadratic	Emax	Cubic	Logistic	Emax4
Linear	1.5	1.5	18.0	1.2	1.3	0.0	0.7	1.0
Quadratic	0.045	0.719	4.7	6.4	5.5	4.4	5.0	3.9
Emax	0.045	0.433	3.9	5.6	6.6	7.3	6.6	5.0
Cubic	0.045	0.380	3.9	5.3	6.5	7.4	6.7	5.5
Logistic	0.045	0.380	3.9	5.3	6.5	7.4	6.7	5.5
Emax4	0.154	0.154	3.9	4.0	4.0	4.6	4.6	10.5

The end


1.5
1.0
0.5
0.0
Dose ($\times 10^6$ IU/m^2)
0
10
20
30
40
Observation Number

The end


Maximum Treg Change (%)
40
30
20
10
0
0.0
0.5
1.0
1.5
Dose ($\times 10^6$ IU/m^2)

	Model Doses Selected	Models Converged
Start (Patient 11)	Emax	Li, Q, E, C, Lo
	Emax (top dose)	Li, Q, E, C, Lo
	Quadratic	Li, Q, E, Lo
	Emax	Li, Q, E, C, Lo
	Quadratic	Li, Q, E
	Quadratic	Li, Q, E
	Quadratic	Li, Q, E
	Emax	Li, Q, E
	Logistic	Li, Q, E, C, Lo
	Logistic	Li, Q, E, C, Lo, E4
	Logistic	Li, Q, E, C, Lo, B
	Quadratic	Li, Q, E, C, Lo
	Emax4	Li, Q, E, C, Lo, E4
	Cubic	Li, Q, E, C
	Cubic	Li, Q, E, C
	Quadratic/Emax/Cubic	Li, Q, E, C
	Cubic	Li, Q, E, C
	Emax	Li, Q, E, C, Lo, E4
End (Patient 39)	Cubic	Li, Q, E, C, Lo, E4

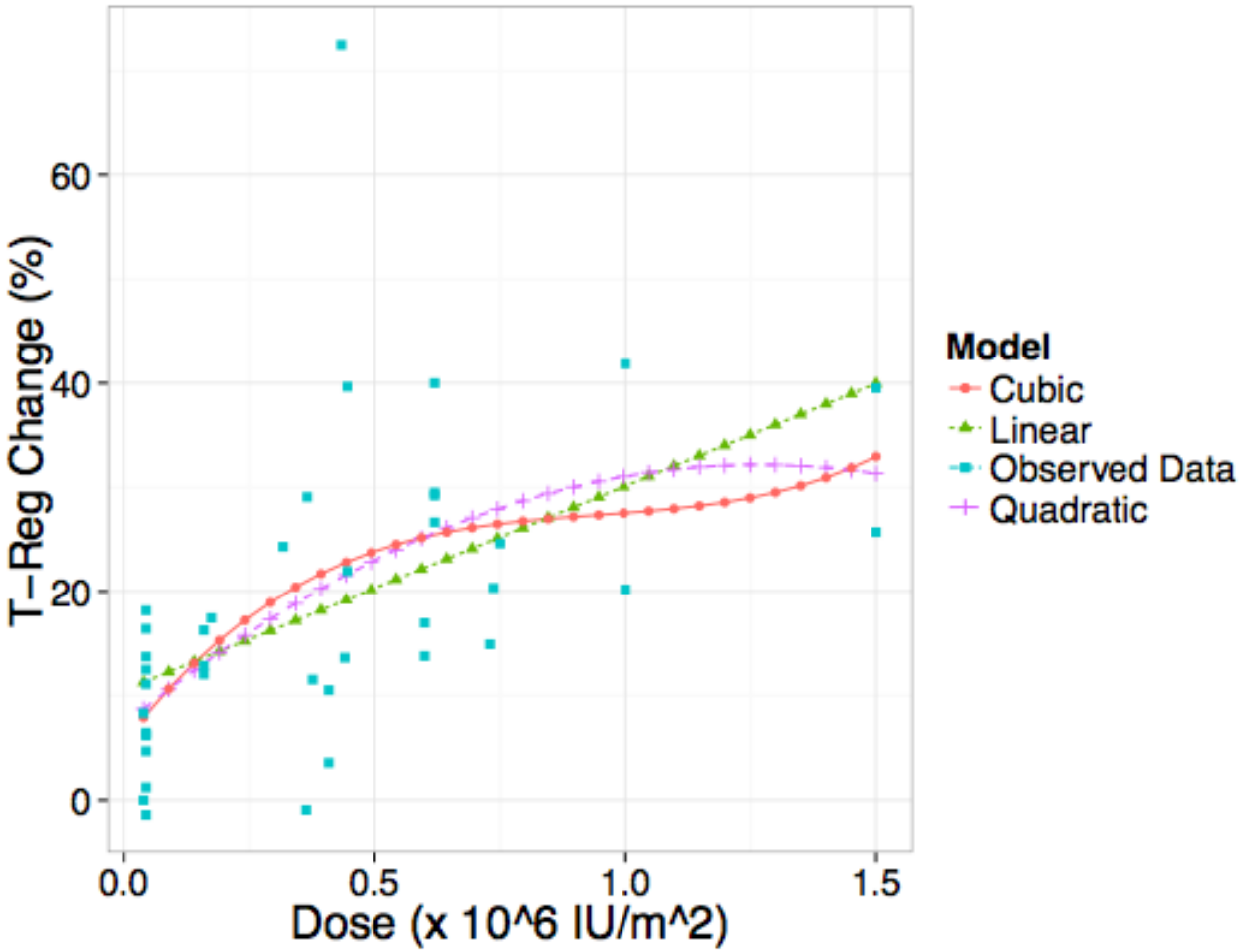
Li = Linear Q = Qudratic, E = Emax, C = Cubic,Lo = Logisitic, E4 = Emax4 and B = Bespoke

- Surprisingly good convergence!
- Great residuals and other diagnostic checks.
- An emerging trend towards cubic from quadratic/Emax

Lessons to be learnt

- The methods were very flexible.
- Doses were selected based on the model fit BUT also on the desire to experiment as scientists.
- There was pressure NOT to dose the smallest dose all the time!
- There were other data other lab measurements that might also suggest other doses
- An upper limit really came into effect due to injection reaction sites (0.7 upwards)
- An outlier at patient 38?
- three-way discussions very informative.
- Problems with the maximum Treg value when low dose.
- The lowest dose changed due to pharmacy problems

Outlier



This person was a protocol violator as they had an infection

Create model weights based on goodness of fit

$$AIC_c = AIC + \frac{2K(K+1)}{n-K-1}$$

where n is sample size and K is number of parameters

$$\Delta(AIC_{c_i}) = AIC_{c_i} - min(AIC_c)$$

AIC_{c_i} is the AIC_c for model i and min() term is the smallest AIC_c for any model

Define weights as (re-estimated at each interim)

$$w_i = \frac{\exp(-0.5\Delta AIC_{c_i})}{\sum_{i=1}^{m} \exp(-0.5\Delta AIC_{c_i})}$$

Model robust extension to optimality criteria

i is the model index and k is the last fully observed patient and want to find (d^*, d^{**}) that minimises

$$\sum_{i=1}^{m} w_i \, Var_{k+2,i}(d_{0.1}, d_{0.2} | \hat{\theta}^{(k,i)})$$

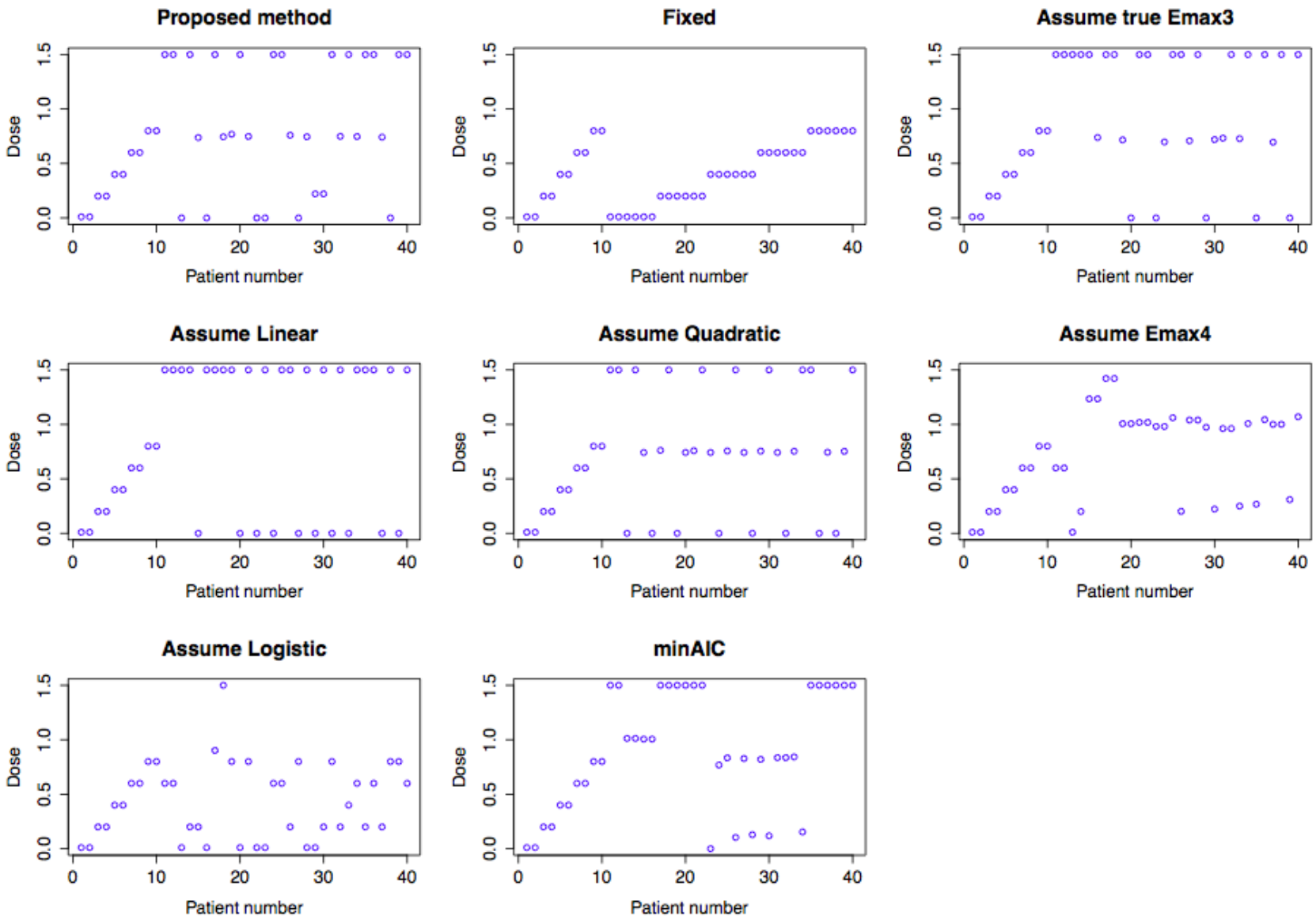
$$Var_{k+2,i}(d_{0.1}, d_{0.2} | \hat{\theta}^{(k,i)}) =$$

$$\left[\frac{\partial g_i(0.1, \hat{\theta}^{(k,i)})}{\partial \theta}, \frac{\partial g_i(0.2, \hat{\theta}^{(k,i)})}{\partial \theta} \right]^T Var^*_{k+2,i}(\hat{\theta}^{(k,i)} | d^*, d^{**}) \left[\frac{\partial g_i(0.1, \hat{\theta}^{(k,i)})}{\partial \theta}, \frac{\partial g_i(0.2, \hat{\theta}^{(k,i)})}{\partial \theta} \right]$$

$$Var^*_{k+2,i}(\hat{\theta}^{(k,i)} | d^*, d^{**}) =$$

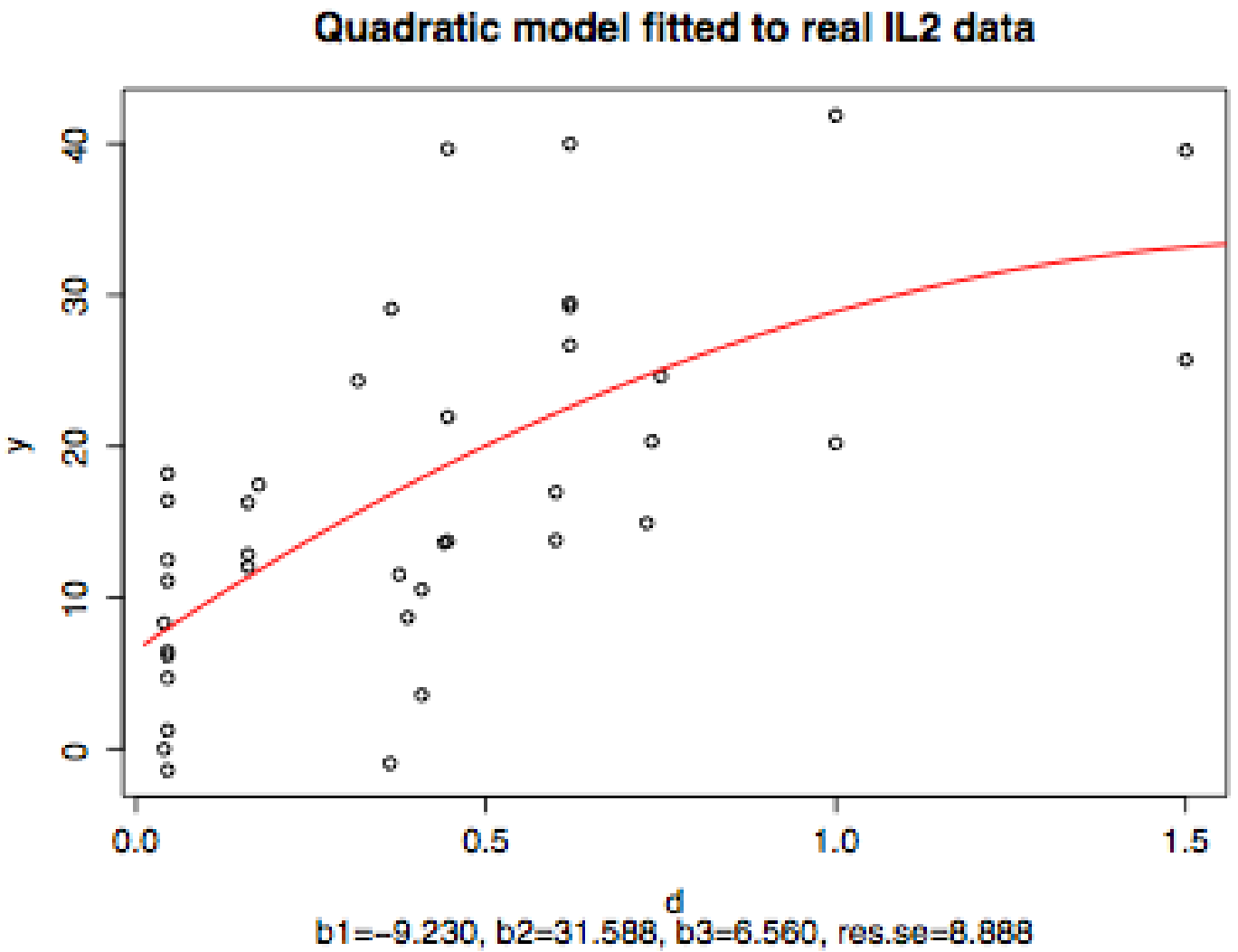
$$\sigma_e^2 \left(M_{k,i}(\hat{\theta}^{(k,i)}) + \frac{\partial f_i(d^*, \hat{\theta}^{(k,i)})}{\partial \theta} \frac{\partial f_i{}^T(d^*, \hat{\theta}^{(k,i)})}{\partial \theta} + \frac{\partial f_i(d^{**}, \hat{\theta}^{(k,i)})}{\partial \theta} \frac{\partial f_i{}^T(d^{**}, \hat{\theta}^{(k,i)})}{\partial \theta} \right)^{-1}$$

Example simulation

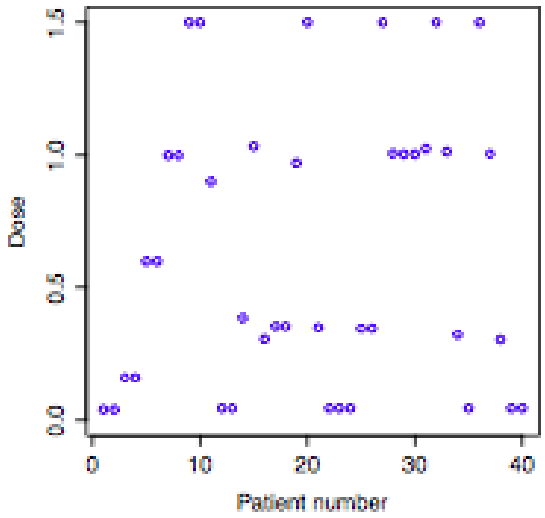


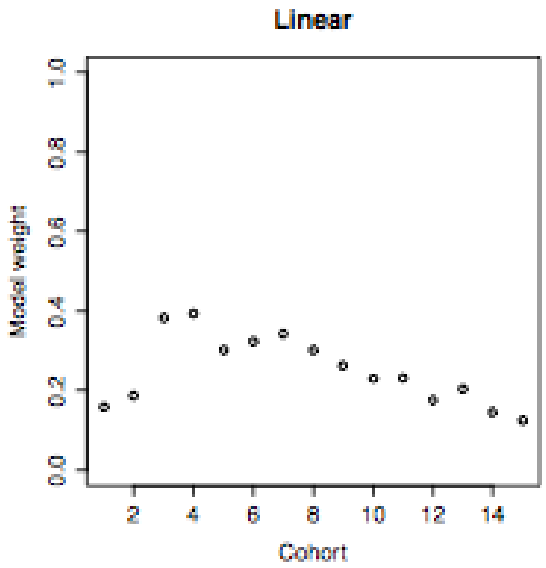
"True" model fitted to IL-2 data

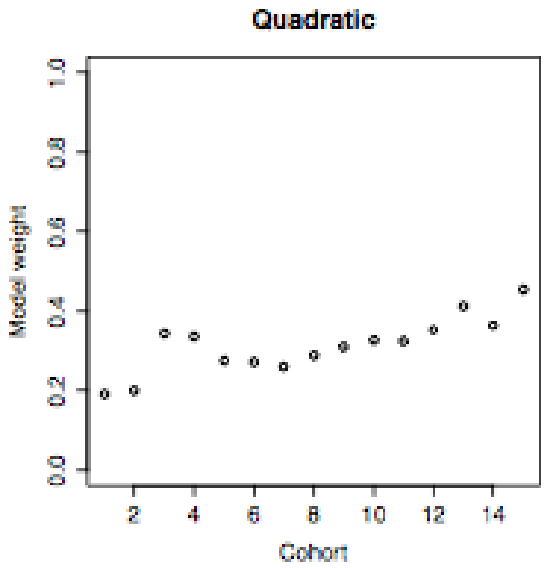
Quadratic model had lowest AIC_c

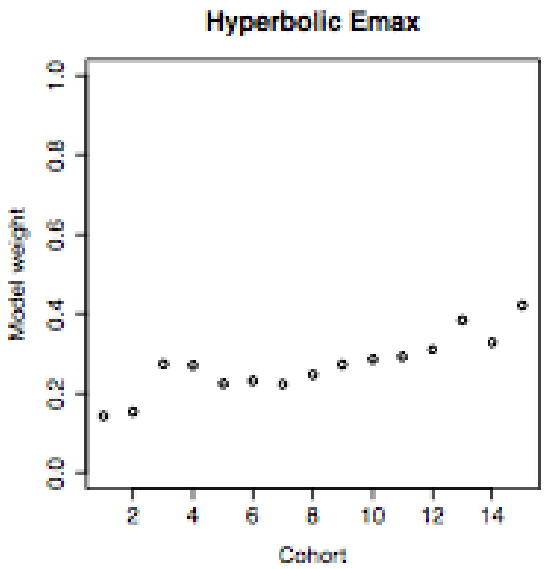


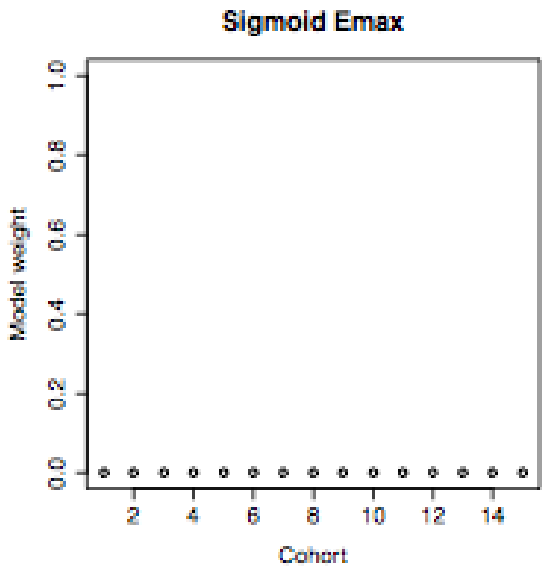
One simulation for model-robust sequential IL-2 study

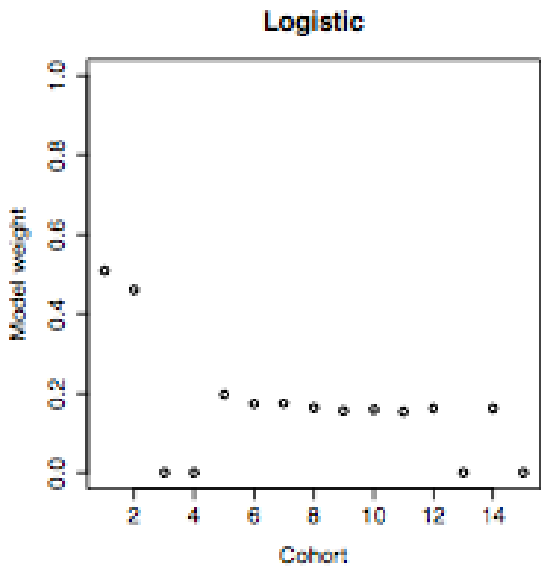






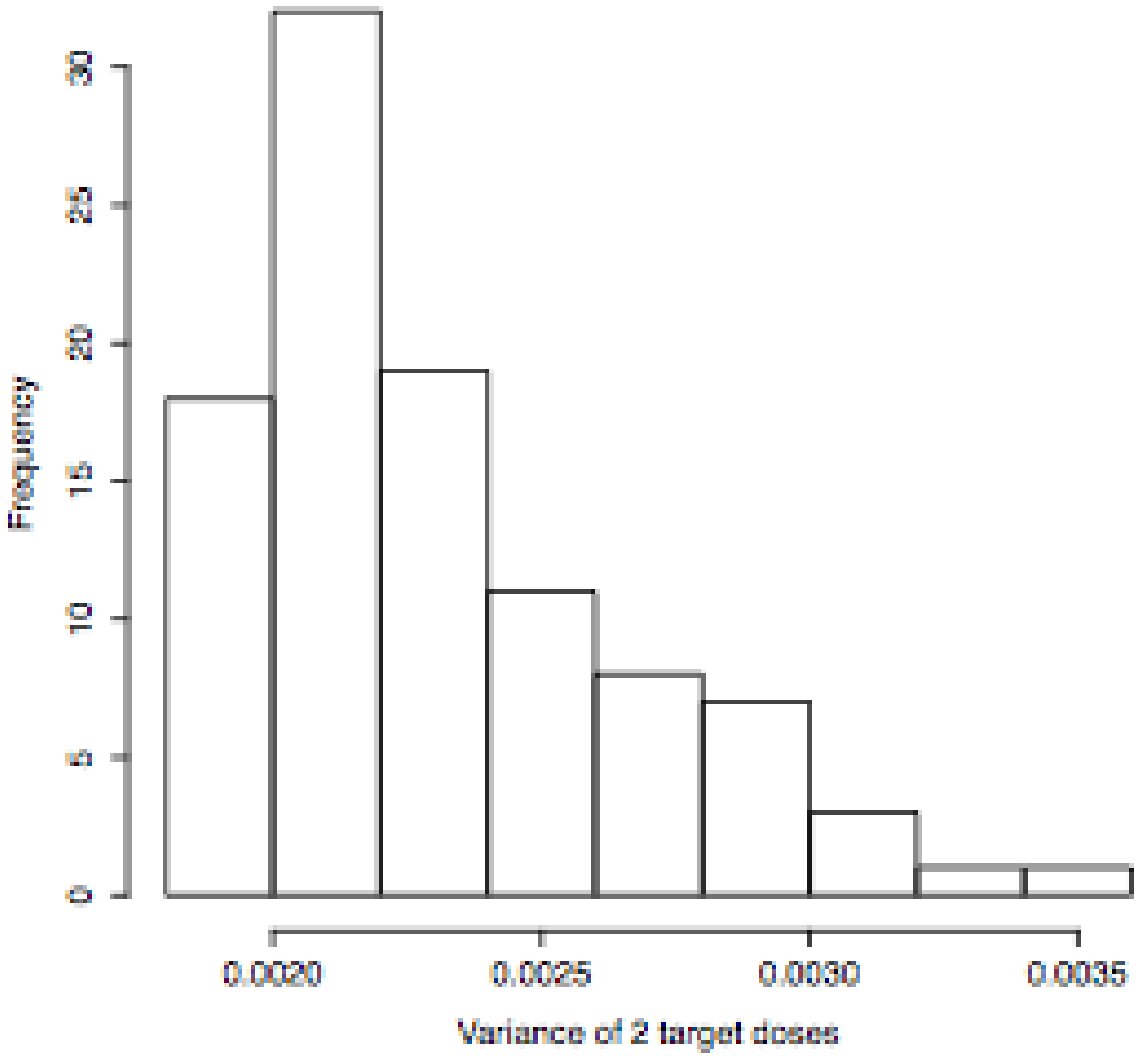






Variance improvement

Trace of variance-covariance matrix in IL-2 was 0.00327 and the histogram of values obtained by simulation is below



Conclusions

- Described two methods to handle two targets and multiple models
- Always have a polynomial in the model set
- Model robust methods work well in simulations
- A three-way vote in the dose determining committee with a supportive clinician is the way to go

Recruitment has started for a repeat dosing study, with a multivariate outcome to determine the best dose/dosing interval