1) Toxicity:

$$mean = ANETS = \xi$$

$$Let\ \xi\ be\ the\ ANETS.$$

$$variance = \xi \cdot \frac{(1-\xi)}{N} = \sigma^2$$

Under the setting of EWOUC-NETS, we have

$$\xi|x_i = F(\beta_0 + \beta_1 x_i) = \frac{\exp(\beta_0 + \beta_1 x_i)}{1 + \exp(\beta_0 + \beta_1 x_i)}$$

$$\xi|x_i = inverse\ logit\ (\beta_0 + \beta_1 x_i)$$

Re-parameterization:

$$\beta_0 = \frac{X_{min} logit\left(\tilde{\theta}\right) - \gamma_T logit(\rho_0)}{X_{min} - \gamma_T}$$

$$\beta_1 = \frac{logit(\rho_0) - logit(\tilde{\theta})}{X_{min} - \gamma_T}$$

$$logit(\xi|x_i) = \frac{(\gamma_T - x_i) \cdot logit(\rho_0) - (x_i - x_{min}) \cdot logit(\tilde{\theta})}{\gamma_T - x_{min}}$$

$$where\ \gamma_T = maximum\ tolerated\ dose$$

$$\rho_0 = NETS\ at\ the\ starting\ dose\ x_{min}$$

$$\tilde{\theta} = target\ normalized\ equivalent\ toxicity\ score$$

For each dose level, we have one $\xi|x_i$.

Marginal density function for toxicity:

$$\pi_T = \frac{1}{\sqrt{\xi|x_i(1-\xi|x_i)/N}} \frac{\Phi(\frac{x_i - \xi|x_i}{\sqrt{\xi|x_i(1-\xi|x_i)}})}{\Phi(\frac{1-\xi|x_i}{\sqrt{\xi|x_i(1-\xi|x_i)/N}})\Phi(\frac{-\xi|x_i}{\sqrt{\xi|x_i(1-\xi|x_i)/N}})}$$

2) Efficacy

$$\pi_E = f(y_E|x) = \frac{1}{\sqrt{2\pi\sigma_i{}^2}} \exp\{-\frac{(y_E - \mu_i)^2}{2\sigma_i{}^2}\}$$

Where $\mu_i = 1 - \frac{1}{1+(x/\beta_2)^{\beta_3}}$ and $\sigma_i{}^2 = \sigma^2 x^\lambda$

Comment: here the μ_i has been normalized and range from 0 to 1.

3) Joint distribution of (S, Y_E):

$$f(y_E, S) = f(S)f(y_E|S)$$

Given S, we assumed that the distribution of y_E is normal.

$$f(y_E|S) = \frac{1}{\sqrt{2\pi\sigma_i{}^2}}\exp\left[-\frac{\{y_E - \mu_i - \tau(S - \xi|x_i)\}^2}{2\sigma_i{}^2}\right]$$

Where τ is the parameter for the regression of y_E on S. Large absolute values of τ indicate a strong correlation between the two outcomes. When τ = 0, the two outcomes are independent given the dose level of agent A in the model. The correlation based on this model is

$$\rho(y_E, S|x) = \frac{\tau}{\sqrt{\tau^2 + \frac{\sigma_i{}^2}{\xi(1-\xi)}}}$$

1) Selling point: continuous toxicity endpoint as NETS ranging from 0 to 1, instead of 0 and 1 (binary).
2) We used EWOUC (over- and underdose control)
3) Efficacy is truncated normal distributed in simulation (more meaning).
4) Reduced the parameters and we standardized the efficacy within 0 and 1.