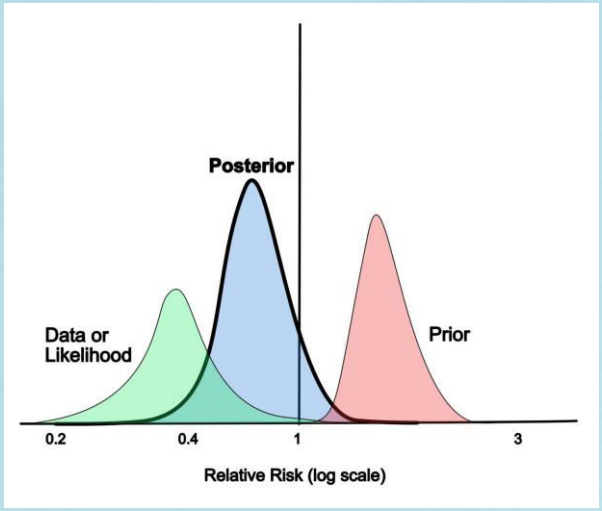

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A Novel COLOR Code and Sequential Adaptive Models for the estimation of Maximum Tolerated Dose in Early Phase – 1 Dose Escalation Studies

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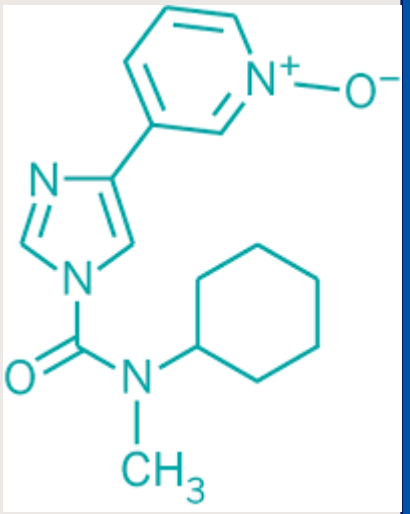
Disclaimer

- The views and opinions expressed in this presentation are the views, thoughts, and opinions belonging solely to the *presenter*, and not necessarily to the presenter's employer/organization/committee/other groups or individual.
- This presentation is intended to exhibit, the novel adaptive designs used for estimating the Maximum Tolerated Dose (MTD) in Phase – 1 oncology trials.
- No data or confidential information belonging to *Novo Nordisk* has been used in this presentation.

AGENDA

1. Abstract and Motivation
2. Introduction to Dose Escalation
3. Need for Novel Dose Escalation Designs
4. Objectives and Design Methodology
5. A Novel COLOR Code Rule Based Design
6. Sequential Frequentist Modelling of PK profiles
7. Bayesian Framework for Modelling Toxicity and Efficacy
8. Estimation of Cohort Toxicity effect using Hierarchical Bayesian Design
9. Comparison of results
10. Concluding remarks



Abstract

- ***Bayesian decision procedures*** for early Phase – 1 oncology clinical studies were described by Zhou, Whitehead *et.al* $(2006)^{[1]}$. The occurrence of a Dose Limiting Toxicity [DLT] was the primary variable of interest in Zhou $(2006)^{[3]}$.
- The systematic procedures described in $^{[3]}$ however failed to account for PK/PD dynamics, subject, cohort and treatment effects.
- Anti-factor measurements $(Xa)_{ij}$ and occurrence of a DLT are primary areas of interest in this study.
- The grading of dose toxicity levels of the cytotoxic drug into 5 categories namely low utility gain (**LUG**), highly recommended (**HR**), not recommended (**NR**), dose limiting event (**DLE**), maximum gain under constraint (**MUG**) based on a 'therapeutic window' is finally achieved for each subject.
- 'Response adaptive hierarchical dose escalation designs' $^{[4,5]}$ are developed taking the implements of Algorithm based [**COLOR** code design], Sequential Frequentist and Bayesian methodologies.

Safety

Optimal dose?

Adverse events

Rising costs

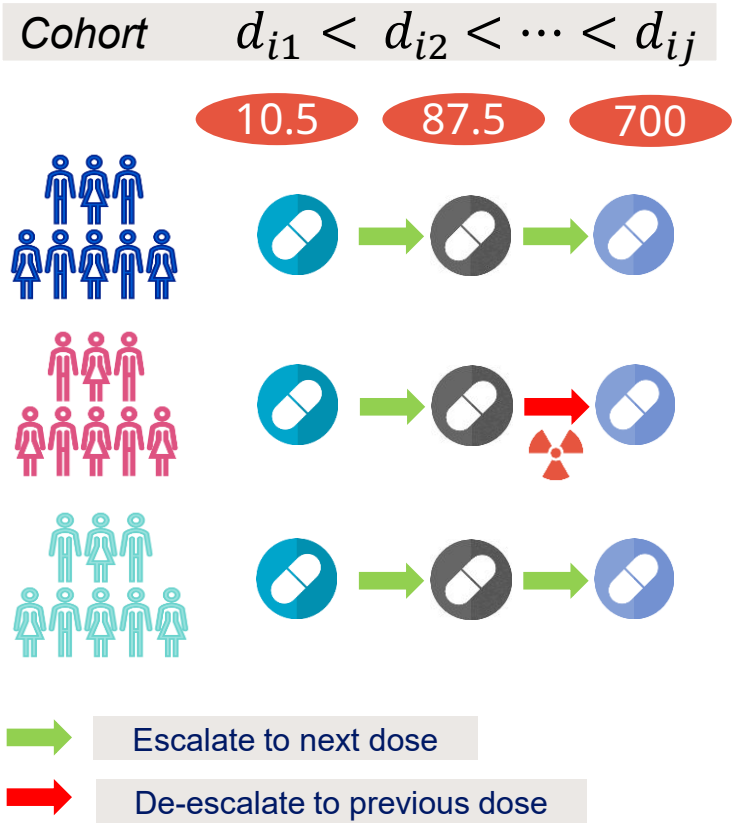
[1-5] Papers by Whitehead et.al on Bayesian decision procedures for early Phase-1 dose escalation designs – Refer to Reference [Slide 22]

DLT – Dose Limiting Toxicity; PK/PD – Pharmacokinetics/Pharmacodynamics; $(Xa)_{ij}$ - Anti-factor measurement for subject 'i' at dose level/period 'j'.

Introduction to Dose Escalation Studies

Series of discrete dose levels is administered to a cohort of subjects

d_{ij} – j^{th} dose administered to i^{th} subject



Two responses assessed at each stage of dose escalation – **Desirable Outcome (DO)** and **Dose Limiting Event (DLE)**.

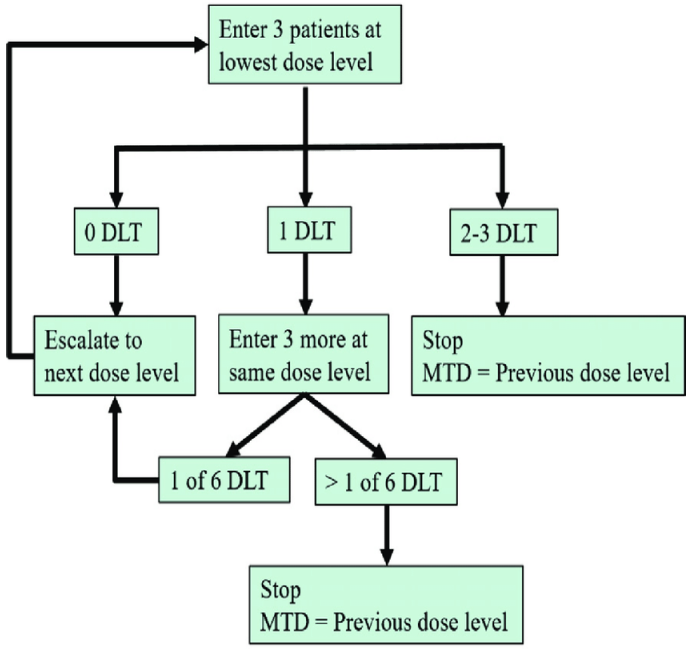


Fig 1: *Schematic representation of* 3+3 *Rule based design*

Objectives

- Estimate Maximum Tolerated Dose **(MTD)** based on acceptable limits of dose limiting toxicities **(DLT).**
- Traditional v/s Model based approaches for dose-response relationship.
- Assume a true rate of **MTD** (δ) in (δ_1, δ_2) and determine the dose level for which probability of toxicity $p(d_{ij}) < \delta$.

Need for Novel Dose Escalation (DE) Designs

Why COLOR Code Design?

- Lack of statistical methodologies and formal guidelines.
- Poor estimate of MTD and optimal dose level.
- Preliminary design prior to model based approaches.
- Higher operational costs and long duration.

Why Sequential Frequentist Design?

- Improve the estimate of MTD from previous cohorts.
- Estimate the probability of PK profile exceeding a threshold for an untested subject.
- Recommend MSD based on sequential ML approach.
- Predecessor to response adaptive designs.

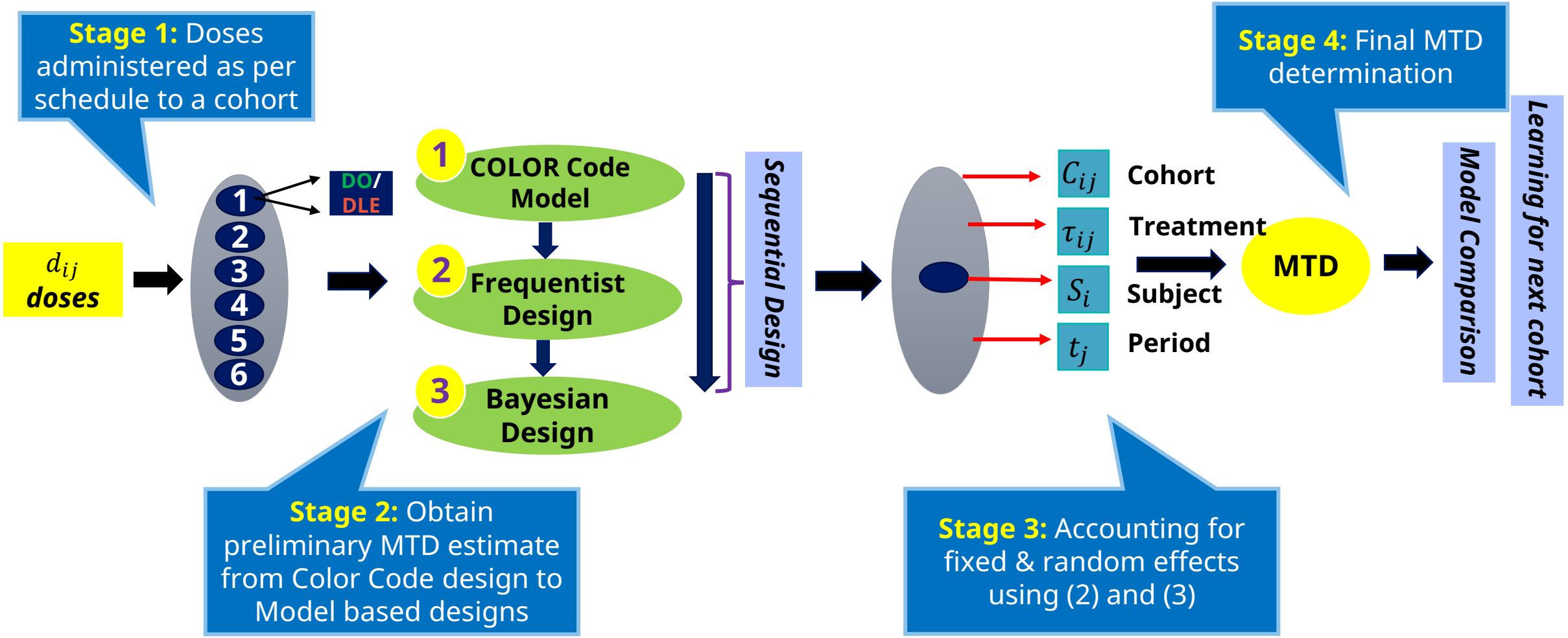
Why Response Adaptive Bayesian Design?

- Obtain updated priors to maximize $p_{success}$.
- Predict the MTD accurately at different dose levels.
- Improve guidance to optimal dose recommendation.
- Account for cohort, subject, period and treatment effects.

Response Adaptive Hierarchical DE Design

MTD – Maximum Tolerated Dose; MSD – Maximum Safe Dose; ML – Maximum Likelihood Estimation; PK – Pharmacokinetic; $p_{success}$ - Probability of success for subsequent phases of study

Objectives


Stage 1: Doses administered as per schedule to a cohort
d_{ij} doses
1
2
3
4
5
6
DO/ DLE
1 COLOR Code Model
2 Frequentist Design
3 Bayesian Design
Sequential Design
Stage 2: Obtain preliminary MTD estimate from Color Code design to Model based designs
C_{ij} Cohort
τ_{ij} Treatment
S_i Subject
t_j Period
Stage 3: Accounting for fixed & random effects using (2) and (3)
MTD
Stage 4: Final MTD determination
Model Comparison
Learning for next cohort

Design Methodology

Framework

- Let S_i denote the subjects in the trial and d_{ij} denote the dose administered to the i^{th} subject in the j^{th} dosing period.
- Let $(Xa)_{ij} \sim Exp(1/\lambda)$ represent the anti-factor level of i^{th} subject for j^{th} dose. The pharmacokinetic profile is given by

$$P = \{d_i, (Xa)_{ij}\}\ i = 1, 2, \ldots n; j = 1, 2, \ldots k.$$

Proposed Data Layout

Dose	S_1	S_2	.....	S_n
d_1	$(Xa)_{11}$	$(Xa)_{21}$	.....	$(Xa)_{n1}$
d_2	$(Xa)_{12}$	$(Xa)_{22}$	.....	$(Xa)_{n2}$
⋮	⋮	⋮		⋮
⋮	⋮	⋮		⋮
D_1^*	$(Xa)_{12}^*$	$(Xa)_{22}^*$	.....	$(Xa)_{n2}^*$
⋮	⋮	⋮		⋮
⋮	⋮	⋮		⋮
D_s^*	$(Xa)_{1s}^*$	$(Xa)_{2s}^*$	.....	$(Xa)_{ns}^*$
d_k	$(Xa)_{1k}$	$(Xa)_{2k}$	.....	$(Xa)_{nk}$

Fig 2: *Proposed data layout for anti factor measurements for each subjects and dose (Real-R, Dummy-D)*

Parametric models for dose - response relationship

- Relationship between p(DLE) and dose levels

$$p_{\mathrm{DLE}}(d_{ij}) = \frac{\exp(\beta_1 + \beta_2 \log d_{ij})}{1 + \exp(\beta_1 + \beta_2 \log d_{ij})}$$

- Modelling response | No Adverse events.

$$y_{ij} = \theta_1 + \theta_2 \log d_{ij} + s_i + \varepsilon_{ij}$$

where $s_i \sim N(0, \tau^2)$, and $\varepsilon_{ij} \sim N(0, \sigma^2)$

MSD – Maximum Safe Dose; ML – Maximum Likelihood; pDLE(d_ij) – Probability of a DLT of administering jth dose to ith subject; $\beta_1, \beta_2, \theta_1, \theta_2, s^2$ - To be estimated using Frequentist and Bayesian Approaches

A Novel COLOR Code Rule based design – Algorithm

Construction of utility functions

- Determine utility function curves for each subject considering real (R) and dummy (D) dose levels.

1 Dose levels ~ Fibonacci dist. PK profiles at R and D.

$$P = \{d_j, (Xa)_{ij}\}$$

2 Construction of utility function at each dose level

$$U(S_i) = f(d_j)$$

3 Pre-specified threshold set for toxicity (γ = 20%)

What would be anticipated response at each dose level?

- Prior to administering next higher dose, anticipated response is evaluated at next dose levels for each subject.

$$\widehat{Xa_{ij}} = (\mathrm{Opt(Xa)_{ij}} \mid \mathrm{d_j}) = \frac{(\mathrm{Xa_{ij}} - \ln(2) \times \mathrm{m}[(\mathrm{Xa})_{\mathrm{ij}}])^2}{\mathbf{M}(1 - \ln(2))}$$

How is MTD determined?

- Compute the measure K and choose the real dose level d_j^* for which $K(d_j^*) <\approx \gamma$

$$K = min(|Xa_{ij} - \widehat{Xa_{ij}}|)$$

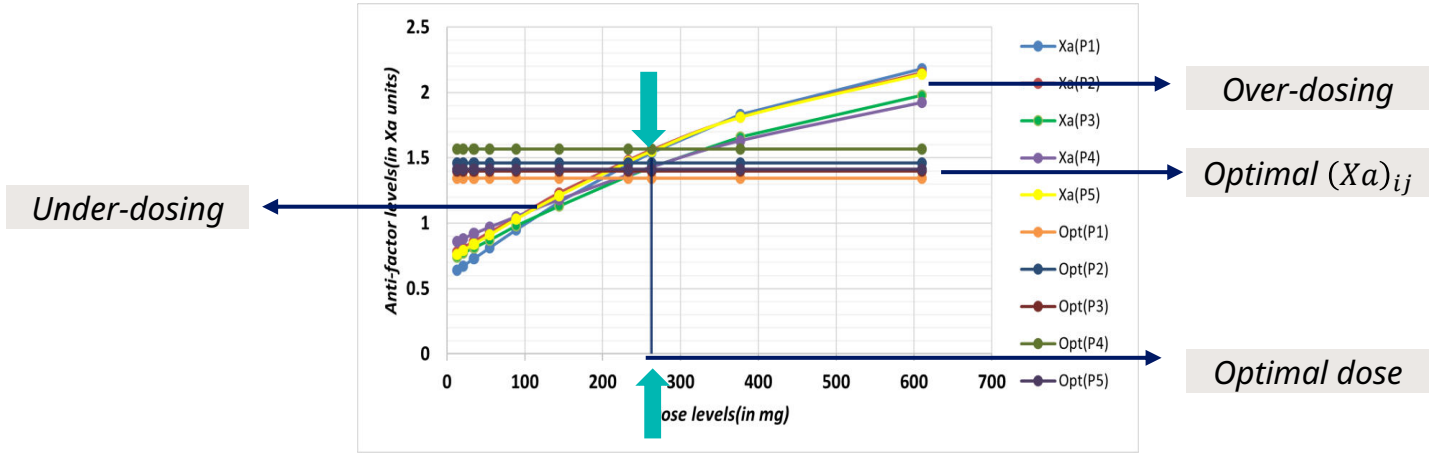
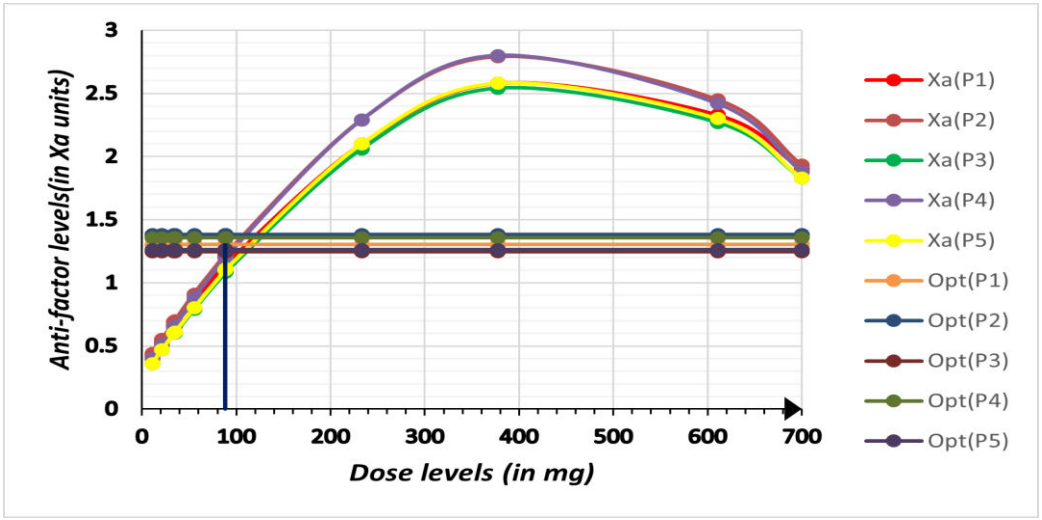


Fig 3(A): *Determination of MTD using Color Code Design*

Estimation of MTD using COLOR Code design – Results

Dose levels	Decision	S1	S2	S3	S4	S5	S1*	S2*	S3*	S4*	S5*
10.5	LUG®	0.43	0.44	0.36	0.4	0.36	0.290	0.259	0.156	0.173	0.143
21	LUG®	0.53	0.55	0.47	0.51	0.47	0.496	0.503	0.411	0.439	0.404
34	LUG®	0.66	0.69	0.6	0.65	0.6	0.656	0.688	0.600	0.650	0.600
35	LUG®	0.67	0.7	0.6	0.66	0.61	0.663	0.695	0.600	0.660	0.610
55	LUG®	0.86	0.91	0.79	0.88	0.8	0.664	0.692	0.657	0.691	0.663
88	MUG/Co	1.14	1.22	1.08	1.2	1.1	0.191	0.105	0.243	0.113	0.218
89	MUG/Co	1.15	1.23	1.09	1.21	1.11	0.163	0.075	0.217	0.083	0.192
233	DLE	2.1	2.29	2.06	2.29	2.1	5.722	7.240	5.644	7.394	5.951
377	DLE	2.58	2.79	2.54	2.8	2.58	11.170	13.501	11.053	13.847	11.473
610	DLE	2.33	2.45	2.27	2.42	2.3	8.125	9.047	7.806	8.861	8.050
700	DLE	1.9	1.93	1.83	1.88	1.83	3.942	3.847	3.641	3.565	3.575

Subject 1-5 (87.5 mg)



Dose levels	Decision	S6	S7	S8	S9	S10	S6*	S7*	S8*	S9*	S10*
34	LUG®	0.73	0.86	0.81	0.92	0.84	0.72841	0.80982	0.77003	0.77563	0.79779
35	LUG®	0.73	0.86	0.81	0.92	0.84	0.72841	0.80982	0.77003	0.77563	0.79779
55	LUG®	0.81	0.93	0.87	0.97	0.91	0.7766	0.80815	0.77568	0.74977	0.80076
89	LUG®	0.95	1.04	0.98	1.05	1.03	0.76262	0.74232	0.72635	0.67519	0.73309
144	LUG®	1.16	1.23	1.13	1.18	1.21	0.50705	0.44669	0.5346	0.46687	0.45921
233	MUG/Co	1.45	1.48	1.36	1.37	1.47	0.3087	0.2934	0.03839	0.03167	0.30154
263	MUG	1.54	1.56	1.54	1.57	1.55	0.67103	0.61449	0.72237	0.80541	0.62243
377	DLE	1.83	1.81	1.86	1.63	1.81	2.19026	1.88123	2.44904	1.08732	1.94749
610	DLE	2.18	2.15	1.98	1.922	2.14	4.73879	4.24429	3.26507	2.78738	4.25076
987	DLE	2.09	2.15	2.02	2.06	2.1	4.00876	4.24429	3.55751	3.78023	3.93455
1050	DLE	1.99	2.08	1.98	2.05	2.03	3.25827	3.69745	3.26507	3.7042	3.40576

Subject 6-10 (233 mg)

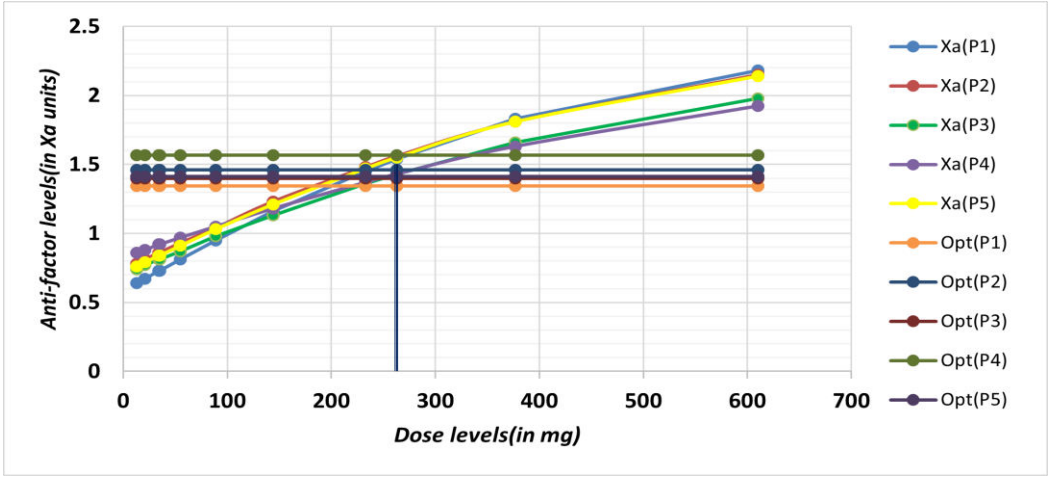


Fig 3(B): *Classification of doses into 5 brackets based on therapeutic window*

Sequential Frequentist Analysis – Algorithm

Objective/Methodology

- To estimate TD20 with a target dose toxicity of 20%.
- Consider PK profiles for real (R) & dummy (D) doses levels given by

$$P_R = \{d_j, (Xa)_{ij}\} \quad P_D = \{D_m^*, (Xa)_{im}^*\}$$

- Obtain ML estimates for two lowest dose levels $\boldsymbol{d_i}, \boldsymbol{d_j}; j > i$ and model PK responses by

$$Y_f \sim N\left(e^{\theta_1} + e^{\theta_2} \log\left(d_f^*\right), \sigma^2 + \tau^2\right)$$

Maximum Safe Dose (MSD)

- To find the dose level, whose probability of exceeding ***L*** (threshold) is very low($\boldsymbol{c_0}$) [**Safe dose with maximum efficacy**]
- Can next dose level be administered to next cohort of subjects safely?

[MSD Criterion]

$$\frac{L - \left(\exp^{\tilde{\theta}_1} + \exp^{\tilde{\theta}_2} l_{ij}\right)}{\sqrt{\tilde{\sigma^2} + \tilde{\tau^2}}} = 1.65$$

How is MTD determined?

- Maximum Likelihood estimates of $\boldsymbol{\beta_1, \beta_2, \theta_1, \theta_2, s^2}$ are derived sequentially.
- Maximum Safe dose (MSD) is derived by the criterion, where $\boldsymbol{c_0}$ (constraint) is set by the clinician prior. **MTD** is set to d_f^*

$$\mathcal{P}\left(y_{ij} > L | d_f^*\right) \leq c_0$$

ML – Maximum Likelihood Estimates; PK – Pharmacokinetic; MTD – Maximum Tolerated Dose; MSD – Maximum Safe Dose; TD20 – Dose Level at which 20% risk of toxicity is observed

Estimation of MTD using Sequential Frequentist Analysis

Model	Pseudo-doses	Threshold dose	$\log(d_{ij})$	MSD	Decision
Model 1	$(10.5, 35)$	1300	4.49	89.12	Escalate to 55 mg
Model 2	$(10.5, 55)$	1300	4.71	111	Escalate to 87.5 mg
Model 3	$(10.5, 89)$	1300	4.487	88.867	Escalate to 87.5 mg
Model 4	$(10.5, 262.5)$	1300	4.486	88.7	De-escalate to 87.5 mg
Model 5	$(10.5, 144)$	1300	4.53	92.77	87.5 - Recommended
Model 6	$(10.5, 233)$	1300	4.56	96.11	87.5 - Recommended
Model 7	$(10.5, 1050)$	1300	4.48	88.68	87.5 - Recommended

Can 55 mg be administered?	**YES**
Can 87.5 mg be administered?	**YES**
Can 233 mg be administered?	**NO**

Optimal dose level?

87.5 mg

Fig 4: *Determination of Optimal dose level using sequential Frequentist modelling*

Response Adaptive Bayesian Design – Algorithm

Objective/Methodology

- Obtain dose-toxicity relationship for lowest and highest dose levels (prior)
- For two consecutive lowest dose levels $\boldsymbol{d_i}, \boldsymbol{d_j}; j > i$ – obtain prior estimates of toxicity for these doses $\boldsymbol{p}(\widetilde{\boldsymbol{d}}_{\boldsymbol{i}}), \boldsymbol{p}(\widetilde{\boldsymbol{d}}_{\boldsymbol{j}})$. Specify the patient gain function and safety constraints.
- Perform simulation under six scenarios and obtain new posterior estimates. Repeat the procedure for all consecutive dose levels till observing a dose limiting event.

Prior dose-response relationship

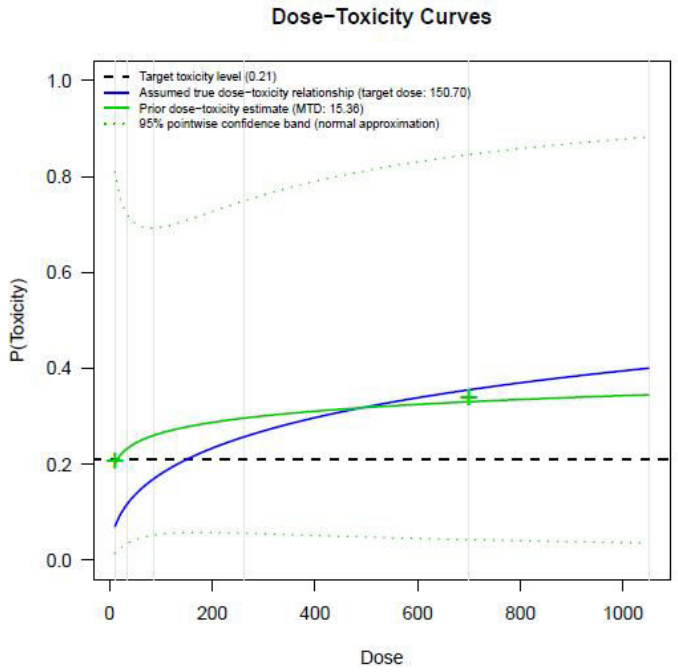


Fig 5: *Dose Toxicity curve in Zhou & Whitehead[1] et.al Study*

How is MTD determined?

- Maximum Likelihood estimates of $\boldsymbol{\beta_1}, \boldsymbol{\beta_2}, \boldsymbol{\theta_1}, \boldsymbol{\theta_2}, \boldsymbol{s^2}$ from Frequentist model used as priors.
- Independent priors (Pessimistic, conjugate, clinical) are attached to $\boldsymbol{\beta_1}, \boldsymbol{\beta_2}, \boldsymbol{\theta_1}, \boldsymbol{\theta_2}, \boldsymbol{s^2}$ and the posterior distribution of these unknown parameters is obtained sequentially considering the PK profiles of the previous set of subjects dosed.

PK – Pharmacokinetic

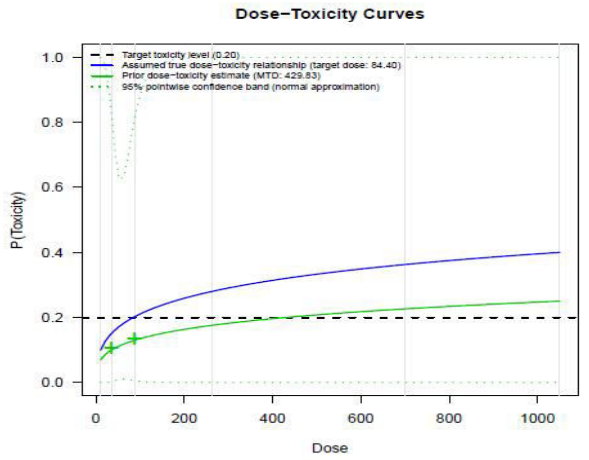
Illustration of Response Adaptive Bayesian Decision procedure

Prior information modelling

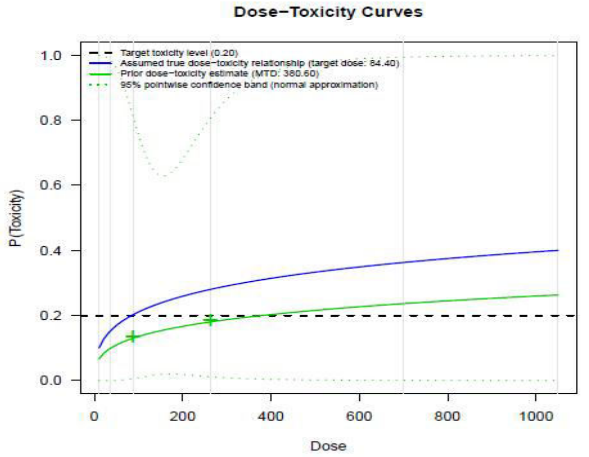
Stage-1	Low	High	Priori recommended dose
Priori doses	10.5	35	35*
Priori toxicity rate	0.078	0.101	87.5
Sequential Priors(θ_1, θ_2)	−3.35	0.32	
Stage-2	Low	High	Priori recommended dose
Priori doses	35	87.5	87.5*
Priori toxicity rate	0.1	0.13	262.5
Sequential Priors(θ_1, θ_2)	−3.35	0.32	
Stage-3	Low	High	Priori recommended dose
Priori doses	87.5	262.5	87.5*
Priori toxicity rate	0.13	0.18	262.5
Sequential Priors(θ_1, θ_2)	−3.47	0.35	
Stage-4	Low	High	Priori recommended dose
Priori doses	262.5	700	87.5*
Priori toxicity rate	0.18	0.26	262.5
Sequential Priors(θ_1, θ_2)	−3.89	0.4204	
Stage-5	Low	High	Priori recommended dose
Priori doses	700	1050	262.5*
Priori toxicity rate	0.26	0.3	87.5

Response Adaptive procedure for sequential dose escalation

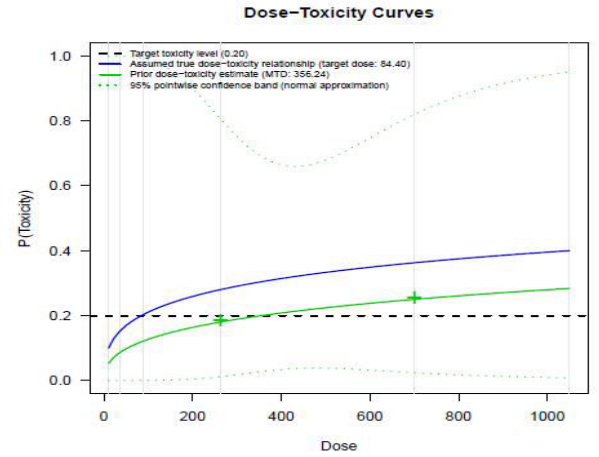
Stage 1,2 dose escalation



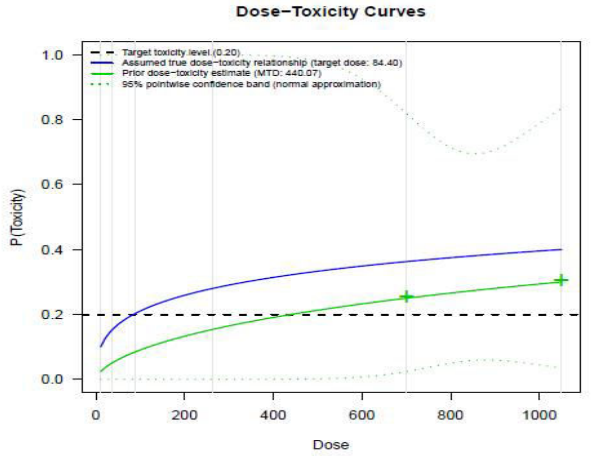
Stage 3 dose escalation



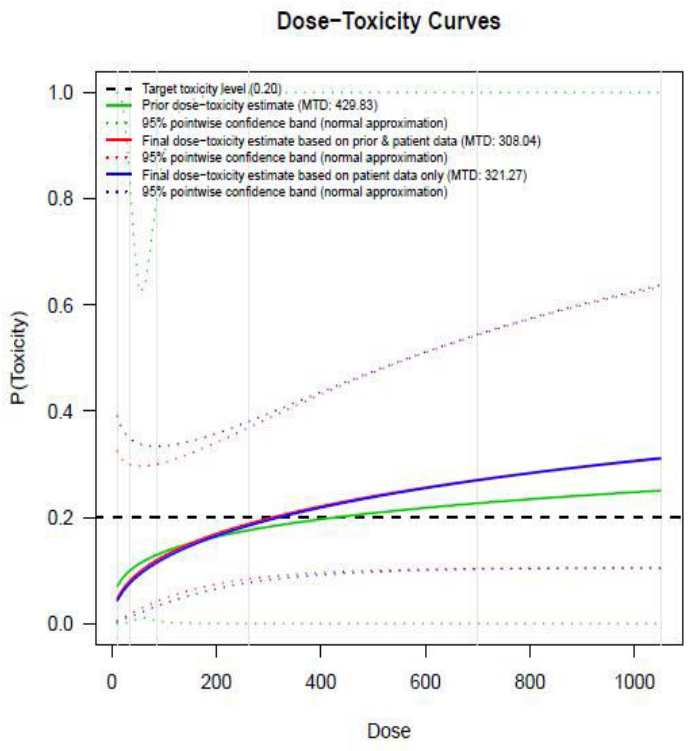
Stage 4 dose escalation



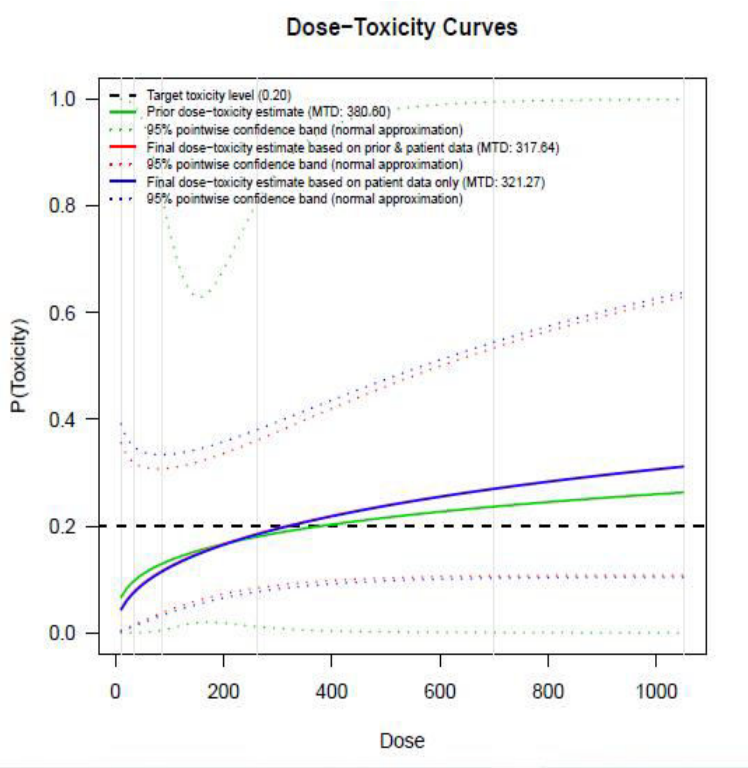
Stage 5 dose escalation



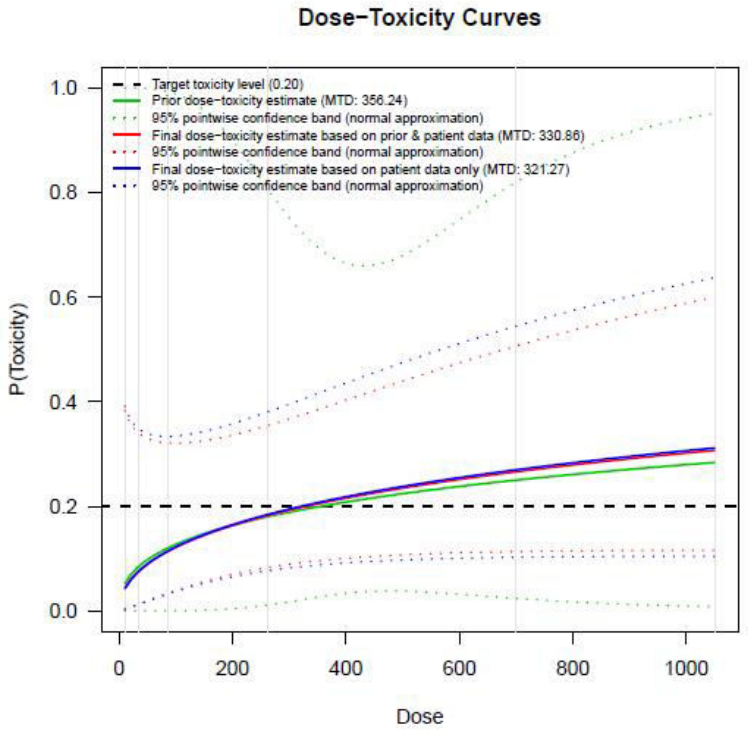
Final dose recommendation – RABTP (Simulations)
[*Response Adaptive Bayesian Theoretic Decision Procedure*]



Stage 1,2 dose escalation



Stage 3 dose escalation



Stage 4 dose escalation

Final dose recommendation – RABTP (Simulations)
[*Response **A**daptive **B**ayesian **T**heoretic Decision **P**rocedure*]

Parameter	Mean	sd	MC error	95% HPD interval	sample	Status
θ_1	-3.909	1.866	0.01815	(-7.959, -0.623)	215500	-
θ_2	0.4191	0.3274	0.00316	(-0.1882 , 1.1)	215500	-
$p_{10.5}$	0.07873	0.07398	5.791×10^{-4}	(0.004269 ,0.2794)	215500	Low Utility Gain
p_{35}	0.1013	0.06659	4.933×10^{-4}	(0.01449, 0.2653)	215500	Low Utility Gain
$p_{87.5}$	0.1297	0.06426	3.815×10^{-4}	(0.03303, 0.2784)	215500	Recommended
$p_{262.5}$	0.1838	0.07451	1.632×10^{-4}	(0.06468, 0.3516)	215500	Highly Recommended
p_{700}	0.2553	0.1105	4.864×10^{-4}	(0.07661 , 0.5)	215500	Not Recommended
p_{1050}	0.2906	0.1327	7.491×10^{-4}	(0.07661, 0.581)	215500	Not Recommended

Fig 5: *Determination of Optimal dose level using Response Adaptive Bayesian modelling*

Optimal dose level?

262.5 mg

- At dose 700 mg, the probability of DLE exceeds the threshold level of 20%

Estimation of Cohort Effects in modelling binary measures of undesirable events.

Central Questions?

- Dependency among PK measurements.
- Quantify the correlation among responses recorded from same individual.
- What percent of response can be attributed to different cohorts?
- **Which cohort of subjects are at a greater risk of observing a DLE?**

Model specification

$$p(y_{ij} = 1|d_{ij}) = \frac{\exp\left[\theta_1 + \theta_2 \log(d_{ij}) + \theta_3\right]}{1 + \exp\left[\theta_1 + \theta_2 \log(d_{ij}) + \theta_3\right]}$$

$$\text{logit}(p[k]) = \theta_1 + \theta_2 \log(dose[k]) + \theta_3, k = 1, 2, \cdots m$$

Bayesian hierarchical model

- Joint Prior

$$h_0(\Theta) \propto e^{-\frac{\sum_{j=1}^{3}(\theta j - \mu_j)^2}{2\sigma_j^2}}$$

- Likelihood

$$L(\Theta \mid x) = \prod_{i=1}^{r}[p(d_{ij})]^{y_{ij}} \prod_{i=r}^{n-r}[1 - p(d_{ij})]^{1-y_{ij}}$$

- Posterior Distribution

$$h(\Theta \mid \boldsymbol{x}) \propto \prod_{i=1}^{r}\left(\frac{e^{\theta_1+\theta_2\log(d)+\theta_3}}{1+e^{\theta_1+\theta_2\log(d)+\theta_3}}\right)^{y_{ij}} \times \prod_{i=r}^{n-r}\left(\frac{1}{1+e^{\theta_1+\theta_2\log(d)+\theta_3}}\right)^{1-y_{ij}} \times e^{-\frac{\sum_{j=1}^{3}(\theta j - \mu_j)^2}{2\sigma_j^2}}$$

DLE – Dose Limiting Event; PK – pharmacokinetic

Which Cohort is at a greater risk of observing a DLE?

Parameter	Mean	sd	MC error	95% HPD interval	sample	Decision
θ_1	-4.67	2.319	0.01431	(-9.601, -0.5064)	39036	-
θ_2	0.5199	0.4097	0.00252	(-0.2466 ,1.37)	39036	-
$\theta_3(1)$	-0.1544	0.7344	0.003623	(-1.699 ,1.31)	39036	-
$\theta_3(2)$	-0.1903	0.716	0.003744	(-1.713, 1.217)	39036	-
$\theta_3(3)$	-0.2499	0.7008	0.003814	(-1.755, 1.085)	39036	-
$\theta_3(4)$	1.131	0.7941	0.004268	(0.1422 , 2.765)	39036	-
$\theta_3(5)$	-0.4735	0.6985	0.003437	(-1.994 , 0.7811)	39036	-
$\theta_3(6)$	-0.1502	0.679	0.003563	(-1.57 , 1.197)	39036	-
$p_{DLE}(1)$	0.05514	0.06757	3.549×10^{-4}	$(9.979\times10^{-4}, 0.2474)$	39036	Escalate
$p_{DLE}(2)$	0.07274	0.06879	3.578×10^{-4}	(0.00397 ,0.2572)	39036	Escalate
$p_{DLE}(3)$	0.0933	0.07264	4.041×10^{-4}	(0.009349 , 0.2824)	39036	Escalate
$p_{DLE}(4)$	0.3628	0.1665	8.714×10^{-4}	(0.09764 ,0.7189)	39036	NR(De-escalate)
$p_{DLE}(5)$	0.1826	0.1189	6.204×10^{-4}	(0.02326 , 0.4653)	39036	NR(De-escalate)
$p_{DLE}(6)$	0.2618	0.1468	7.855×10^{-4}	(0.04277 , 0.5954)	39036	NR(De-escalate)
sd	0.7151	0.2423	0.001419	(0.1038 , 0.9916)	39036	-

Fig 6: *Output of Simulation runs for estimation of cohort effects and its associated probability of toxicity using WINBUGS*

95% HPD Interval – 95% Highest Posterior Density Credible Interval.; NR – Not recommended; DLE – Dose Limiting Event; sd- standard deviation.

MCMC Convergence Tests

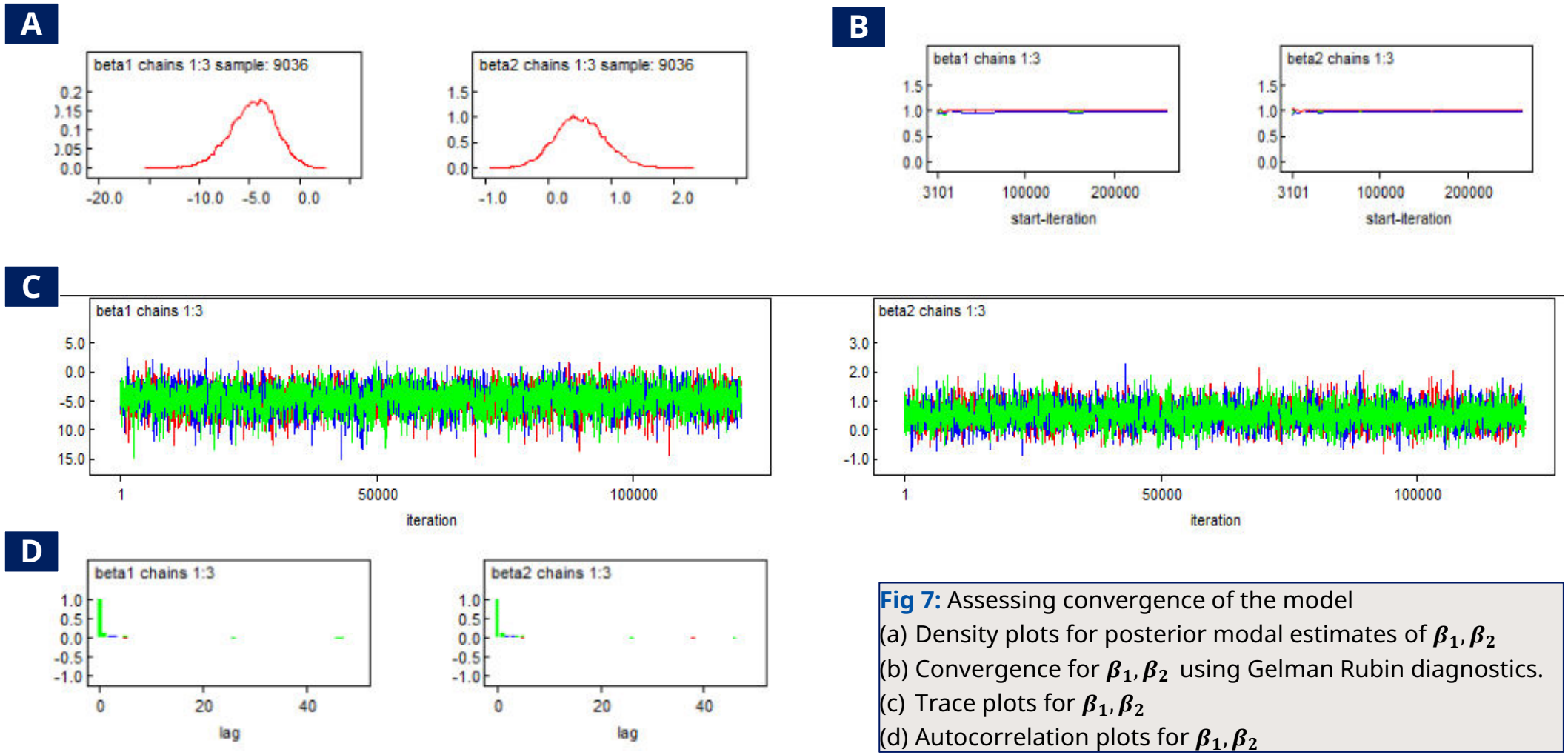


Fig 7: Assessing convergence of the model
(a) Density plots for posterior modal estimates of $\boldsymbol{\beta_1}, \boldsymbol{\beta_2}$
(b) Convergence for $\boldsymbol{\beta_1}, \boldsymbol{\beta_2}$ using Gelman Rubin diagnostics.
(c) Trace plots for $\boldsymbol{\beta_1}, \boldsymbol{\beta_2}$
(d) Autocorrelation plots for $\boldsymbol{\beta_1}, \boldsymbol{\beta_2}$

Comparison of MTD results – Summary

Model	MTD estimate
Original Model (Zhou & Whitehead)	87.5 mg (C1) & 262.5 mg (C2)
Novel COLOR Code Model	87.5 mg (C1) & 262.5 mg (C2)
Sequential Frequentist Model	87.5 mg
Response Adaptive Bayesian Design	262.5 mg
Cohort Effect Adaptive Bayesian Design	87.5 mg

Fig 8: *Comparison of MTD estimates of various design propositions*

C1 – Cohort 1 comprising of Subjects 1-5 ; C2 – Cohort 2 comprising of Subjects 6-10

Discussion

> “Far better an approximate answer to the right question, which is often vague, than the exact answer to the wrong question, which can always be made precise – John. W. Tukey.”

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