

Meeting2

Kuan Liu

Aug 03 2021

Chapter 3 Phase I

Generally speaking the Objectives of Phase I study is safety and dosage. This chapter focuses on Phase I methods to identify the maximum tolerated dose (MTD). Key elements of Phase I studies including,

- (0) study population (healthy volunteers or people with disease)
- (a) starting dose (e.g. LD_{10})
- (b) toxicity profile and dose-limiting toxicity (DLT)
- (c) target toxicity level (TTL)
- (d) dose escalation scheme (dose increment, dose assignment and cohort size)

3.1 Rule-based design for determining maximum tolerated dose (MTD)

3+3 design (Storer EB, 1989)

- widely used, implementation does not require a computer
- simplicity: dose escalation and de-escalation decisions are based on a set of prespecified rules
- Example 3.2, page 90, 3+3 can be inefficient with low starting dose and small to moderate increment.

Pharmacologically guided dose escalation

- considered more efficient than 3+3, but doesn't work for all agents and there are challenges in getting timely pharmacokinetic results.

Accelerated titration designs and other rule-based designs

- variation of 3+3, allow inpatient dose escalation - reduce number of patients
- drawbacks: mask of efficacy and toxicity (delayed)

Other rule-based designs

Newest one, the i3+3 design (Liu M, 2020). Set of dose $d = 1, \dots, D$ and pre-specified i) target toxicity rate, p_T (e.g., $p_T = 0.3$) and the equivalence interval (EI), mathematically as $[p_T - \epsilon_1, p_T + \epsilon_2]$ (e.g., $[0.25, 0.35]$). EI provides a range around p_T so that doses with toxicity probabilities inside EI are considered as MTD - allows some variabilities.

Table 1 of 3

Table 1. The dose-finding algorithm of the i3 + 3 design. Notation: 1) d : the current dose that is being tested in the trial; 2) n : the number of patients at the current dose; 3) x : the number of patients with DLTs at the current dose. The target toxicity probability is assumed to be p_T and the equivalence interval is denoted as $EI = [p_T - \epsilon_1, p_T + \epsilon_2]$. A value is "below" the EI means that the value is smaller than $(p_T - \epsilon_1)$, the lower bound of the EI. A value is "inside" the EI means that the value is larger than or equal to $(p_T - \epsilon_1)$ but smaller than or equal to $(p_T + \epsilon_2)$. A value is "above" the EI mean that the value is larger than $(p_T + \epsilon_2)$.

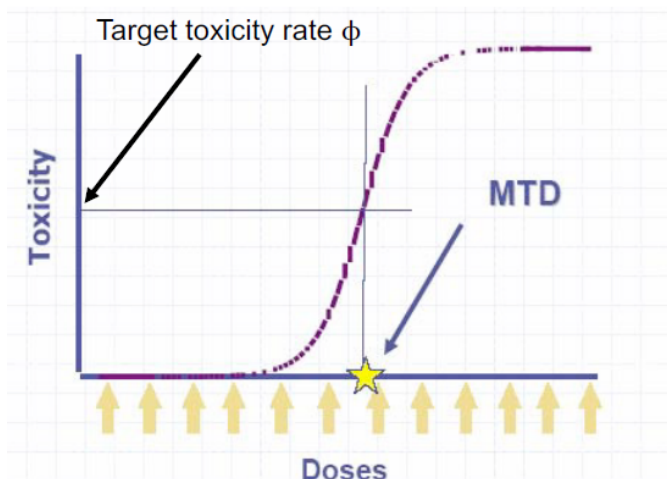
Current dose: d , No. enrolled: n , No. DLTs: x	
Condition	Next dose level
$\frac{x}{n}$ below EI	$d + 1$
$\frac{x}{n}$ inside EI	d
$\frac{x}{n}$ above EI and $\frac{x-1}{n}$ below EI	d
$\frac{x}{n}$ above EI and $\frac{x-1}{n}$ inside EI	$d - 1$
$\frac{x}{n}$ above EI and $\frac{x-1}{n}$ above EI	$d - 1$

Summary

simple but potentially inefficient.

3.2 Model-based designs

These designs assume a monotonic dose-response relationship with defined dose-toxicity curve and target toxicity level. Works well under Bayesian framework.



Continual reassessment method (CRM)

- common model for dose-toxicity curve: hyperbolic tangent, logistic, power. Model is updated based on accrued data (Bayesian adaptation)
- more likely to identify correct MTD comparing to 3+3
- Not well-accepted in original format due to safety considerations, if pre-specified model were incorrect.
- online shiny app, <https://trialdesign.org/one-page-shell.html#BMACRM>

Escalation with overdose control (EWOC)

- same as CRM except the way it selects each successive new dose
- unlike CRM that select the new dose using the posterior mode or mean, EWOC use the feasibility bound. A feasibility bound $\alpha < 0.5$ corresponds to placing a higher penalty on overdosing than on underdosing.

```
library(R2jags)
library(runjags)

filename <- "BUGSmodel.txt"
cat("
model{
  for (i in 1:N){
# Likelihood
    Y[i]~dbern(p[i])
    logit(p[i])<- (1/(gamma - Xmin))*(gamma*logit(rho0)
      - Xmin*logit(theta)+(logit(theta)-logit(rho0))*X[i])
  } # end of for loop
# Priors
    gamma ~ dunif(Xmin, Xmax)
    rho0 ~ dunif(0,theta)
  } # end of BUGS code

",file=filename
)

# Data (1st patient 140, no tox):
data1<-list(Y=c(0), X=c(140), Xmin=140, Xmax=425, theta=0.333, N=1)

# Data (1st patient 140, no tox; 2nd patient 210, no tox):
data2<-list(Y=c(0,0), X=c(140,210), Xmin=140, Xmax=425, theta=0.333, N=2)

# Data (1st patient 140, no tox; 2nd patient 210, tox):
data3<-list(Y=c(0,1), X=c(140,210), Xmin=140, Xmax=425, theta=0.333, N=2)

# Data (1st patient 140, no tox; 2nd patient 210, no tox;
# 3rd patient 300, no response yet):
data4<-list(Y=c(0,0,NA), X=c(140,210,300), Xmin=140, Xmax=425, theta=0.333, N=3)

#Inits:
init<-list(list(rho0=0.05, gamma=160),list(rho0=0.05, gamma=160))
```

```
#First patient;
jags.fit <- jags(data=data1, inits=init, parameters.to.save=c("rho0", "gamma"),
  jags.seed = 100, n.iter=11000, model.file="BUGSmodel.txt", n.chains = 2, n.burnin = 1000)
```

```
## Compiling model graph
##   Resolving undeclared variables
##   Allocating nodes
## Graph information:
##   Observed stochastic nodes: 1
##   Unobserved stochastic nodes: 2
##   Total graph size: 22
##
## Initializing model
```

```
jagsfit.mcmc<- as.mcmc(jags.fit)
summary(jagsfit.mcmc)
```

```
##
## Iterations = 1001:10991
## Thinning interval = 10
## Number of chains = 2
## Sample size per chain = 1000
##
## 1. Empirical mean and standard deviation for each variable,
##    plus standard error of the mean:
##
##              Mean          SD Naive SE Time-series SE
## deviance    0.3522  0.22876 0.005115      0.005113
## gamma      281.9077 83.75355 1.872786      1.828104
## rho0        0.1560  0.09502 0.002125      0.002124
##
## 2. Quantiles for each variable:
##
##              2.5%       25%       50%       75%      97.5%
## deviance 1.019e-02  0.15812  0.3326  0.5387  0.7787
## gamma    1.482e+02 208.48489 280.9243 355.1453 418.1232
## rho0     5.081e-03  0.07601  0.1532  0.2361  0.3225
```

```
#Second patient;
jags.fit <- jags(data=data2, inits=init, parameters.to.save=c("rho0", "gamma"),
  jags.seed = 100, n.iter=11000, model.file="BUGSmodel.txt", n.chains = 2, n.burnin = 1000)
```

```
## Compiling model graph
##   Resolving undeclared variables
##   Allocating nodes
## Graph information:
##   Observed stochastic nodes: 2
##   Unobserved stochastic nodes: 2
##   Total graph size: 28
##
## Initializing model
```

```
jagsfit.mcmc<- as.mcmc(jags.fit)
summary(jagsfit.mcmc)
```

```
##
## Iterations = 1001:10991
## Thinning interval = 10
## Number of chains = 2
## Sample size per chain = 1000
##
## 1. Empirical mean and standard deviation for each variable,
##    plus standard error of the mean:
##
##              Mean          SD Naive SE Time-series SE
## deviance    0.9274   0.60213 0.013464      0.013840
## gamma      299.8911  72.69829 1.625583      1.894083
## rho0        0.1508   0.09667 0.002162      0.002218
##
## 2. Quantiles for each variable:
##
##              2.5%        25%        50%        75%        97.5%
## deviance  9.410e-02   0.50254   0.8851   1.2981   1.9559
## gamma    1.715e+02  240.23007 300.8069 361.7748 418.2730
## rho0     6.233e-03   0.06394   0.1437   0.2309   0.3224
```

Time-to-event monitoring (TITE-CRM)

Quick Summary on CRM based approaches

Pros:

- Solid statistical foundation
- Flexible and efficient
- Better performance than rule-based

Cons:

- Performance can be compromised when the model is misspecified
- Need specialized expertise to select prior and model
- Work like a black box, challenging to communicate with non-statisticians

Toxicity intervals and Ordinal toxicity intervals

- allow the use of a range of acceptable toxicity levels
- this methods is introduced to incorporate uncertainty in estimating mean toxicities
- does not skip does and stops early for excessive toxicity if the lowest does is found to be excessively toxic

3.3 Efficacy versus toxicity

- dose finding incorporating both efficacy and toxicity endpoints

- Use for Phase I/II design, seamless phase I and II
- *EffTox*, [link to software](#), [link to paper](#)

Pair of binary outcomes, (Y_E, Y_T) follow with marginal probability in logit form as

$$\begin{aligned} \text{logit}(\pi_T) &= \mu_T + \beta_T x \\ \text{logit}(\pi_E) &= \mu_E + \beta_{E,1}x + \beta_{E,2}x^2 \end{aligned}$$

where x is the dosing variable. The bivariate joint likelihood $P(Y_E = a, Y_T = b \mid \theta)$ captures the dependency between the two outcomes, where $a \in \{0, 1\}$, $b \in \{0, 1\}$ and θ presents the vector of parameters.

At each dose update decision, the dose x is acceptable if

$$P\{\pi_E(x, \theta) \leq \pi_{\bar{E}}(x, \theta) \mid D_n\} > p_E$$

and

$$P\{\pi_T(x, \theta) < \pi_{\bar{T}}(x, \theta) \mid D_n\} < p_T$$

p_E and p_T are pre-defined gatekeepers for meeting minimum efficacy and maximum toxicity. Larger p_E more likely to exclude low efficacy doses and larger p_T more likely to exclude excessive toxicity doses.

The utility (desirability measure, the larger the better) of dose x with $\pi_E(x, \theta)$ and $\pi_T(x, \theta)$ - which is used to assess efficacy-toxicity trade-off is

$$u(\pi_E, \pi_T) = 1 - \left[\left(\frac{1 - \pi_E}{1 - \pi_E^*} \right)^p + \left(\frac{\pi_T}{\pi_T^*} \right)^p \right]^{\frac{1}{p}}$$

where π_E^* represents the smallest acceptable efficacy response rate and π_T^* represents the highest acceptable toxicity level.

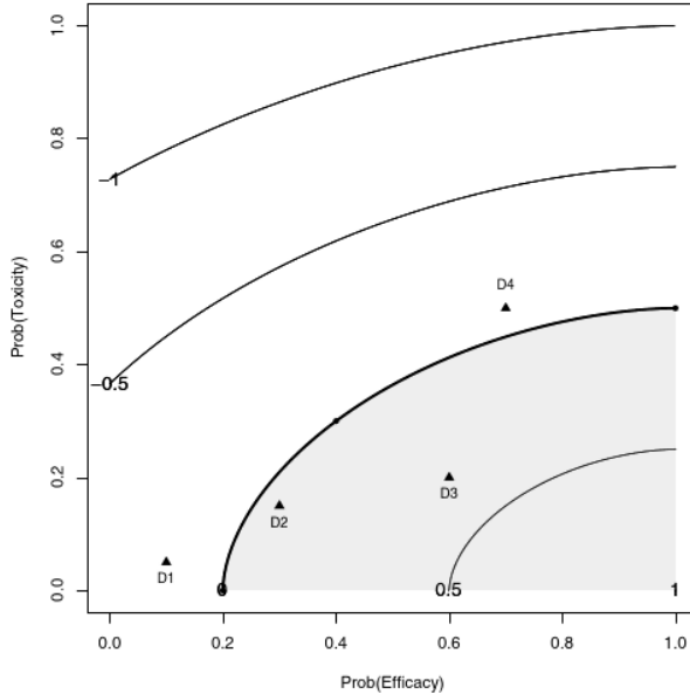


Figure 3.16 *Contour plot of the desirability measure by probabilities of toxicity and efficacy. The three design points are shown as circles, while the four doses are shown as triangles. The shaded area has desirability measure greater than 0, and is thus the “acceptable” dose region.*

	Dose			
	1	2	3	4
true Pr(efficacy)	0.10	0.30	0.60	0.70
true Pr(toxicity)	0.05	0.15	0.20	0.50
true Pr(efficacy w/o toxicity)	0.05	0.10	0.20	0.30
desirability measure	-0.133	0.055	0.333	-0.094
ave # patients treated	3.4	12.0	34.0	10.6
(% of patients treated)	(5.7%)	(20.0%)	(56.7%)	(17.7%)
selection probability	0.001	0.133	0.756	0.110

Table 3.3 *Operating characteristics of the EffTox design with four doses, maximum sample size of 60, and cohort size of 3 based on 1000 simulations.*

3.4 Combination therapy

- mathematically similar to efficacy and toxicity joint modelling, now we joint model two or more toxicity models for each combination therapy
- Gumbel model, good but might be sensible to changes of the algorithm
- Bivariate CRM
- Combination therapy with bivariate response (toxicity and efficacy)
- Bivariate logistic model

Additional Readings

1. Phase 0 (a proof of principle trial involving small number of patients), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3902019/>
2. Seamless early-phase designs in oncology, <https://academic.oup.com/jnci/article/111/2/118/5245491>
3. Model-assisted phase I design, Bayesian optimal interval design (BOIN) (Liu and Yuan, 2015)