

Paper AS02

Dose-Finding Schemes in Clinical Trials

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CRO

Agenda

Motivation

Theoretical background

Modified continual reassessment model (mCRM)

The mCRM at work

Toxicity data & Sample study design

PROC MCMC

Recommended dose

Comparison & Summary

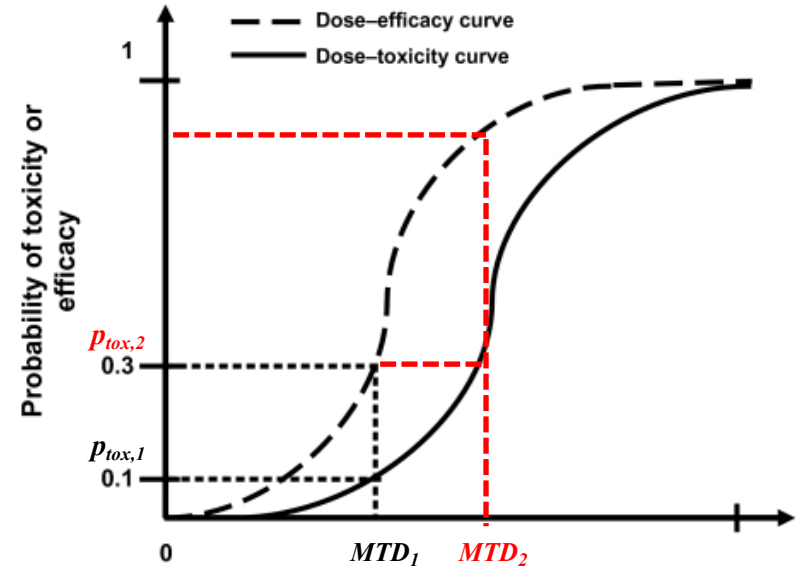
mCRM vs. 3+3 design

Motivation

- The higher the dose, the higher the efficacy –
AND the higher the risk of undesired side effects!

Motivation

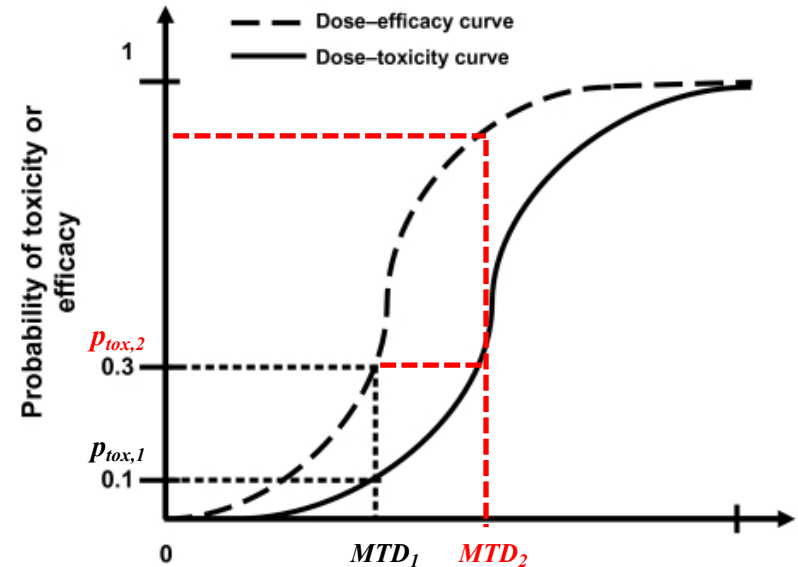
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From: Le Tourneau C, Lee J, Siu L. J Nat Canc Inst. **101** (2009) 708-20.

Motivation

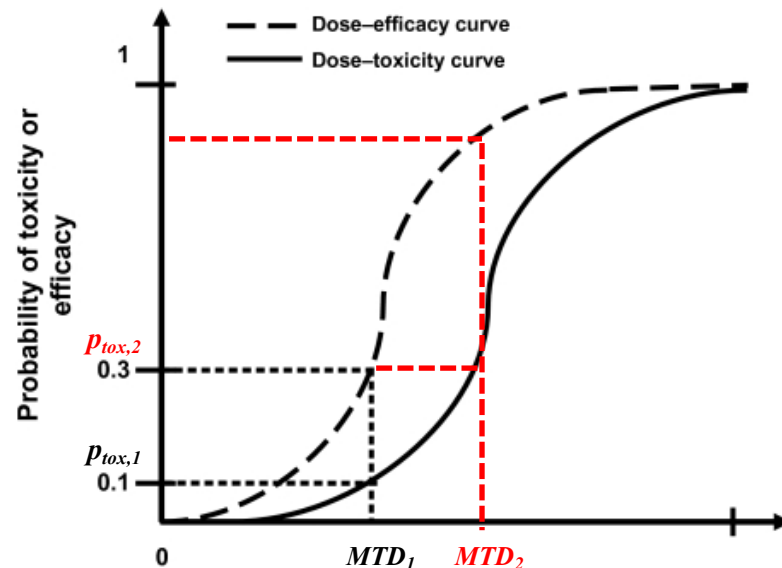
- The higher the dose, the higher the efficacy – AND the higher the risk of undesired side effects!
- Goal: Estimate maximum tolerable dose (MTD)



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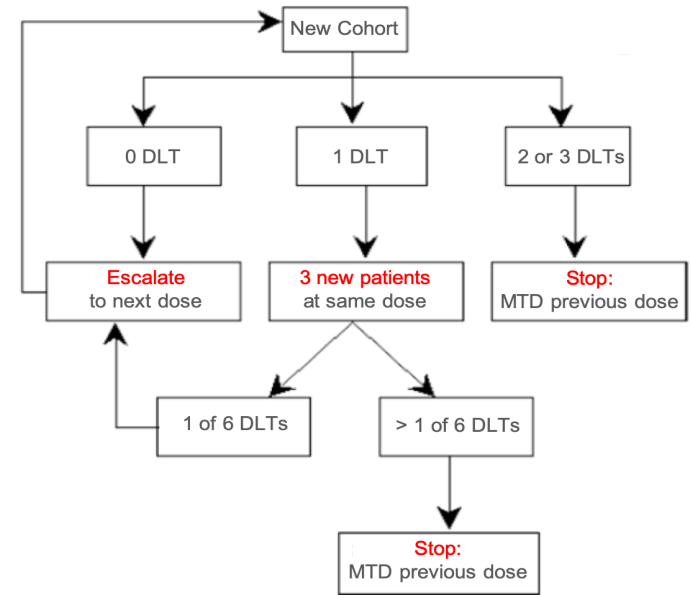
- The higher the dose, the higher the efficacy – AND the higher the risk of undesired side effects!
- Goal: Estimate maximum tolerable dose (MTD)
- Use as few patients as possible
- Phase I study: dose-finding design, e.g.
3+3 design, mTPI, mCRM, ...
- Most common approach: 3+3 design



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Motivation

- Traditional 3+3 design (3 patients per cohort):



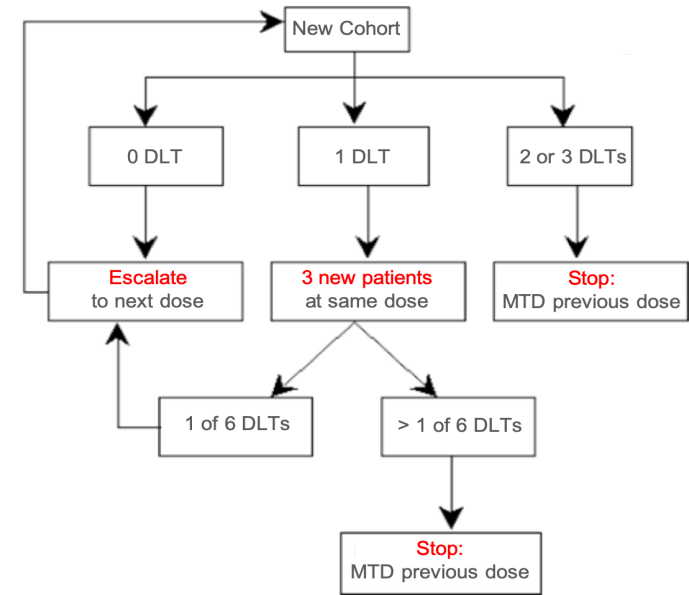
DLT = Dose limiting toxicity, MTD = maximum tolerable dose

Motivation

- Traditional 3+3 design (3 patients per cohort):
- FDA [*Guidance: Clin. Consid. for Therap. Cancer Vaccines*]:
“Many cancer vaccine trials have used the ‘3+3 design’, and the results show that, except in very rare situations, an MTD for a cancer vaccine may not be identified. [...] Therefore, this ‘3+3 design’ may not be the most suitable approach to gathering information from early phase trials of cancer vaccines, and alternative trial designs should be considered.”

→ More sophisticated dose-finding methods needed

- Greater safety of patients possible



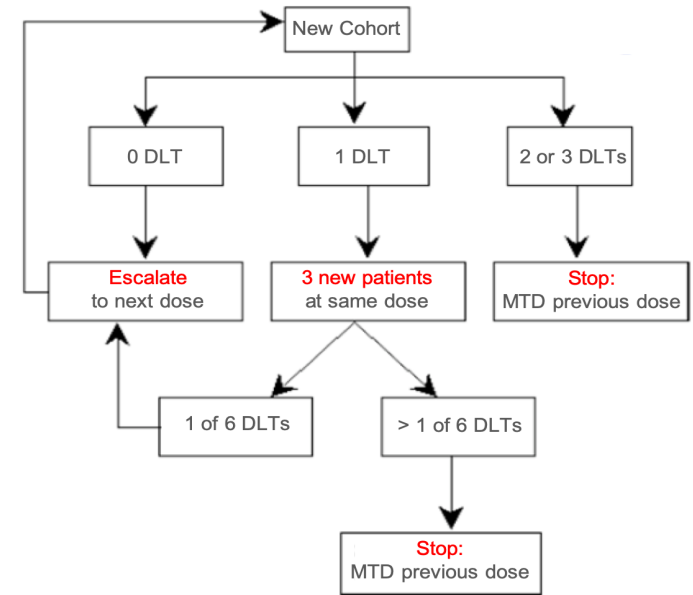
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- Greater safety of patients possible
- In this talk: mCRM (for mTPI see paper)



DLT = Dose limiting toxicity, MTD = maximum tolerable dose

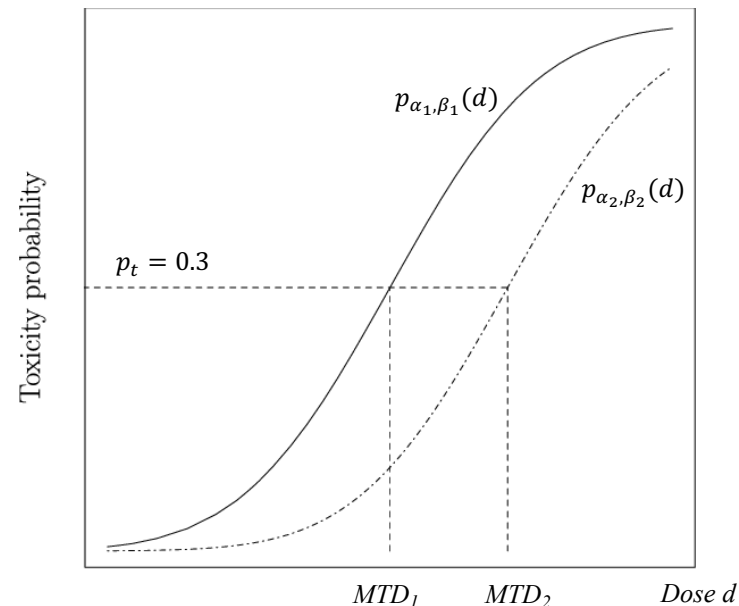
Theoretical background – mCRM

- Model for dose-toxicity probability relationship:

$$\text{logit}(p) = \ln\left(\frac{p}{1-p}\right) = \alpha + \beta d$$

- Maximum tolerable dose (MTD) via $p = p_t$, e.g. 30%:

$$MTD = \frac{\ln\left(\frac{p_t}{1-p_t}\right) - \alpha}{\beta} = \frac{\ln\left(\frac{3}{7}\right) - \alpha}{\beta}$$



Adapted from: Yang X and Keying Y. *A phase I dose-finding study based on polychotomous toxicity responses*, 2012.

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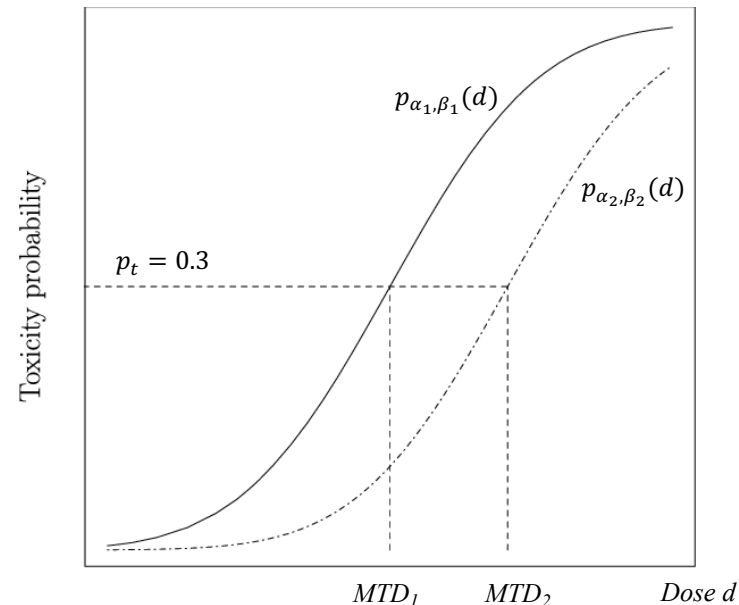
$$MTD = \frac{\ln\left(\frac{p_t}{1-p_t}\right) - \alpha}{\beta} = \frac{\ln\left(\frac{3}{7}\right) - \alpha}{\beta}$$

- Bayesian approach (x DLTs out of n):

$$f_{\text{posterior}}((\alpha, \beta)|(n, x)) \sim p_{\alpha, \beta}^x (1 - p_{\alpha, \beta})^{n-x} f_{\text{prior}}(\alpha, \beta)$$

- Choice of prior distributions:

- Normal for α : $\mathcal{N}(\mu = -3, \sigma = 1)$
- Positive Normal for β : $\mathcal{N}_+(\mu = 0.0015, \sigma = 0.003)$



Adapted from: Yang X and Keying Y. *A phase I dose-finding study based on polychotomous toxicity responses*, 2012.

Theoretical background – mCRM

- How to simulate posterior distribution $f_{\text{posterior}}$?

→ MCMC = **Markov chain Monte Carlo algorithm**

Once simulated, following parameters interesting:

- Probability of dose d being MTD, i.e. probability that d is maximum dose where $p < p_t$
- Probability $T(d)$ that DLT rate is below p_t
- Expectation value $E(p|d)$ of DLT rate for dose d

Theoretical background – mCRM

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 - Probability $T(d)$ that DLT rate is below p_t
 - Expectation value $E(p|d)$ of DLT rate for dose d
- Safety is of utmost importance
 - Monitoring $T(d)$ and $E(p|d)$
 - Plus: Additional safety rules!

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- Expectation value $E(p|d)$ of DLT rate for dose d
- Safety is of utmost importance
 - Monitoring $T(d)$ and $E(p|d)$
 - Plus: Additional safety rules!

Additional safety rules:

- Safety rule 1 (termination): The MTD is precisely estimated, i.e. the inter-quartile range of the MTD distribution is less than a certain percentage P_{term} of its median.
- Safety rule 2 (high toxicity): Minimum dose tested is toxic, i.e. $T(d_1) < 1 - \xi$.
- Safety rule 3 (low toxicity): Maximum possible dose is safe, i.e. $T(d_l) > \xi$.
- Safety rule 4 (maximum number of patients): Total sample size for next dose is equal to N .

The mCRM at work – Toxicity data & Study design

Subject identifier	Cohort	Treatment arm	DLT flag
1001	1	100 mg	N
1002	1	100 mg	N
1003	1	100 mg	N

Comparability to modified 3+3 design:

- Discrete doses 100mg, 200mg, ..., 1000mg
- Cohorts of 3 patients
- MTD target probability p_t of 30%

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Only number of DLTs per cohort important



Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0

Variable names: COHORT, N, DOSE, DLTS

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Variable names: COHORT, N, DOSE, DLTs

The mCRM at work

```
%MACRO mtd_estimation(  
    indat    =  
    , DLTrate = 0.3  
    , doses   = %str(100 200 300 400 500 600 700 800 900 1000)  
);
```

```
%MEND mtd_estimation;
```

The mCRM at work – PROC MCMC

```
%MACRO mtd_estimation(  
    indat      =  
    , DLTrate = 0.3  
    , doses    = %str(100 200 300 400 500 600 700 800 900 1000)  
);  
  
%* MCMC algorithm to compute posterior distr. of alpha, beta;  
PROC MCMC data=&indat. ntu=1000 nmc=20000  
    nthin=10 outpost=&indat.out seed=112358;  
  
    mu_a = -3.0; sigma_a = 1;  
    PRIOR alpha ~ normal(mu_a, var=sigma_a**2);  
    PARMS (alpha) -3.0;  
  
    mu_b = 0.0015; sigma_b = 0.003;  
    f_b = -(beta-mu_b)**2/2/sigma_b**2 - 1.e16*(1-sign(beta));  
    PRIOR beta ~ general(f_b);  
    PARMS (beta) 0.0015;  
  
    p = logistic(alpha + beta*dose);  
    MODEL dlts ~ binomial(n,p);  
  
RUN;                                     %MEND mtd_estimation;
```

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%MACRO mtd_estimation(  
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RUN;
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Variables of input data

```
%MEND mtd_estimation;
```

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    p = logistic(alpha + beta*dose);
    MODEL dlts ~ binomial(n,p);
RUN;

% Computation of Pr(d<MTD), T(d), E(p|d): [...]

% Safety rules 2 and 3: [...]

/* Coefficient of variation (Safety rule 1);
ODS OUTPUT summary = &indat.out_median_iqr_mtd;
PROC MEANS DATA = &indat.out_mtd p50 qrange;
    VAR mtd;
RUN;
ODS OUTPUT CLOSE;

%MEND mtd_estimation;
```

The mCRM at work – PROC MCMC

```
%MACRO mtd_estimation(
    indat =
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    VAR mtd;
RUN;
ODS OUTPUT CLOSE;

/* Prob. of dose d being the MTD, i.e. prob.
that d is max dose with p < p_t;
PROC FREQ data=&indat.out_mtd noprint;
    TABLES mtd / nocum out=&indat.out_final;
    format mtd dosefmt.;
RUN;

%MEND mtd_estimation;
```

The mCRM at work – PROC MCMC

```
%MACRO mtd_estimation(
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PROC MEANS DATA = &indat.out_mtd p50 qrange;
    VAR mtd;
RUN;
ODS OUTPUT CLOSE;

/* Prob. of dose d being the MTD, i.e. prob.
that d is max dose with p < p_t;
PROC FREQ data=&indat.out_mtd noprint;
    TABLES mtd / nocum out=&indat.out_final;
    format mtd dosefmt.
RUN;

%MEND mtd_estimation;
```

The mCRM at work – PROC MCMC

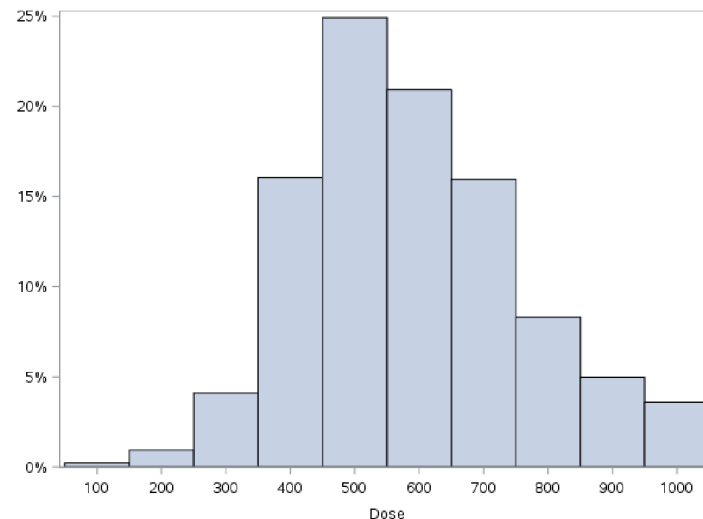
```
PROC FORMAT;
  VALUE dosefmt
    low - 100 = '0'
    100 <- 200 = '100'
    200 <- 300 = '200'
    300 <- 400 = '300'
    400 <- 500 = '400'
    500 <- 600 = '500'
    600 <- 700 = '600'
    700 <- 800 = '700'
    800 <- 900 = '800'
    900 <- 1000 = '900'
    1000 <- 1100 = '1000'
    1100 <- 1200 = '1100'
    1200 <- 1300 = '1200'
    1300 <- 1400 = '1300'
    1400 <- 1500 = '1400'
    1500 <- high = '>1500';
RUN;
```

Discrete dose levels

The mCRM at work – PROC MCMC

```
PROC FORMAT;
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    low - 100 = '0'
    100 <- 200 = '100'
    200 <- 300 = '200'
    300 <- 400 = '300'
    400 <- 500 = '400'
    500 <- 600 = '500'
    600 <- 700 = '600'
    700 <- 800 = '700'
    800 <- 900 = '800'
    900 <- 1000 = '900'
    1000 <- 1100 = '1000'
    1100 <- 1200 = '1100'
    1200 <- 1300 = '1200'
    1300 <- 1400 = '1300'
    1400 <- 1500 = '1400'
    1500 <- high = '>1500';
RUN;
```

Discrete dose levels → $\Pr(d \leq MTD)$ histogram:



The mCRM at work – Sample Scenario

- Start with 3 patients at 100 mg and no DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0

Input data (`&indat.`)

The mCRM at work – Sample Scenario

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PROC
MCMC



Input data (&indat.)

Output data (&indat.out_mtd.)

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PROC
MCMC



Dose d	Frequency count	Prob. (%) of dose d being the MTD
0	22	1.10
100	46	2.30
200	110	5.50
300	150	7.50
400	169	8.45
500	162	8.10
600	131	6.55
700	119	5.95
800	108	5.40
900	99	4.95
1000	77	3.85

Input data (&indat.)

Output data (&indat.out_mtd.)

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900	99	4.95
1000	77	3.85

Input data (&indat.)

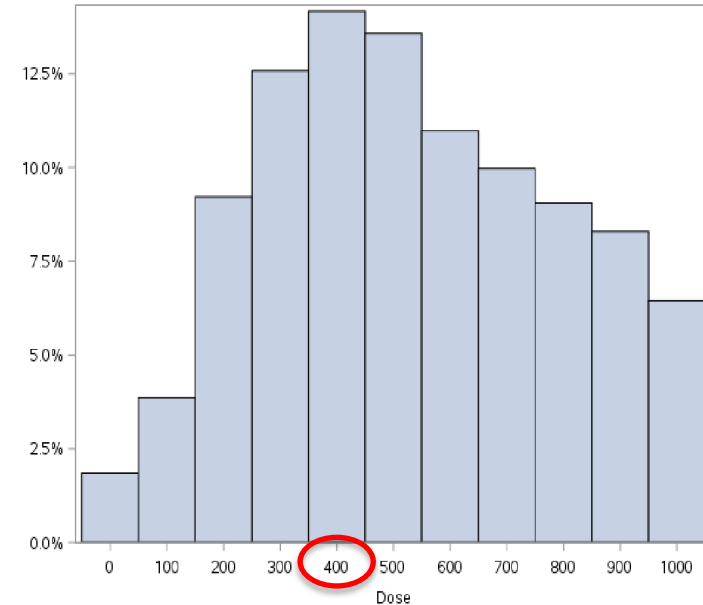
Output data (&indat.out_mtd.)

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Input data (&indat.)

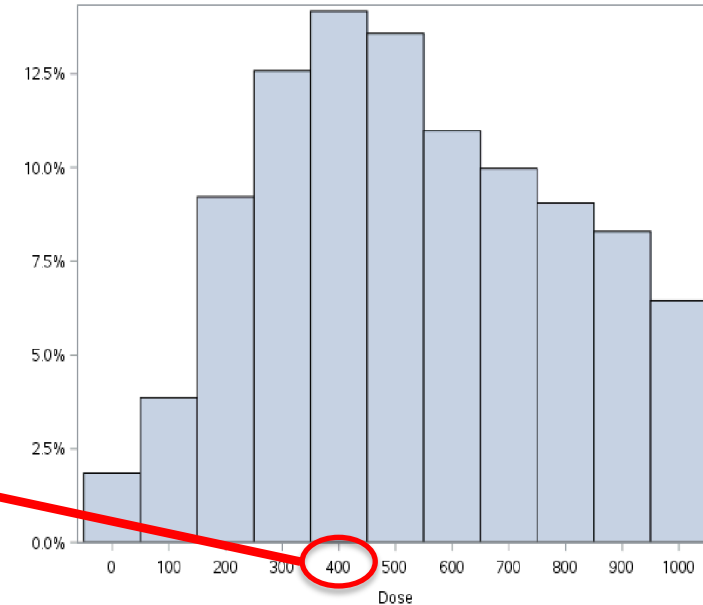
Output data (&indat.out_mtd.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 400 mg

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	

PROC
MCMC



Input data (&indat.)

Output data (&indat.out_mtd.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 400 mg, again no DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0



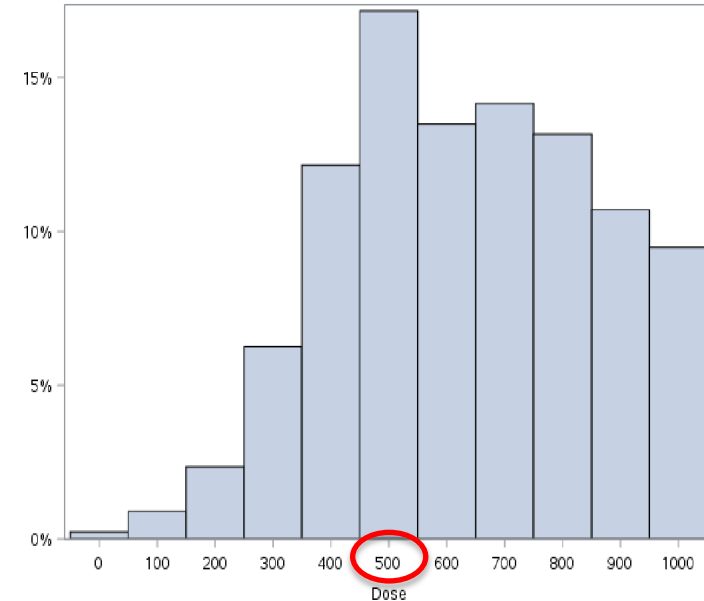
Input data (&indat.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 400 mg, again no DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0

PROC
MCMC



Input data (&indat.)

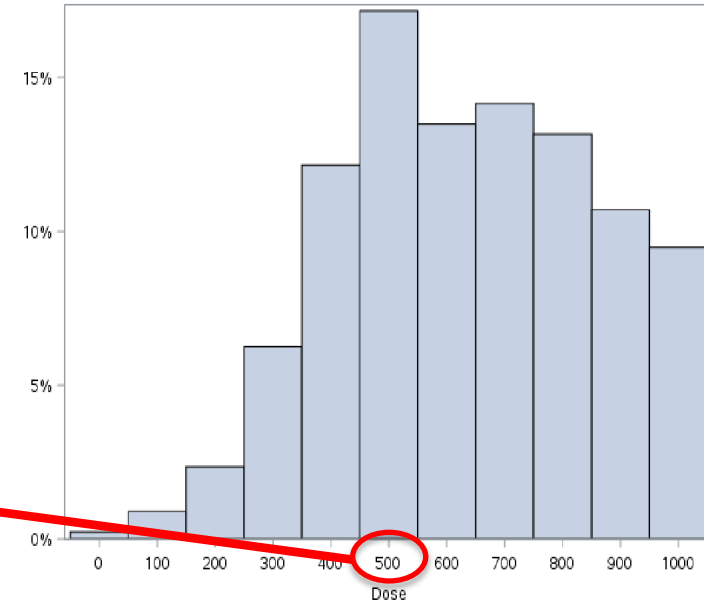
Output data (&indat.out_mtd.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 500 mg

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	

PROC
MCMC



Input data (&indat.)

Output data (&indat.out_mtd.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 500 mg, again no DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0

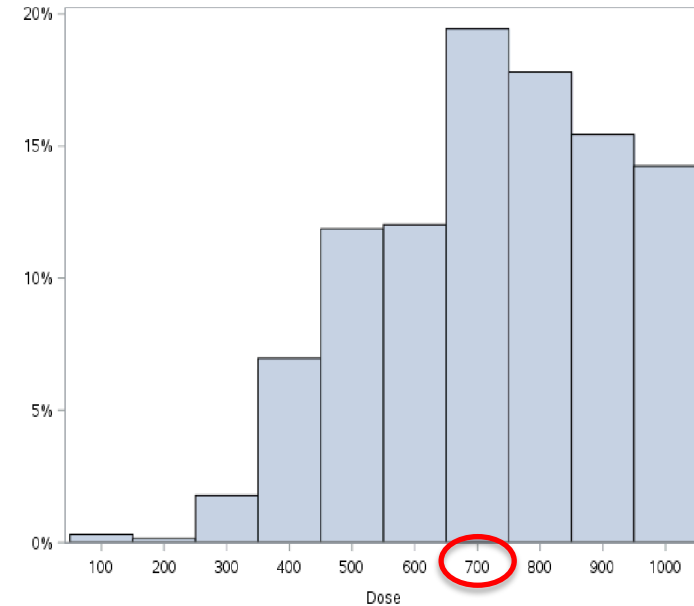
Input data (&indat.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 500 mg, again no DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0

PROC
MCMC



Input data (&indat.)

Output data (&indat.out_mtd.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 700 mg, now 2 DLTs

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0
4	3	700 mg	2

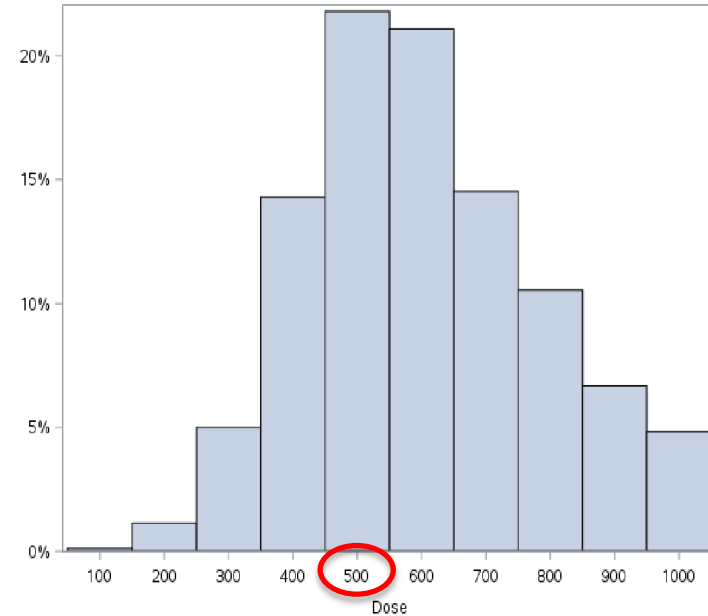
Input data (`&indat.`)

The mCRM at work – Sample Scenario

- Add 3 more patients at 700 mg, now 2 DLTs

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0
4	3	700 mg	2

PROC
MCMC



Input data (&indat.)

Output data (&indat.out_mtd.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 500 mg with one DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0
4	3	700 mg	2
5	3	500 mg	1

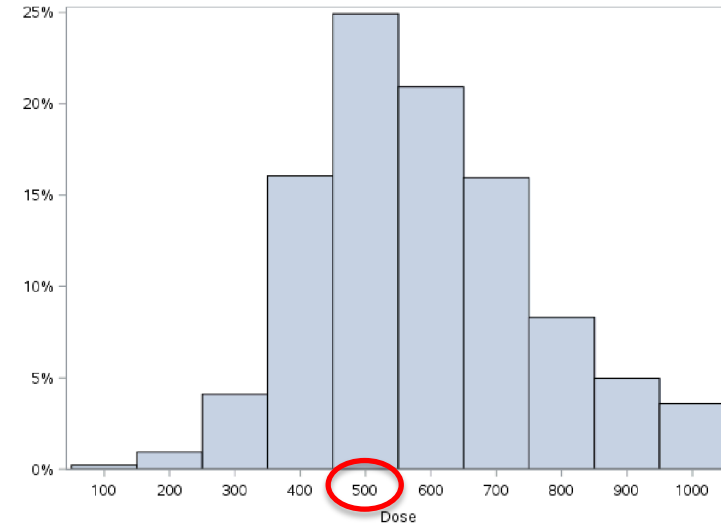
Input data (&indat.)

The mCRM at work – Sample Scenario

- Add 3 more patients at 500 mg with one DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0
4	3	700 mg	2
5	3	500 mg	1

PROC
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Input data (&indat.)

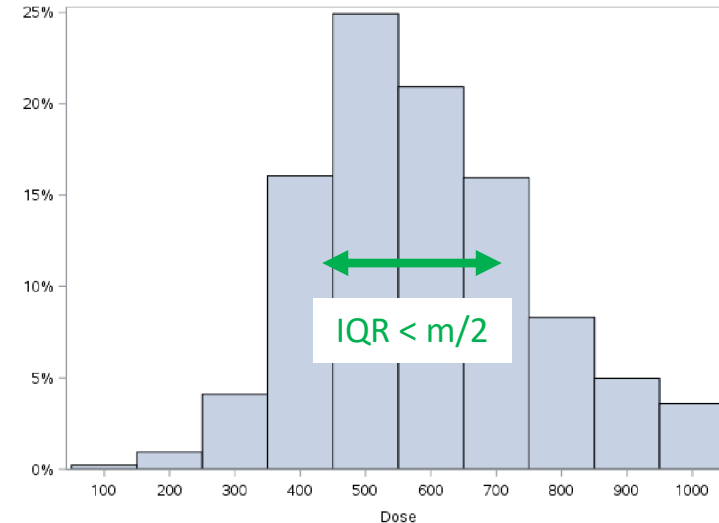
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3	3	500 mg	0
4	3	700 mg	2
5	3	500 mg	1

Input data (&indat.)

PROC
MCMC
+ Safety
rule 1



The mCRM at work – Sample Scenario

- Add 3 more patients at 500 mg with one DLT

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0
4	3	700 mg	2
5	3	500 mg	1

Input data (&indat.)

PROC
MCMC



+ Safety
rule 1

- Safety rule 1 (termination): The MTD is precisely estimated, i.e. the inter-quartile range of the MTD distribution is less than a certain percentage P_{term} ($= 1/2$) of its median.

Note to the log:

Limit for coefficient of variation reached: $CV(MTD) = 0.425 < 1/2$, i.e. IQR less than half of median
=> MTD precisely estimated!

Safety rule matched: Note to the log

The mCRM at work – Sample Scenario

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3	3	500 mg	0
4	3	700 mg	2
5	3	500 mg	1

Input data (&indat.)

PROC
MCMC



+ Safety
rule 1

- Safety rule 1 (termination): The MTD is precisely estimated, i.e. the inter-quartile range of the MTD distribution is less than a certain percentage P_{term} ($=1/2$) of its median.

Note to the log:

Limit for coefficient of variation reached: $CV(MTD) = 0.425 < 1/2$, i.e. IQR less than half of median
=> MTD precisely estimated!

Safety rule matched: Note to the log

The mCRM at work – Sample Scenario Summary

- Final sample size: 5 x 3 pts. = 15 pts.
- Number of DLTs: 3

Cohort	Number of subjects	Treatment arm	Number of DLTs
1	3	100 mg	0
2	3	400 mg	0
3	3	500 mg	0
4	3	700 mg	2
5	3	500 mg	1

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5	3	500 mg	1

- Skipped dose levels:
200mg, 300mg, 600mg
- Recommended dose (for $p_t = 0.3$):
500mg
- Narrow final probability distribution
 $\Pr(d \leq MTD)$

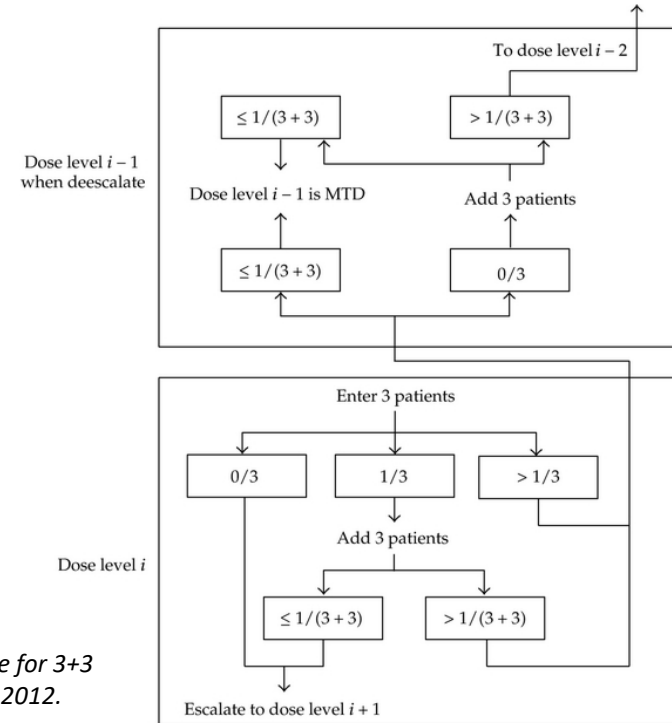
```
graph TD
    subgraph "Dose level i"
        A[Enter 3 patients] --> B[0/3]
        A --> C[1/3]
        A --> D[> 1/3]
        B --> E[Escalate to dose level i + 1]
        C --> F[Add 3 patients]
        D --> G[To dose level i - 1]
        F --> H[≤ 1/(3+3)]
        F --> I[> 1/(3+3)]
        H --> E
        I --> J[Add 3 patients]
        J --> K[0/3]
        J --> L[≤ 1/(3+3)]
        J --> M[> 1/(3+3)]
        K --> E
        L --> N[Dose level i - 1 is MTD]
        M --> G
    end
    subgraph "Dose level i - 1 when deescalate"
        N --> O[≤ 1/(3+3)]
        O --> P[Add 3 patients]
        P --> Q[0/3]
        P --> R[≤ 1/(3+3)]
        Q --> N
        R --> N
    end
```

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Comparison with 3+3 design

Similar scenario for **modified 3+3 design**
(also dose de-escalation allowed):

Cohort	Number subjects	Dose 3+3 design	# DLTs 3+3 design
1	3	100 mg	0
2	3	200 mg	0
3	3	300 mg	0
4	3	400 mg	0
5	3	500 mg	0
6	3	600 mg	0
7	3	700 mg	2
8	3	600 mg	1



From: Zhao Y. *Escalation scheme for 3+3 design with dose de-escalation*, 2012.

Comparison with 3+3 design

Sample data: **modified 3+3 design** vs. **mCRM**

Cohort	Number subjects	Dose 3+3 design	# DLTs 3+3 design	Dose mCRM	# DLTs mCRM
1	3	100 mg	0	100 mg	0
2	3	200 mg	0	400 mg	0
3	3	300 mg	0	500 mg	0
4	3	400 mg	0	700 mg	2
5	3	500 mg	0	500 mg	1
6	3	600 mg	0		
7	3	700 mg	2		
8	3	600 mg	1		

Comparison with 3+3 design

Sample data: **modified 3+3 design** vs. **mCRM**

Cohort	Number subjects	Dose 3+3 design	# DLTs 3+3 design	Dose mCRM	# DLTs mCRM
1	3	100 mg	0	100 mg	0
2	3	200 mg	0	400 mg	0
3	3	300 mg	0	500 mg	0
4	3	400 mg	0	700 mg	2
5	3	500 mg	0	500 mg	1
6	3	600 mg	0		
7	3	700 mg	2		
8	3	600 mg	1		

Comparison summary:

Category	3+3	mCRM
Number of treated patients	24	15
Number of observed DLTs	3	3
Recommended dose (RD)	600 mg	500 mg
Expected DLT rate at RD	0.17	0.22
Prob. RD less or equal MTD	67.1 %	80.8 %

Summary

- Macro with PROC MCMC step to successfully implement mCRM
- Not in the talk: Macro for mTPI-ESD-table to implement the mTPI method (see paper)

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- Not in the talk: Macro for mTPI-ESD-table to implement the mTPI method (see paper)
- Designs like mCRM (or mTPI) perform better than 3+3 design in many cases:
 - Multiple dose levels (even continuous doses possible), variable cohort sizes
 - Flat dose-toxicity probability relationship → **Skipping dose levels**
 - Smaller amount of patients needed to be treated

Summary

- Macro with PROC MCMC step to successfully implement mCRM
- Not in the talk: Macro for mTPI-ESD-table to implement the mTPI method (see paper)
- Designs like mCRM (or mTPI) perform better than 3+3 design in many cases:
 - Multiple dose levels (even continuous doses possible), variable cohort sizes
 - Flat dose-toxicity probability relationship → **Skipping dose levels**
 - Smaller amount of patients needed to be treated
- **Take home message** [FDA Guidance: *Clinical Considerations for Therapeutic Cancer Vaccines*]:

“[... In some cases] alternative dose-escalation approaches, such as [...] continuous reassessment, may be considered instead of the standard ‘3+3 design’.”

Thank you!

Thank you!

...and please check out my paper AS02 !