Practical considerations: Protocol development and Software

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Protocol development – Step 1

Clinical questions:

1. How many patients?
2. How many dose levels?
3. Actual amount of dosage
4. How long will the trial take to complete?

Cost. Resources.

1. Sample Size

- 15 for 3 levels
- 20-25 for 5-8 levels
- Since we reach the MTD faster, we could test more dose levels w/o increasing the sample too much.
- 3+3 sample size depends on # levels
  - 5 levels : 30 pts
  - 6 levels: 36 pts

Fixed sample size or stopping rules

- Fixed sample size is easier
  - Cost, resources known (RSA)
- Fixed SS with option to stop early if 6 pts at the MTD
- Stopping rules
  - Confidence intervals (practically not useful, unless n>36)
  - Probability(all remaining patients be treated at same level and MTD will be the same)

Stopping rules – confidence intervals

O' Quigley, Pepe, Fisher (1990)

Sample size is not fixed, continue accrual until

$$\int_{a_L}^{a_U} f(a,\Omega_j)da = 1-\gamma$$

$$\{\psi(x_i,a_L),\psi(x_i,a_U)\} \in R, R \text{ neighborhood } \theta$$

CI on unknown dose parameter

Highest posterior interval (asymmetric)

Normal approximation (symmetric)

Stopping rules – binary tree

Probability(all remaining patients will be treated at same level and MTD will be the same)

Binary trees (O'Quigley, Reiner 1998)

$$\mathcal{P}_{j,n} = \Pr\left\{x_{j+1} = x_{j+2} = \cdots = x_{n+1} \,\middle|\, \Omega_j\right\}$$

2. How many levels

- Not a statistical question
- Discrete and pre-specified
- Pre-clinical data gives them an estimate of MTD in other species
- Typically: 5-6 levels (2 below, 2 above)
- Clinicians decide and we can work around that

3. Actual amount of dosage

Dose selection

Fibonacci sequence: 1,1,2,3,5,8,13,21,…

% increase: 100, 50, 67, 60, 62,…

Modified Fibonacci: % increase in dose levels
100, 67, 50, 40, 33, 33,…

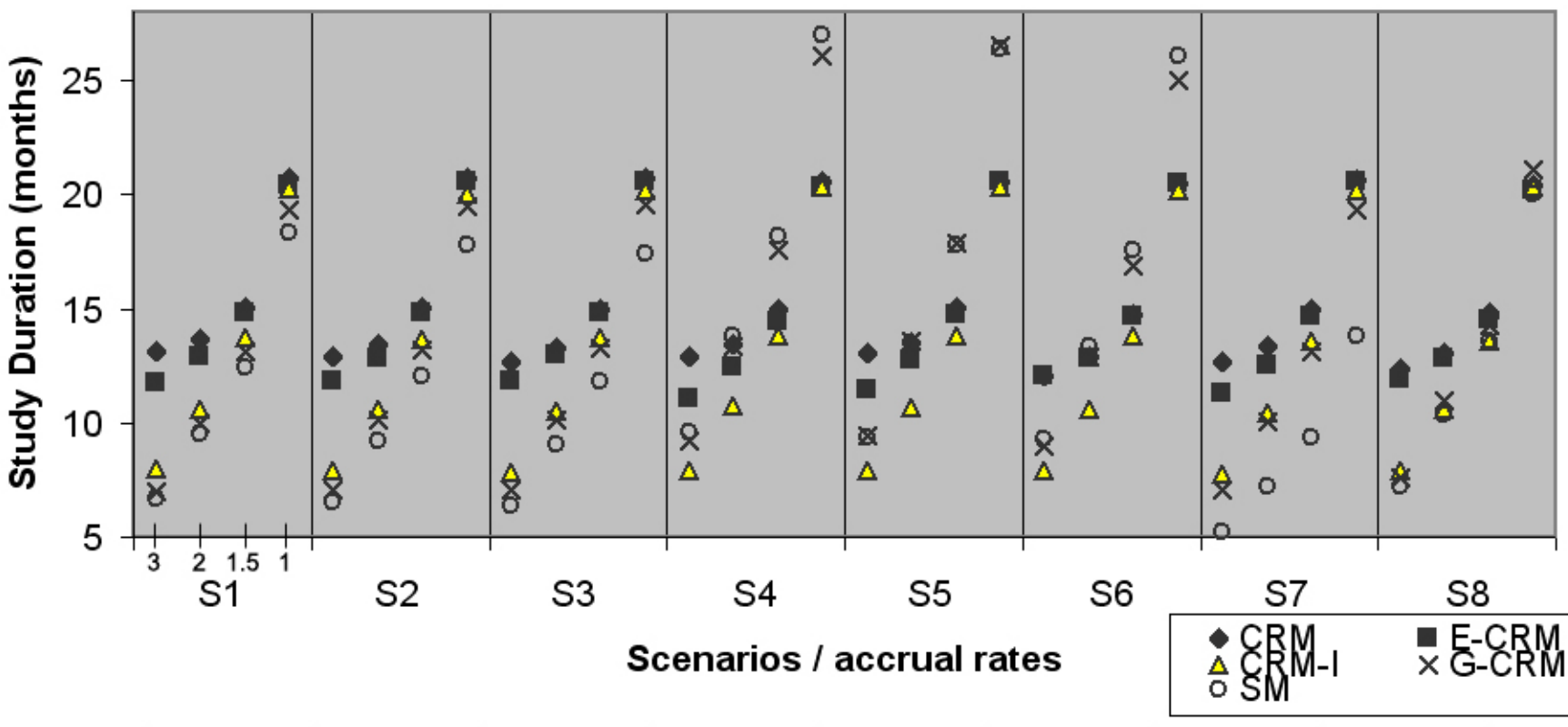
Example: 50mg,100mg, 167mg, 250 mg, 350 mg,..

4. Trial duration

Depends on:

- Accrual rate (1 or 3 pts /month)
- DLT observation period (21, 28 days)
- Grouped inclusions (allow > 1 patient per level)

Trial Duration



CRM	20	20	20	20	20	20	20	20
E-CRM	20	20	20	20	20	20	20	20
CRM-I	20	20	20	20	20	20	20	20
G-CRM	18	18	18	27	27	27	18	21
SM	18	18	18	27	27	27	12	18

Software – Trial duration

1. dfcrm R package (Ken Cheung)
http://cran.rproject.org/web/packages/dfcrm/
dfcrm.pdf
titecrm: one dose assignment
titesim: operating characteristics, trial duration

2. CRM R package (Qianxing Mo)
http://cran.rproject.org/web/packages/CRM/
CRM.pdf
crmsiminc: OC, trial duration

Protocol development – Step 2

Statistical questions:

1. Which model?
2. How many parameters?
3. Bayesian or Likelihood?
4. Prior distribution
5. Skeleton values

Operating Characteristics

- Model, skeleton, prior are chosen
- Evaluate OC
- Define target rate 20-30%
- Cohort size
- Restrict dose jumps to no more than a level

Writing the Statistical section

- No updated formal guidelines by FDA (1994)
- Describe CRM in words and with a model
- Provide OC section (optional; recommended)
  - Committees Review
  - Stage 1 data (True DLT rates)
- Rigid versus flexible
- Fixed sample or stopping rules

Statistical Section

A two-stage CRM will be used at the beginning of a trial until a DLT is observed (accelerated stage), and then the CRM is in effect at the second stage after the first DLT or when dose level 6 (28 mg) is reached, whichever occurs first. During the accelerated stage one patient is accrued at a time, escalation to the next dose is permitted if there is no DLT.

We will examine 10 dose levels, 6 during the accelerated stage and the remaining during the model-based phase.

Dose levels	1	2	3	4	5	6	7	8	9	10
Dose mg/m^2	1	2	4	8	16	28	36	40	45	50

Our initial estimates of DLT probabilities are: 0.05, 0.08, 0.1, 0.12, 0.2, 0.25, 0.3, 0.4, 0.45,and 0.5 for doses 1-10, respectively. Thus, our a priori belief is that dose 6 (28 mg/m^2 of drug a) is the MTD which is very conservative. The starting dose level will be dose level 1 at 1 mg/m^2. We assume that the dose-toxicity follows a hyperbolic tangent model as follows:

P(DLT=yes)=((tanhx+1)/2)^a;

where a is the unknown parameter that we need to estimate in order to determine which dose is the MTD and x corresponds to a standardized dose unit. The dose unit x can be solved by setting a=1.0 and using the initial estimates of DLT probabilities shown above for each dose level (0.05, 0.08, 0.1, 0.12, 0.2, 0.25, 0.3, 0.4, 0.45,and 0.5). A value of a=1.0 indicates that our prior beliefs were correct; while a value of a less than 1.0 indicates that the drug is more toxic and a value of greater than 1.0 indicates the drug is less toxic than previously believed. To reflect the uncertainty in our prior probability estimates, we assume an exponential distribution (prior distribution) with mean 1.0 (O'Quigley).

We will enroll 27 evaluable patients; it is expected that the trial will be open to accrual for 18-30 months. The sample size of 27 patients was selected based on simulated studies. All patients will be evaluable for safety analysis if they receive at least one dose of iso-fludelone. Additional subjects will be enrolled to replace any subjects who are enrolled, but do not receive treatment. Patients who die during the study period for reasons not related to toxicity or do not complete the required safety observation time interval (one cycle) will be described and evaluated separately. Patients not meeting the eligibility criteria and other major protocol violations will be described.

Operating characteristics

Through 1000 simulated trials following the methodology referenced in Iasonos et. al with the above parameters we expect the method to behave in the following way, assuming three different hypothetical scenarios for the true toxicity rates at each dose level.

Table 9: Hypothetical True Toxicity Rates

Dose levels	1	2	3	4	5	6	7	8	9	10
Scenario 1	.05	.08	.10	.15	.25	.30	.35	.40	.50	.60
Scenario 2	.05	.07	.08	.10	.15	.20	.25	.40	.45	.50
Scenario 3	.01	.05	.07	.08	.10	.15	.20	.25	0.3	0.33
Scenario 4	.001	.01	.05	.07	.08	.10	.15	.19	.22	.25

Table 10: Percent of simulated trials that selected each dose under each scenario

Dose levels	1	2	3	4	5	6	7	8	9	10
Scenario 1	0	.7	3	18	34	20	18	6	1.4	0
Scenario 2	0	.1	.2	3	15	22	39	18	2	.5
Scenario 3	0	0	0	.5	5	11	24	28	15	17
Scenario 4	0	0	0	.2	.5	3	14	22	18	42

Table 11: Percent of patients treated at each dose under each scenario

Dose levels	1	2	3	4	5	6	7	8	9	10
Scenario 1	6	6	7	16	24	16	15	7	2	1
Scenario 2	5	5	5	8	16	18	24	14	4	2
Scenario 3	4	4	4	6	9	12	19	18	10	13
Scenario 4	4	4	4	4	6	8	15	17	13	26

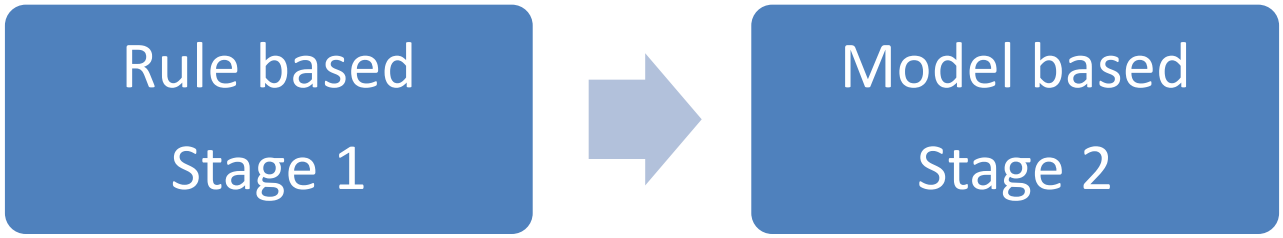
Example ongoing trial at MSKCC

- Investigators wanted to test k=10 dose levels
- Some pre-clinical data suggested the neighborhood of MTD
- Two stage design to eliminate levels far away from MTD
- Accelerated design followed by CRM

Two stage designs

O'Quigley, Shen (1996) Biometrics

1) Why two stage designs?



- 0/3 then escalate
- 1/3 stay and expand to 6
- 2/3 or 2/6 de-escalate

2) switch to stage 2 after the 1st DLT (heterogeneity)

PU-H71 clinical trial at MSKCC

	Accelerated stage					CRM stage				
Dose Levels	d1	d2	d3	d4	d5	**d6**	**d7**	**d8**	d9	d10
Actual dose *(mg/m²)*	10	20	35	50	60	**80**	**100**	**120**	140	160
Skeleton /initial rates	.05	.08	.10	.12	.20	**.25**	**.30**	**.40**	.55	.70

First in humans - No clinical data

Pre clinical data with a lot of uncertainty

140 *mg/m²* was lethal in dogs

80-100 *mg/m²* is expected MTD

Iso-fludelone clinical trial at MSKCC

	Accelerated stage						CRM stage			
Dose Levels	d1	d2	d3	d4	d5	d6	**d7**	**d8**	**d9**	d10
Actual dose *(mg/m²)*	1	2	4	8	16	28	**36**	**40**	**45**	50
Skeleton /initial rates	.05	.08	.10	.12	.20	.25	**.30**	**.40**	**.45**	.50

- Because this is a different formulation of an approved drug, safety profile is somewhat known
- Area of MTD is 36 to 45 *mg/m²*

Iasonos and O'Quigley, 2012 Stats Med

- Propose: setting the parameters at the end of stage 1 before modeling initiates
- Use the stage 1 data to inform the choice of CRM tuning parameters
- Until now, parameters for CRM were selected up front, at the design stage

Protocol development and approval

- Getting timely IRB approval from multiple sites
- Protocol Scientific Review
  - Iasonos, Gonen, Bosl, JCO 2015
  - Provides guidelines on the scientific review of model based Phase I protocols
  - Petroni G et al. Stats Med 2016
  - timing and responsibility of data and model updates

- Provide Operating Characteristics
  - How accurate ?
  - At which levels will patients be treated?
  - Aggressive vs conservative dose escalation?

Software

Software for Drug Combinations

http://www.faculty.virginia.edu/model-based_dose-finding/

Wages, Conaway, O'Quigley, Biometrics, 2011

Available R Code:

- Phase I Trials of Combinations of Agents - Implementation
- Phase I Trials of Combinations of Agents - Simulation
- Phase I Trials for Multiple Treatment Schedules - Simulation

- Nonparametric Optimal Benchmark

Software for Retrospective analysis

Iasonos and Ostrovnaya 2011, Stats Med

http://onlinelibrary.wiley.com/doi/10.1002/sim4206/suppinfo

- Supplementary material
  CMLE R function
  Input: matrix data, target rate and min, max
  Output: MTD, predicted DLT probabilities

Iasonos and Ostrovnaya 2011, Stats Med
http://onlinelibrary.wiley.com/doi/10.1002/sim4206/suppinfo

Software for more advanced problems

- TITE CRM

dfcrm R package (Ken Cheung)

http://cran.rproject.org/web/packages/dfcrm/

Software for more advanced problems

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getprior: skeleton so that OC are met

cohere : coherence status of 2 stage CRM

crmsens: model sensitivity via indifference intervals

Writing your own software

CRM is based on a binomial likelihood

Functions in R to find MLE

optimize

optim

To integrate posterior density

integrate

SIMPLE

CRM: sequential estimation

How to estimate a?

Likelihood CRM:

$$\mathcal{L}_N(a) = \sum_{j=1}^{N} [y_j \frac{\psi'}{\psi}(x_j, a) + (1 - y_j) \frac{-\psi'}{1-\psi}(x_j, a)].$$

Bayesian CRM:

$$f(a, \Omega_{j+1}) = \frac{g(a) \prod_1^j \phi(d_l, y_l, a)}{\int g(u) \prod_1^j \phi(d_l, y_l, u)\, du}$$

where $\phi(d_j, y_j, a) = \psi^{y_j}(d_j, a) (1 - \psi(d_j, a))^{(1-y_j)}$

and $g(a)$ is the prior density.

Software

MDAnderson Cancer Center

https://biostatistics.mdanderson.org/

SoftwareDownload/Default.aspx

- CRM Simulator (1990 O'Quigley et al)
- BMA CRM (Yin and Yuan, JASA 2009)
- Bivariate extension of the CRM

Other software

- Babb, J., Rogatko, A., Zacks, S. (1998). EWOC

http://biostatistics.csmc.edu/ewoc/index.php

http://sisyphus.emory.edu/ewoc.html

- Chen Z, et al 2012 "Dose escalation with overdose control using a quasi-continuous toxicity"

THANK YOU

Questions

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