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Answer to the Question # 01

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Continual Reassessment Method (CRM) (1990) design for Phase I

(a)

CRM is a model-based approach which identifies the Maximum Tolerated Dose (MTD) of a new drug or treatment in a phase I clinical trial. CRM is a Bayesian adaptive design, and it uses a statistical model to determine the probability of dose-limiting toxicities (DLTs) at different dose levels. After that it adapts the dose level for the next cohort of patients based on the observed toxicity outcomes.

It is explained below how to set up this model and its parameters:

1) **Define a set of possible dose levels:** The first step of CRM is to define a set of possible dose levels that will be used in the trial. These dose levels cover the expected range of doses that will be used in later phases of development.

2) **Setting up prior probabilities for the probability of DLT at each dose level:** For each dose level, assign a prior probability distribution for the probability of DLT. The choice of prior distribution should be based on any available preclinical and clinical data on toxicity outcomes for the drug or treatment.

3) **Determine the Target Toxicity Rate (TTR):** The TTR is the probability of DLT at the target dose level, which is the dose level that is believed to be closest to MTD. The TTR is determined based on the available preclinical and clinical data on toxicity outcomes, and it should be a clinically relevant threshold for toxicity.

4) **Select a dose-toxicity model:** The dose-toxicity model represents the relationship between dose level and probability of DLT. The most common model used in CRM is a logistic regression model, but other models can also be used.

5) **Estimate the parameters of the dose-toxicity model:** The parameters of the dose-toxicity model, including the intercept and slope, need to be estimated based on the available preclinical and clinical data on toxicity outcomes.

   The CRM model involves **two key parameters**: **a)** Target Toxicity Rate (TTR) and **b)** Dose Toxicity Curve. The TTR means the probability of DLT at the target dose level, which is the dose level that is believed to be closest to the MTD. The dose-toxicity curve represents the relationship between dose level and probability of DLT and is typically modeled using a logistic regression function.

   To estimate these parameters, the prior distributions for the TTR and dose-toxicity curve need to be specified based on available preclinical and clinical data. The prior distributions are then updated after each cohort based on the observed DLTs using Bayesian updating techniques. The updated distributions for these parameters are then used to determine the next dose level to be assigned.

6) **Implement the trial:** The first cohort of patients is typically assigned to the lowest dose level, and the model is updated after each cohort based on the observed DLTs. The model then uses this information to determine the next dose level to be assigned to the next cohort, taking into account the goal of finding the MTD while minimizing the number of patients treated at toxic dose levels.

7) **Update the prior distributions for the dose-toxicity model:** After each cohort, the prior distributions for the dose-toxicity model are updated using Bayesian updating techniques based on the observed DLTs. This information is then used to determine the next dose level to be assigned.

8) **Determine the MTD:** The MTD is typically determined based on the estimated dose-toxicity curve and the target toxicity rate. Once the MTD is identified, the trial can be stopped or expanded to a larger cohort to further confirm the safety and efficacy of the treatment.

Overall, CRM is a powerful tool for efficiently identifying the MTD of a new drug or treatment in a phase I clinical trial. However, careful consideration of prior distributions and careful monitoring of toxicity outcomes are essential to ensure that the trial is conducted carefully.

(b) Simulation #1 - Sample size 20:

Scenario	Dose level	True Toxicity Probability	Mean Number of Patients	Probability of Selected Dose
1	1	0.10	8.17	0.37
	2	0.20	7.48	0.45
	3	0.30	3.18	0.15
	4	0.50	0.79	0.01
2	1	0.20	11.28	0.56
	2	0.30	5.02	0.23
	3	0.45	1.20	0.02
	4	0.60	0.24	0.00
3	1	0.25	11.22	0.51
	2	0.35	3.78	0.14
	3	0.45	0.89	0.01
	4	0.55	0.19	0.00

Simulation #2 - Sample size 36:

Scenario	Dose level	True Toxicity Probability	Mean Number of Patients	Probability of Selected Dose
1	1	0.10	14.11	0.36
	2	0.20	14.86	0.50
	3	0.30	5.38	0.11
	4	0.50	0.83	0.00
2	1	0.20	19.76	0.53
	2	0.30	8.6	0.20
	3	0.45	1.31	0.00
	4	0.60	0.23	0.00
3	1	0.25	18.54	0.43
	2	0.35	5.73	0.10
	3	0.45	1.00	0.00
	4	0.55	0.20	0.00

(C) With different prior skeletons:

Simulation #1 - Sample size 20:

Scenario	Dose level	True Toxicity Probability	Mean Number of Patients	Probability of Selected Dose
1	1	0.10	8.6	0.35
	2	0.20	6.27	0.42
	3	0.30	3.04	0.15
	4	0.50	1.14	0.01
2	1	0.20	10.72	0.51
	2	0.30	3.72	0.15
	3	0.45	1.25	0.02
	4	0.60	0.31	0.00
3	1	0.25	10.17	0.42
	2	0.35	2.67	0.07
	3	0.45	0.88	0.01
	4	0.55	0.25	0.00

Simulation #2 - Sample size 36:

Scenario	Dose level	True Toxicity Probability	Mean Number of Patients	Probability of Selected Dose
1	1	0.10	13.94	0.32
	2	0.20	13.51	0.50
	3	0.30	5.12	0.10
	4	0.50	1.34	0.00
2	1	0.20	18.52	0.48
	2	0.30	5.65	0.1
	3	0.45	1.37	0.00
	4	0.60	0.31	0.00
3	1	0.25	16.06	0.33
	2	0.35	3.52	0.03
	3	0.45	0.94	0.00
	4	0.55	0.26	0.00

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Answer to the Question # 02

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(a)

Doing 10000 simulations for 3+3 using R

Scenario	Dose level	True Toxicity Probability	Mean Number of Patients	Probability of Exceeding MTD
1	1	0.10	3.7203	0.1005
	2	0.20	3.7542	0.2863813
	3	0.30	2.7945	0.5058420
	4	0.50	1.3119	0.8398487
2	1	0.20	4.1493	0.2944
	2	0.30	3.0270	0.4929138
	3	0.45	1.4733	0.7663499
	4	0.60	0.3069	0.9270335
3	1	0.25	4.2633	0.4078
	2	0.35	2.5803	0.6004728
	3	0.45	1.0131	0.7662722
	4	0.55	0.2166	0.8915009

The probability of selecting the dose and **probability of exceeding MTD** are not same. Because the probability of selecting a dose means - the likelihood that a particular dose level will be selected for testing in the trial. This probability is often based on preclinical data, pharmacokinetic modeling, and other information about the drug and the disease being treated.

On the other hand, the probability of exceeding MTD means the likelihood that a particular dose level will cause unacceptable toxicity or adverse events that exceed the predefined MTD. This probability is typically estimated based on the data collected during the trial.

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Answer to the Question # 02

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(b)

The 3+3 design and CRM are both legal approaches to determining the MTD of a new treatment in a clinical trial. The 3+3 design is more simple and more straightforward, it is easy to implement. But it does not have specific dose response modeling and does not provide a formal estimate of the MTD for each trial. On the other hand, CRM is more complex, but allows for more efficient dose finding and provides an estimation of MTD. The choice between these methods depends on the specific context of the trial, including the goals of the trial, the available resources, and the expertise of the investigators**.**

Below I have explained some pros and cons of these models.

3+3 Design

Pros:

1) It is very simple and easy to understand for clinicians, researchers, and patients.
2) Commonly used and well-established approach all over the world for finding dose in phase I trials.
3) As it is very simple to implement, it can quickly identify a safe and tolerable dose for further study.

4) Requires fewer patients than other designs such as CRM.

5) It is useful for drugs with known toxicity profiles.

Cons:

1) It does not allow the estimation of the maximum tolerated dose (MTD).

2) Can be prone to underestimating or overestimating the true MTD.

3) Does not allow for adjustment of the dose during the trial based on accumulating data.

Continual Reassessment Method (CRM)

Pros:

1) It provides a formal estimation of the MTD, along with a confidence interval, which allows for better comparison of results across trials and more informed decision-making.

2) It also provides a dose-response modeling, which can be important for understanding the relationship between dose and response.

3) This model requires fewer patients than the 3+3 design.

4) The dose of the CRM can be adjusted during the trial based on accumulating data. So, it is more efficient and accurate for dose finding.

5) It is less likely to underestimate or overestimate the true MTD than the 3+3 design.

Cons:

1) This design is more complex, and it requires more statistical expertise to implement than the 3+3 design.

2) As it is more complex, it may require more time and resources to plan and execute than the 3+3 design.
3) It may be sensitive to the choice of statistical model that is used for finding dose. And this can affect the results.

4) May not be suitable for drugs with unknown or complex toxicity profiles, as the model may not be able to accurately estimate the MTD in these cases.

Overall, both the 3+3 design and CRM have their own advantages and disadvantages, and the choice of method should depend on the specific context of the trial, including the goals of the trial, the available resources, and the expertise of the investigators.