An overview of modern dose-finding designs for Phase I clinical trials: Part II

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Background - Healthy volunteer studies

Objectives:

Find safe and potentially efficacious doses for study in phase II

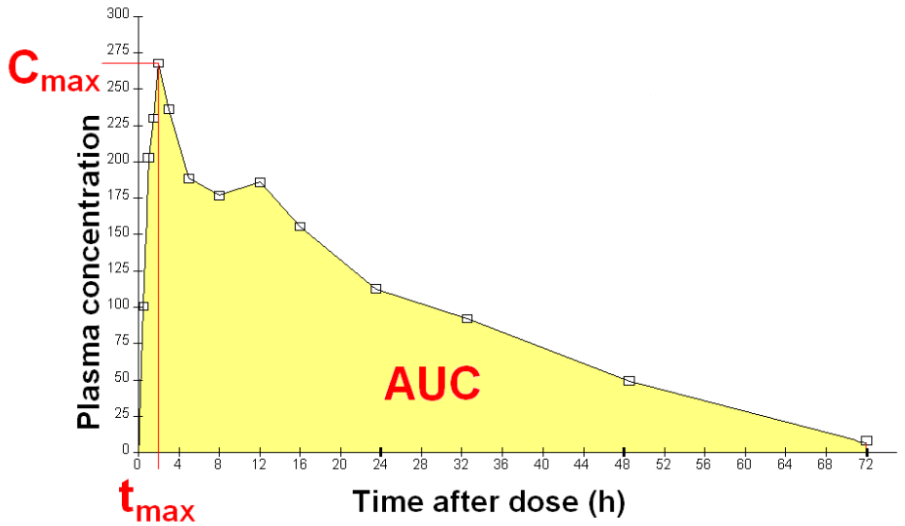
(i) avoid excessive plasma concentrations

(ii) avoid excessive rates of adverse events

The highest dose achieving (i) and (ii) is the maximum tolerated dose (MTD)

Pharmacokinetics Outcomes

- Area under the Curve – AUC
- Maximum Concentration (C_{max})
- The time when the maximum concentration is achieved
  - quantitative summaries



Traditional designs

Cross-over designs

	Subject							
Period	1	2	3	4	5	6	7	8
1	Placebo	Dose 1	Dose 1	Dose 1				
2	Dose 1	Placebo	Dose 2	Dose 2				
3	Dose 2	Dose 2	Placebo	Dose 3				
4	Dose 3	Dose 3	Dose 3	Placebo				
5					Placebo	Dose 4	Dose 4	Dose 4
6					Dose 4	Placebo	Dose 5	Dose 5
7					Dose 5	Dose 5	Placebo	Dose 6
8					Dose 6	Dose 6	Dose 6	Placebo

Bayesian models for the data

Consider the following model to such data

$$y_{ij} = \theta_0 + \theta_1 l_{ij} + s_i + \epsilon_{ij}$$

y_{ij} is the log(AUC) for the ith subject after their j^{th} active dose

l_{ij} is the log of the j^{th} active dose given to the i^{th} subject

$s_i \sim N(0, \tau^2)$ is a random effect for the i^{th} subject

$\epsilon_{ij} \sim N(0, \sigma^2)$ is a random error

$j = 1, \ldots, p_i;\ i = 1, \ldots, n;\ p = p_1 + \cdots + p_n;$

An approach by Whitehead *et.al.* (2001)

A conjugate prior density can be chosen:

- bivariate normal distribution for the vector of intercept and slope: $\boldsymbol{\theta} = (\theta_0, \theta_1)'$
- gamma distribution for the within patient $precision$: $\nu = \sigma^{-2}$
- a fixed value for the *within-subject correlation*: $\rho = \frac{\tau^2}{\tau^2+\sigma^2}$

Predictive distribution for y

Suppose that y is the log(AUC) for a new subject, treated at dose d, where $l = \log d$

It can be shown that the predictive distribution of y is

$$y = (\mu^{(0)} + \mu^{(1)} l) + t\sqrt{\frac{r\beta}{\alpha}}$$

where

$$r = (1-\rho)^{-1} + \boldsymbol{X}'\boldsymbol{Q}^{-1}\boldsymbol{X} \quad \text{and} \quad t \sim t_{2\alpha}$$

A subject who has been treated before has an individual predictive distribution, depending on their previous data.

A Bayesian dose-escalation procedure

- The subjects to be treated during the next period are available
- We have Bayesian subjective distributions for θ, ν and ρ (either prior or posterior)
- Choose the doses to be administered to each subject (or choose to stop the study)

A safety constraint

Too high an AUC may be dangerous

Suppose that L is considered to be upper safe limit for AUC

Only doses d for which the current Bayesian model $\Rightarrow$

$$P(AUC > L \mid d) \leq c_0$$

will be administered: c_0 might be taken as 0.05 or 0.20

If $d^\star$ satisfies

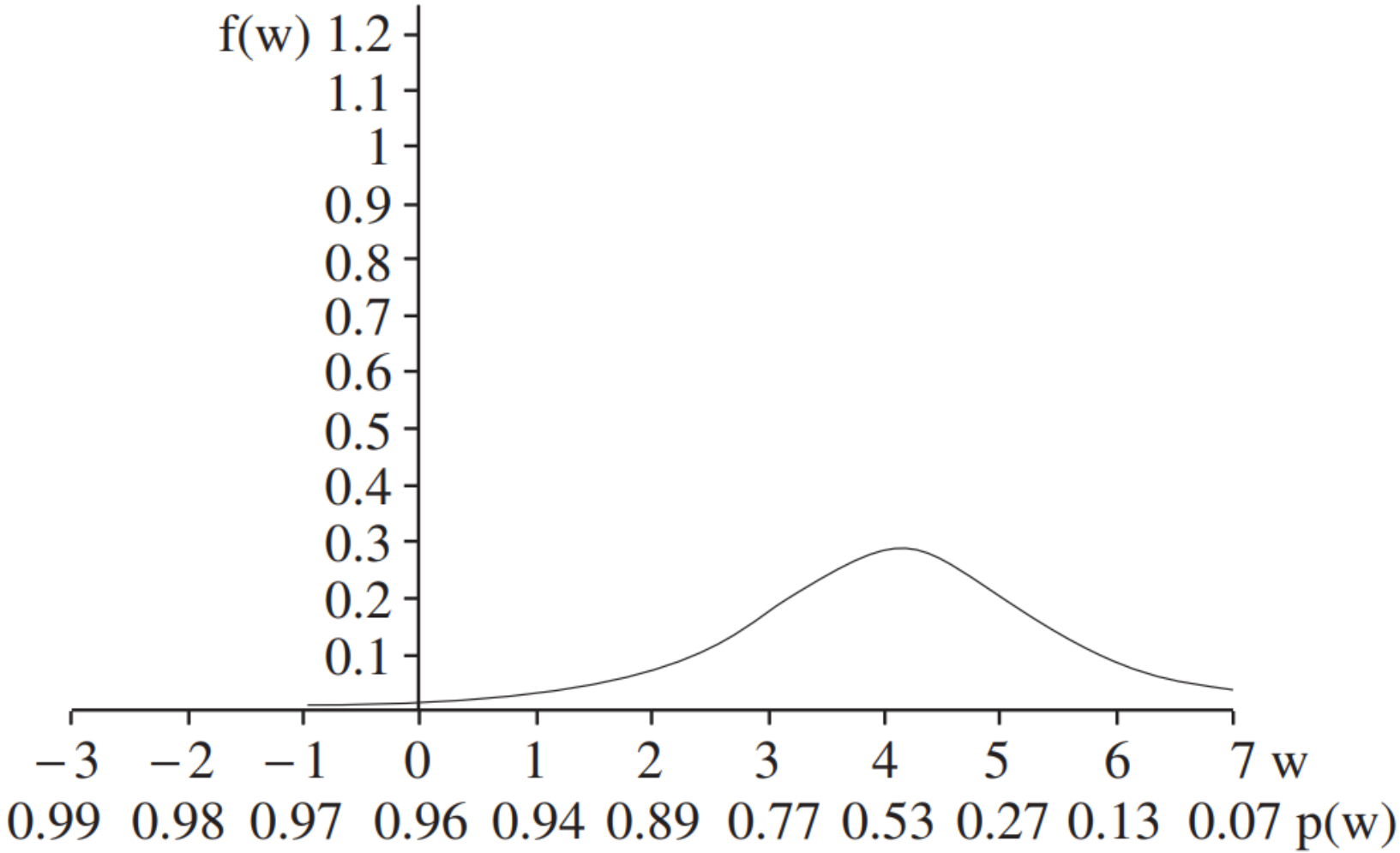
$$P(AUC > L \mid d^*) = c_0$$

then $d^\star$ is called the maximum safe dose

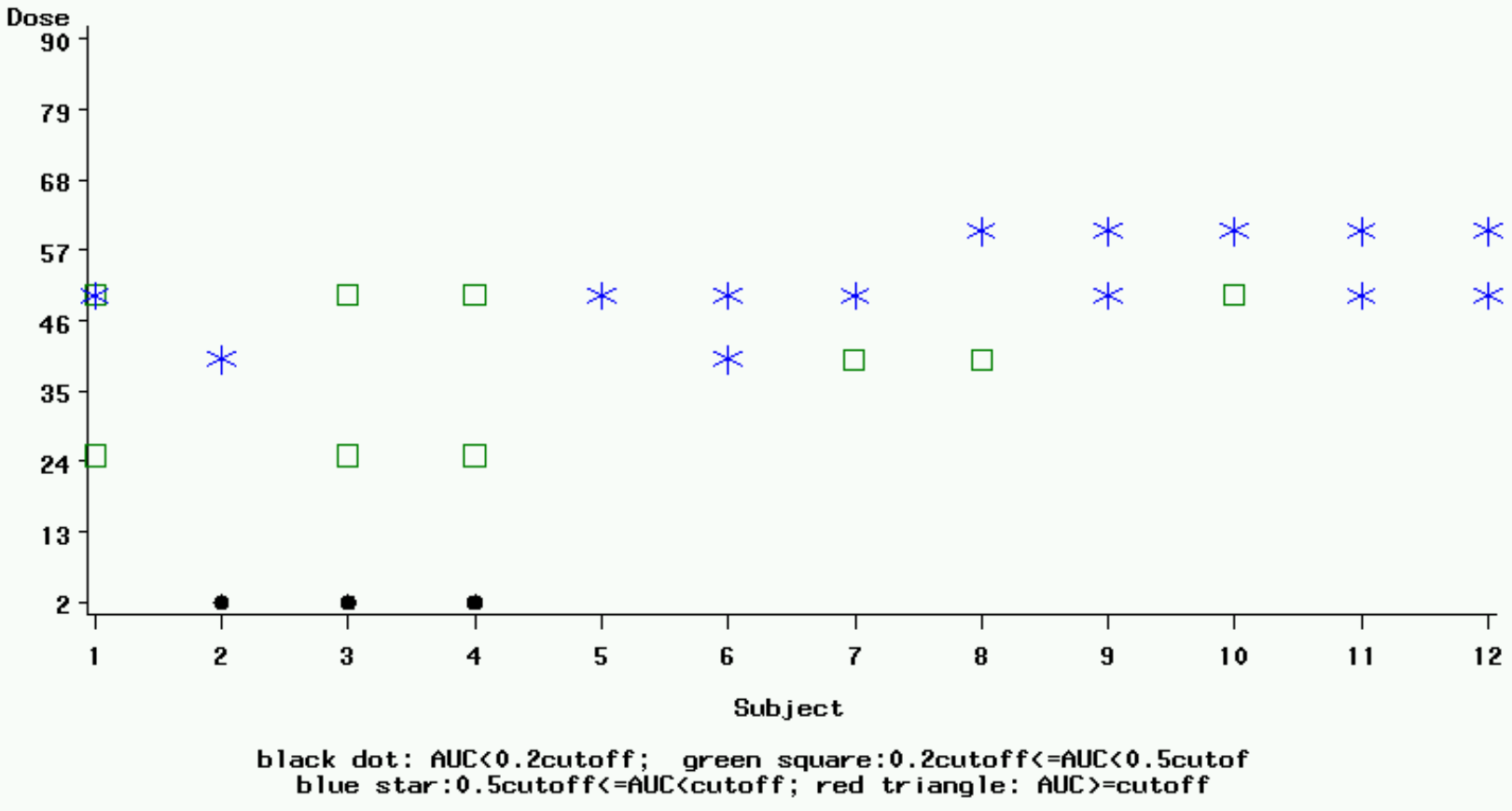
Example

- Doses: 2, 5, 10, 25, 40, 50, 60 and 80 mg
- Maximum number of cohorts: 3
- Number of periods: 4 per cohort
- Number of subjects: 4 per period (one placebo)
- Response: AUC
- Safety cut-off limit (for AUC) : $L = 100$
- Decision criterion: Variance Gain
- Stopping rule: stop when the maximum cohort size is reached or no dose appears safe

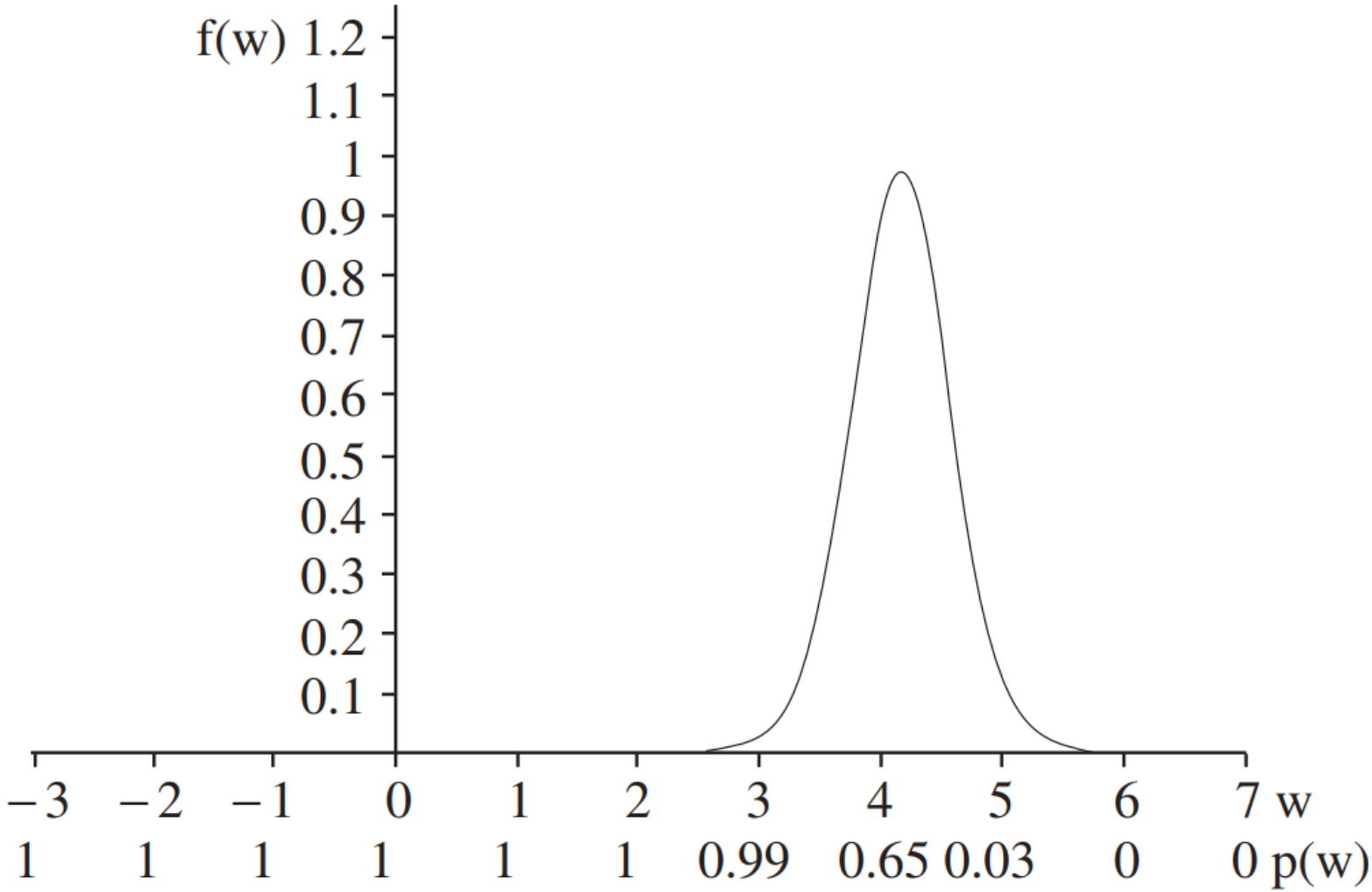
Prior density for log(AUC) of a new, untested subject, at dose 60mg



End of study - plot of subjects by dose



Posterior density for log(AUC) of a new, untested subject at dose 60mg at end of trial



Back to in-patients dose-escalation trials

Single agent dose-escalation designs

Fundamental assumption of many single-agent Phase I designs is a **monotonic** dose-response relationship

Cannot be applied to:

- Combination trials with many treatments
- Scheduling of drugs
- Non-monotonic dose-toxicity relations

Unknown ordering problem. Example

Let us consider drugs combination dose-escalation trial with

- 3 dose levels of drug A: A_1, A_2, A_3
- 3 dose levels of drug B: B_1, B_2, B_3

$(A_1; B_3)$	$(A_2; B_3)$	$(A_3; B_3)$
$(A_1; B_2)$	$(A_2; B_2)$	$(A_3; B_2)$
$(A_1; B_1)$	$(A_2; B_1)$	$(A_3; B_1)$

Even assuming monotonicity one drug being fixed, we cannot order
$(A_1; B_2)$ and $(A_2; B_1)$;
$(A_1; B_3)$ and $(A_2; B_1)$;
$(A_1; B_3)$ and $(A_3; B_1)$ and so on...

Need in Dual Endpoint Extensions

- Many of clinical trial that require to relax monotonicity assumption are in molecularly-targeted agents (MTA);
- For these, the monotonicity assumption might not hold even within the dose.
- Phase I/II studies considering both **activity and toxicity** become more common

We will briefly consider **two designs** that could be applied to a variety of clinical trials with binary toxicity & efficacy endpoints.

- Partial Ordering CRM (POCRM) by Wages *et.al* (2011)
- Information-Theoretic Approach by Mozgunov and Jaki (2019)

Partial ordering CRM (POCRM)
Wages et al. (2011)

Overall Strategy:

1. Define a number of possible toxicity orderings
2. Run a CRM model using each of these orderings
3. Identify the ordering which is the most likely is the true one
4. Apply the original CRM to the estimated ordering.

Partial ordering CRM (POCRM)

- Working model for probability of toxicity for regimen i under ordering m is

$$p_{im} = \pi_{im}^{\alpha_m}$$

- As before, π_{im} are standardized units representing the discrete dose levels (i.e. skeletons of the model)

Example of Working Models

Firstly, define prior toxicity probabilities (skeleton values), e.g.

$$(0.10, 0.20, 0.30, 0.40)$$

Applied to the combination trial with 2×2 doses

Combo 3 $(A_1; B_2)$	Combo 4 $(A_2; B_2)$
Combo 1 $(A_1; B_1)$	Combo 2 $(A_2; B_1)$

	Combinations			
Ordering	1	2	3	4
1	$(0.10)^{\alpha_1}$	$(0.20)^{\alpha_1}$	$(0.30)^{\alpha_1}$	$(0.40)^{\alpha_1}$
2	$(0.10)^{\alpha_1}$	$(0.30)^{\alpha_1}$	$(0.20)^{\alpha_1}$	$(0.40)^{\alpha_1}$

Table: Working models consistent with each ordering

Estimation and allocation

- As data accumulate, estimate α_m for each ordering
- Choose the ordering that the data indicates to be **the most likely** one (denoted by $m^\star$)
- Proceed as with the original CRM
- Repeat the same for the efficacy

Information-Theoretic Design by Mozgunov and Jaki (2019)

Consider a Phase I/II trial with 3 outcomes (under the independence assumption).

Outcome	Probability	Optimal
Efficacy + No Tox	$p_e \times (1 - p_t)$	$\gamma_e \times (1 - \gamma_t)$
No Efficacy + No Tox	$(1 - p_e) \times (1 - p_t)$	$(1 - \gamma_e) \times (1 - \gamma_t)$
Tox	p_t	γ_t

Use the criterion

$$\delta\left(\boldsymbol{\alpha}, \boldsymbol{\gamma}\right) := \frac{\left(\gamma_e \times (1 - \gamma_t)\right)^2}{p_e \times (1 - p_t)} + \frac{\left((1 - \gamma_e) \times (1 - \gamma_t)\right)^2}{(1 - p_e) \times (1 - p_t)} + \frac{(\gamma_t)^2}{p_t} - 1.$$

to govern treatment selection.

Estimates:

$$\hat{p}_t^{(n)} = \frac{x_t}{n}, \qquad \hat{p}_e^{(n)} = \frac{x_e}{n}. \tag{1}$$

and ‘plug-in‘ in the trade-off function

$$\hat{\delta}_j^{(k)} = \delta(\hat{p}_t^{(n)}, \hat{p}_e^{(n)}, \gamma_t, \gamma_e).$$

Conclusion

- Both POCRM and Information-Theoretic methods are very flexible in where they are applicable
  - in terms of type of trials (combination, dose-schedule, combination-schedule)
  - in terms of number of endpoints

- POCRM (being a model-based design) reaches high regimens quicker $\rightarrow$ higher average number of toxicities but also higher average number of responses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