3ODM x PtW, a quantitative framework combining PoC assessment and optimal dose selection in a randomized phase 2 trial

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Background

FDA Project Optimus

Reforming the dose optimization and dose selection paradigm in oncology

- Moving the oncology dose selection from Maximum Tolerated Dose (MTD) to Optimal Dose (OD) before initiating confirmatory trials
- Recommend to perform randomized trials with at least two doses before selecting a Recommended Phase 2 Dose (RP2D)

3-Outcome Decision Making (3ODM) [1]

Decision-making based on 2-outcome is not well suited for exploratory phases

Clinical thresholds:

- **Lower Reference Value (LRV):** smallest clinically meaningful treatment effect for further development
- **Target value (TV):** desirable level of clinical activity to be commercially attractive

Dual criteria:

- **Significance criterion:** What is the probability that the true treatment effect is larger than LRV?
- **Relevance criterion:** What is the probability that the true treatment effect is larger than TV?

Decision rules:

- No-go: $PP(\theta > LRV|p,d) < \tau_{LRV}$ & $PP(\theta > TV|p,d) < \tau_{TV}$
- Go: $PP(\theta > LRV|p,d) > \tau_{LRV}$ & $PP(\theta > TV|p,d) > \tau_{TV}$
- Consider: otherwise

where:

- θ is the true treatment effect
- PP is the posterior probability, based on data (d) and prior (p)
- τ_{LRV} and τ_{TV} are levels of confidence to achieve to meet the significance and relevance criterion, respectively

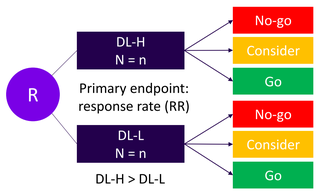
Existing pick-the-Winner (PtW) approaches

How to select the dose?

- Trials do not need to be powered to detect a statistically difference between doses: high (DL-H) and low (DL-L)
- Different approaches have been proposed:
  - Simon et al. [2]: pick the dose with the best point estimate
  - Chen et al. [3]: a 2-stage Simon design is applied to each dose. If both doses meet the final number of responders threshold of the 2-stage Simon design , the selection of the dose is based on the posterior probability that the true response rate (RR) of DL-H is greater than DL-L is greater than a pre-specified threshold. However, no quantitative rule is given regarding the selection of this threshold.

3ODM x PtW

Trial design



Final trial outcome

DL-L	DL-H	Trial outcome
No-go	No-go	No-go
No-go	Consider	Consider DL-H
No-go	Go	Go DL-H
Consider	No-go	Consider DL-L
Consider	Consider	PtW
Consider	Go	PtW
Go	No-go	Go DL-L
Go	Consider	Go DL-L
Go	Go	PtW

The recommended trial 3ODM outcome (last column) based on the two doses 3ODM outcome may be modified according to the trial context

PtW approach

Rule philosophy

- PtW is triggered when both doses achieve either a Consider or Go decision
- Selection of the lowest dose is preferred (based on factors such as better safety, PRO, etc.) except if there is strong evidence that the highest dose yields to greater RR

Statistical rule

Select DL-H if $\mathbf{PP}(RR_{\mathrm{DL-H}} > RR_{\mathrm{DL-L}}|\boldsymbol{d},\boldsymbol{p}) > \boldsymbol{\gamma}$
Otherwise, select DL-L

Where:

- PP is the posterior probability, based on data (d) and prior (p)
- RR_{DL-i} is the RR of dose i (high: H or low: L)
- γ corresponds to the level of confidence to achieve in order to select DL-H. The greater γ, the less likely to select DL-H

Illustrative case study

3ODM parameters

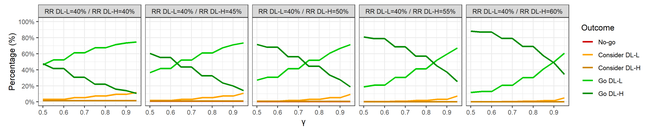
3ODM parameters

- N = 20 (by dose)
- LRV = 20% and $\tau_{LRV} = 0.8$
- TV = 40% and $\tau_{TV} = 0.2$
- Non-informative prior $B(0.5,0.5)$

3ODM decision rules

- No-go if ORR 5≤20 (25%)
- Consider if ORR = 6/20 (30%)
- Go if ORR ≥7/20 (35%)

Operating characteristics according to γ when both doses have a true RR ≥ TV = 40%



Δ% corresponds to the difference in true RR between DL-H and DL-L

How to select γ?

Rule philosophy

Achieve a balance between:

- Maximizing the selection of DL-L when there is no difference in RR
- Maximizing the selection of DL-H when there is Δ% difference in RR between doses, where Δ% is considered clinically meaningful

Statistical rule

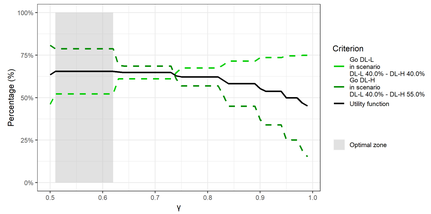
Maximizes the following utility function

$$\gamma = \underset{\gamma \in [0.5,1)}{\operatorname{argmax}} \begin{Bmatrix} w_1 * P(select\ DL-L\ |RR_{DL-L} = RR\%, RR_{DL-H} = RR\%) + \\ w_2 * P(select\ DL-H\ |RR_{DL-L} = RR\%, RR_{DL-H} = RR\% + \Delta\%) \end{Bmatrix}$$

Where:

- RR is the true response rate used to assess the utility function (e.g., TV)
- w_1 and w_2 are pre-defined weights reflecting the importance of the correct decision in either scenario, with $w_1 + w_2 = 1$

Utility function according to γ



Function is maximized when $\gamma \in [0.51 - 0.62]$ under the following parameters

- $RR = \mathrm{TV} = 40\%$
- $w_1 = w_2 = 0.5$
- $\Delta\% = 15\%$

What is the impact on 3ODM operating characteristics?

3ODM operating characteristics (by dose)

True RR	Probability (%) of...		
	No-go	Consider	Go
LRV = 20%	83.9	14.1	1.9
Mid = 30%	30.9	39.5	29.7
TV = 40%	3.5	17.6	78.9

3ODM x PtW operating characteristics

True RR DL-L / DL-H	Probability (%) of...					
	No-go	Consider DL-L	Consider DL-H	Go DL-L	Go DL-H	Go Any
20% / 20%	**64.7**	10.0	8.8	8.5	8.1	**16.6**
30% / 30%	17.3	11.7	8.0	33.8	29.2	63.0
40% / 40%	1.6	3.1	1.6	**52.2**	**41.6**	93.7
40% / 45%	0.7	1.6	0.9	41.4	55.3	96.8
40% / 50%	0.3	0.7	0.5	30.6	68.0	98.6
40% / 55%	0.1	0.3	0.2	**20.8**	**78.7**	99.5
40% / 60%	0.0	0.1	0.1	12.9	87.0	99.8

Multiplicity of doses:

Due to the multiplicity of doses, the likelihood of Go with either dose at the end of trial (Go any) is increased in all scenarios

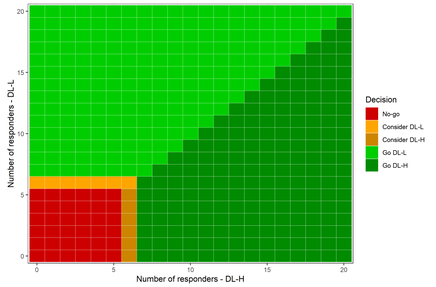
- 3ODM parameters can be adjusted to control the inflation, e.g., a wider consider zone yields better control of Go decision of either dose (Go any), at the expenses of more chance to fall in the inconclusive zone (Consider DL-L or Consider DL-H)

Additional considerations:

- Δ%: the lower Δ%, the larger the sample size needed to ensure adequate probability to select the right dose
  - With typical dose optimization sample size (20-40 per dose), the design will yield suboptimal operating characteristics when Δ%<10%

What is the final trial outcome?

Trial outcome summary matrix



Scenario example when pick-the-winner is triggered

Observed #resp DL-L (outcome)	Observed #resp DL-H (outcome)	$PP(RR_{DL-H} > RR_{DL-L}\|d,p)$	Outcome
6 (Consider)	6 (Consider)	50.0%	Consider DL-L
6 (Consider)	7 (Go)	63.2%	Go DL-H
7 (Go)	7 (Go)	50.0%	Go DL-L
7 (Go)	8 (Go)	62.8%	Go DL-H
8 (Go)	8 (Go)	50.0%	Go DL-L
8 (Go)	9 (Go)	62.5%	Go DL-H
...			

$PP(RR_{DL-H} > RR_{DL-L}|d,p)$ is the posterior probability that the true RR for DL-H is greater than the true RR of DL-L according to the data (d) and prior (p)
Outcome: DL-H is selected if $\mathrm{PP}(\mathrm{RR}_{\mathrm{DL-H}} > \mathrm{RR}_{\mathrm{DL-L}}|d,p) > 60\%$; otherwise, DL-L is selected

Key consideration in implementing 3ODM x PtW approach

When should 3ODM x PtW be considered?

- When a simple quantitative method is needed to guide dose selection in a randomized dose expansion based on a single antitumor activity endpoint. Eventually, the dose selection is made based on an assessment of the totality of data (antitumor activity, safety, PK, PD,...).
- A 2-stage design can be considered, e.g., to allow early futility assessment or consider dropping a dose at IA. Futility rules could be based on the predictive probability of No-go of a dose at the end of the trial.
- Possible extension of the method includes considering multiple endpoints (e.g., activity/safety) (*ongoing work*).

Pros

- Bayesian posterior probability provides a more robust quantitative metric to select the winner, in contrast to the pick-the winner approach from Simon et al. [2] which simply relies on point estimate.
- PtW threshold γ is quantitively optimized in order to balance correct dose selection under clinically meaningful scenarios.
- Provides good operating characteristics with typical dose optimization sample size to identify the optimal dose when the clinically meaningful difference to distinguish two doses is an absolute difference (Δ%) of at least 10%.
- Could leverage historical data through prior distribution if dose-efficacy data are available (e.g., small expansion before dose optimization).

Cons

- Do not characterize the full dose- or exposure-efficacy curve.
- Minimally clinically meaningful difference between two doses Δ% can be difficult to specify (based on historical/competitor data).
- If one dose barely meets the Go criterion and the other barely misses it, the dose selected could be the dose in the Consider zone.
- Do not control for multiple doses (increase the risk of detecting a signal when there is none), although this can be addressed by considering stricter 3ODM parameters (e.g., wider Consider zone).
- Do not account for safety or tolerability in dose selection *(ongoing work).*

References

1. Quan, H., Chen, X., Lan, Y., Luo, X., Kubiak, R., Bonnet, N., & Paux, G. (2020). Applications of Bayesian analysis to proof-of-concept trial planning and decision making. In Pharmaceutical Statistics (Vol. 19, Issue 4, pp. 468–481). Wiley. https://doi.org/10.1002/pst.1985

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3. Chen, D.-T., Huang, P.-Y., Lin, H.-Y., Chiappori, A. A., Gabrilovich, D. I., Haura, E. B., Antonia, S. J., & Gray, J. E. (2017). A Bayesian pick-the-winner design in a randomized phase II clinical trial. In Oncotarget (Vol. 8, Issue 51, pp. 88376–88385). Impact Journals, LLC. https://doi.org/10.18632/oncotarget.19088

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