Seamless phase 2/3 design with benefit-risk driven treatment selection using multi-criteria decision analysis (MCDA)

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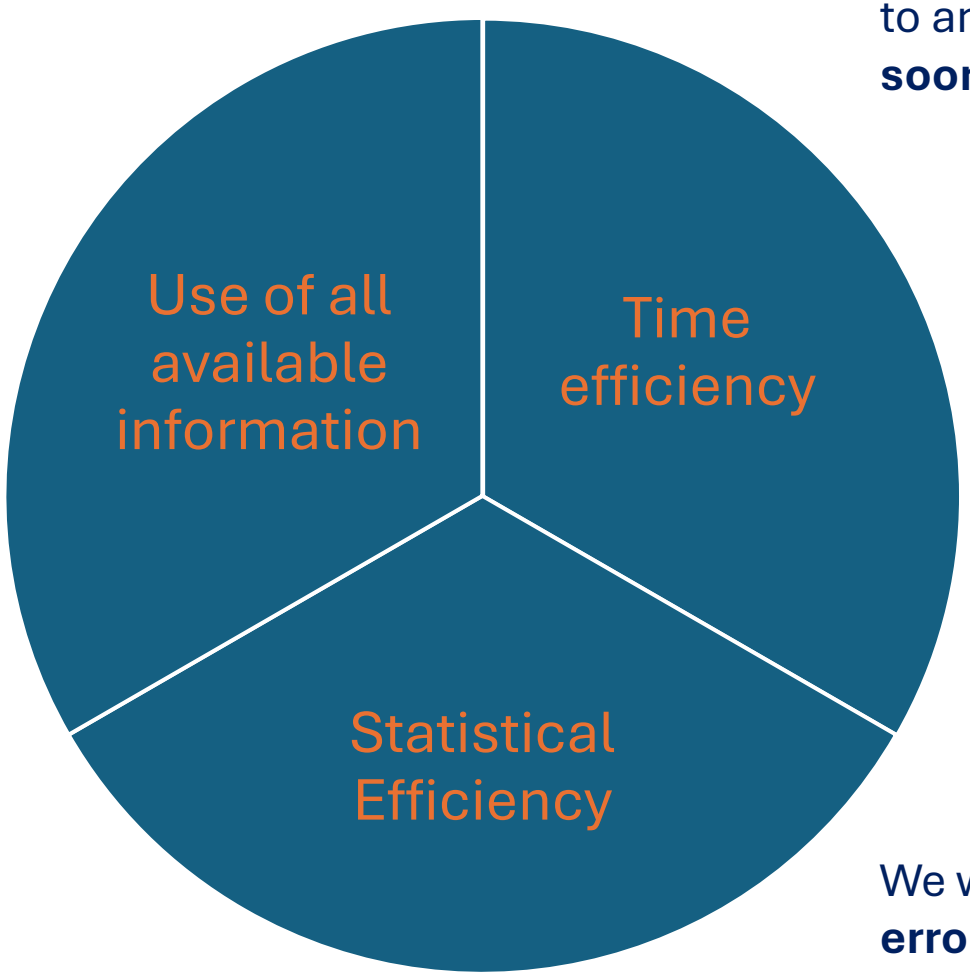
FDA project Optimus

U.S. FOOD & DRUG ADMINISTRATION

- Initiative by the **FDA Oncology Center of Excellence (2021)** to modernize dose optimization in oncology.
- Moves beyond **Maximum Tolerated Dose (MTD)** toward identifying the **Optimal Dose** based on both **efficacy and safety**.
- Emphasizes the need for a **comprehensive benefit-risk analysis** in dose selection.
- Promotes **early-phase studies with multiple dose levels**, integrating pharmacokinetics, pharmacodynamics, and clinical outcomes.
- Aims to improve **patient safety, treatment adherence**, and **overall therapeutic value**.

Motivation

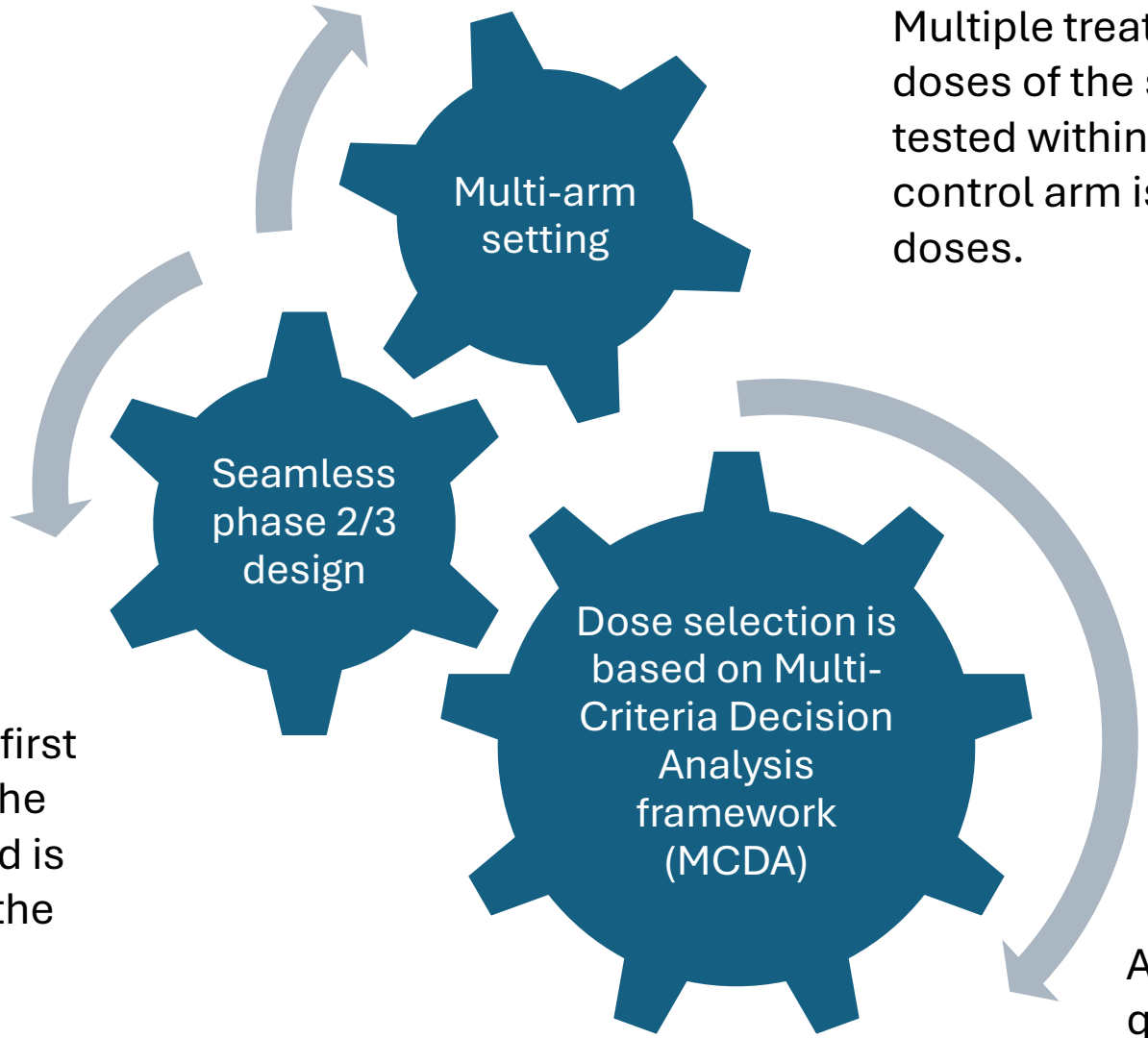
We want to use **all available safety/efficacy information** within the trial to make an informed decision-making.



We want to design a clinical trial able to answer the clinical question **as soon as possible**

We want to guarantee **that type I error is strictly controlled**, while guaranteeing adequate power.

Strategy



Multiple treatments or multiple doses of the same treatment are tested within the same trial. The control arm is shared among all doses.

Two stage design where the first stage is aimed at selecting the «best» arm, while the second is aimed at testing efficacy of the selected arm

Arm selection is based on a quantitative assessment of the benefit-risk profile of the experimental arms tested

Design
Construction

Trial design

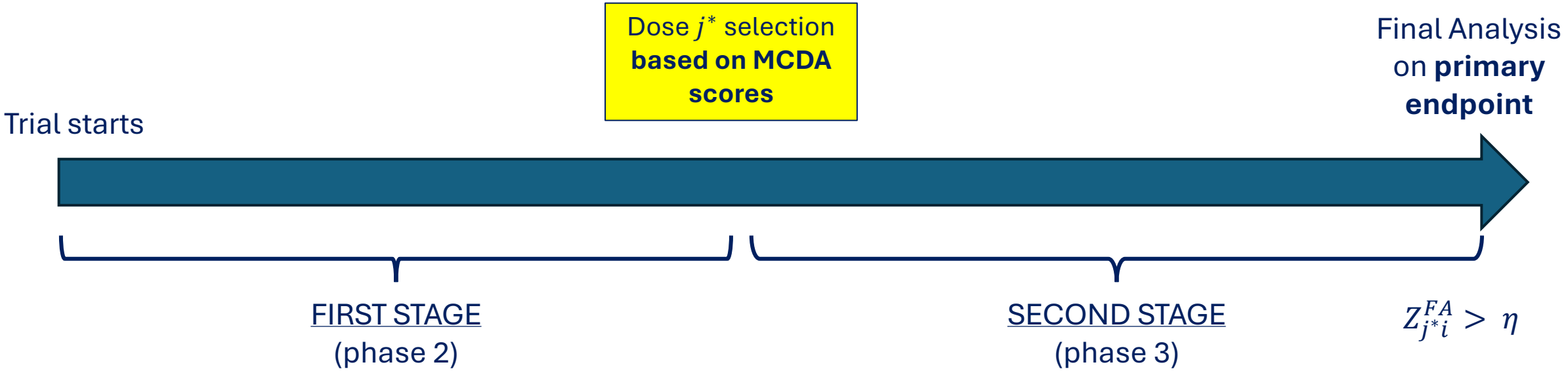
$j = 0,1,2,\dots,J$: index of the dose ($j = 0$ is the control arm)

$i = 1,2,\dots,I$: index of safety/efficacy endpoints ($i = 1$ is the primary efficacy endpoint)

θ_{ji} : j-th parameter of interest for the i-th dose

δ_{ji} : treatment difference in the i-th endpoint related to the j-th dose

$Z_{ji}^{\star}$: Test statistic for the i-th endpoint related to the j-th dose at the time point $\star = IA, FA$



Structure of the parameters MLEs

For each dose j the maximum likelihood estimators of the parameters of interest are supposed to follow a multivariate normal distribution

$$\begin{pmatrix} \hat{\theta}_{j1} \\ \vdots \\ \hat{\theta}_{jI} \end{pmatrix} = Normal\left(\begin{pmatrix} \theta_{j1} \\ \vdots \\ \theta_{jI} \end{pmatrix}, \begin{pmatrix} \sigma_{j1}^2 & \cdots & \rho_{1I}\sigma_{j1}\sigma_{jI} \\ \vdots & \ddots & \vdots \\ \rho_{1I}\sigma_{j1}\sigma_{jI} & \cdots & \sigma_{jI}^2 \end{pmatrix} \right)$$

- The standard errors σ_{ji} depend on the **Fisher information** available
- **Known correlations $\boldsymbol{\rho_{pq}}$** between parameters θ_p and θ_q are assumed known

Note that for many endpoints an asymptotic normal distribution for a transformation of the parameters of interest holds, e.g. the **log odds** for binary endpoints or the **log hazard** for survival endpoints

Multi-criteria decision analysis (MCDA)

It is a **structured approach** for making decisions that involve balancing multiple factors.
For each dose *j,* the true MCDA score is constructed as follows:

- An **upper and a lower bounds θ_{ji}^{U} and θ_{ji}^{L} are elicited**, which are the maximum and minimum values which is reasonable to observe for the corresponding parameters

- A factor-specific score is constructed plugging θ_{ji} in a ***partial value function*** $\boldsymbol{u(x)}$,

$$u(x) = \begin{cases} 0 \\ \frac{x - \theta_{ji}^{L}}{\theta_{ji}^{U} - \theta_{ji}^{L}} \\ 1 \end{cases}$$

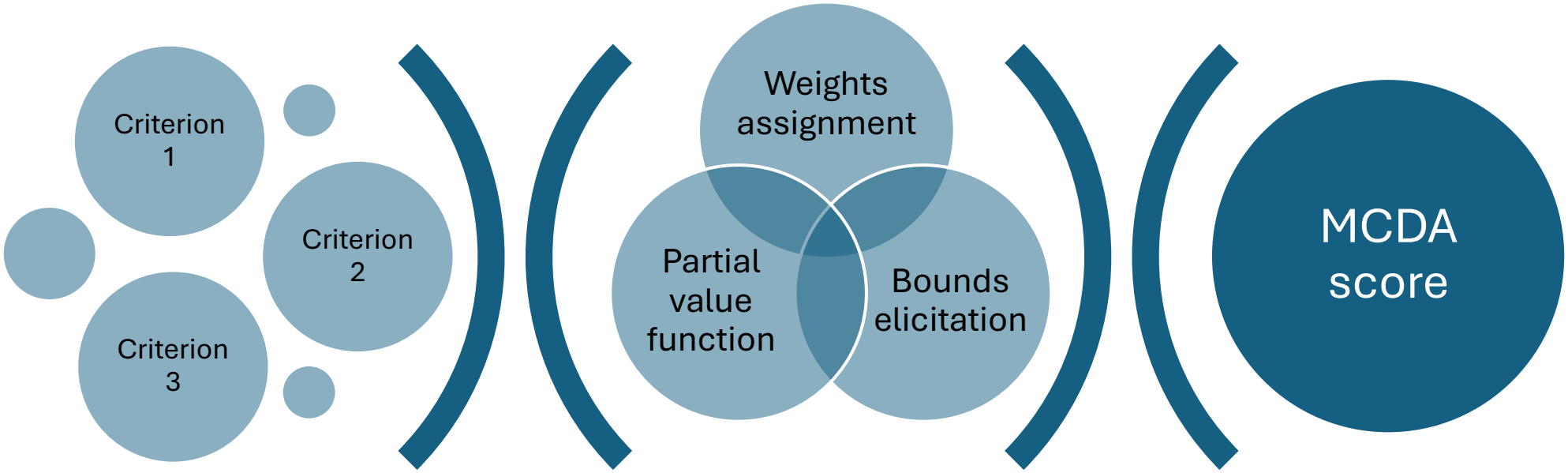
Linear Partial Value Function

- An aggregated score is constructed

$$MCDA_j = \sum_{j=1}^{J} w_j u(\theta_{ij}) \qquad \sum_{i=1}^{I} \omega_i = 1$$

A trivial way to estimate the MCDA scores consists in using the MLEs $\hat{\theta}_{ji}^{IA}$ instead of the true parameters θ_{ji}, however the variability of the estimates is not taken into account.

A visual representation



Criteria which may be relevant for decision making are defined a priori

Weights and bounds are assigned to each criteria based on internal discussion

An overall score is computed for each arm, indicating the overall benefit-risk profile of the specific dose/treatment

Probabilistic MCDA

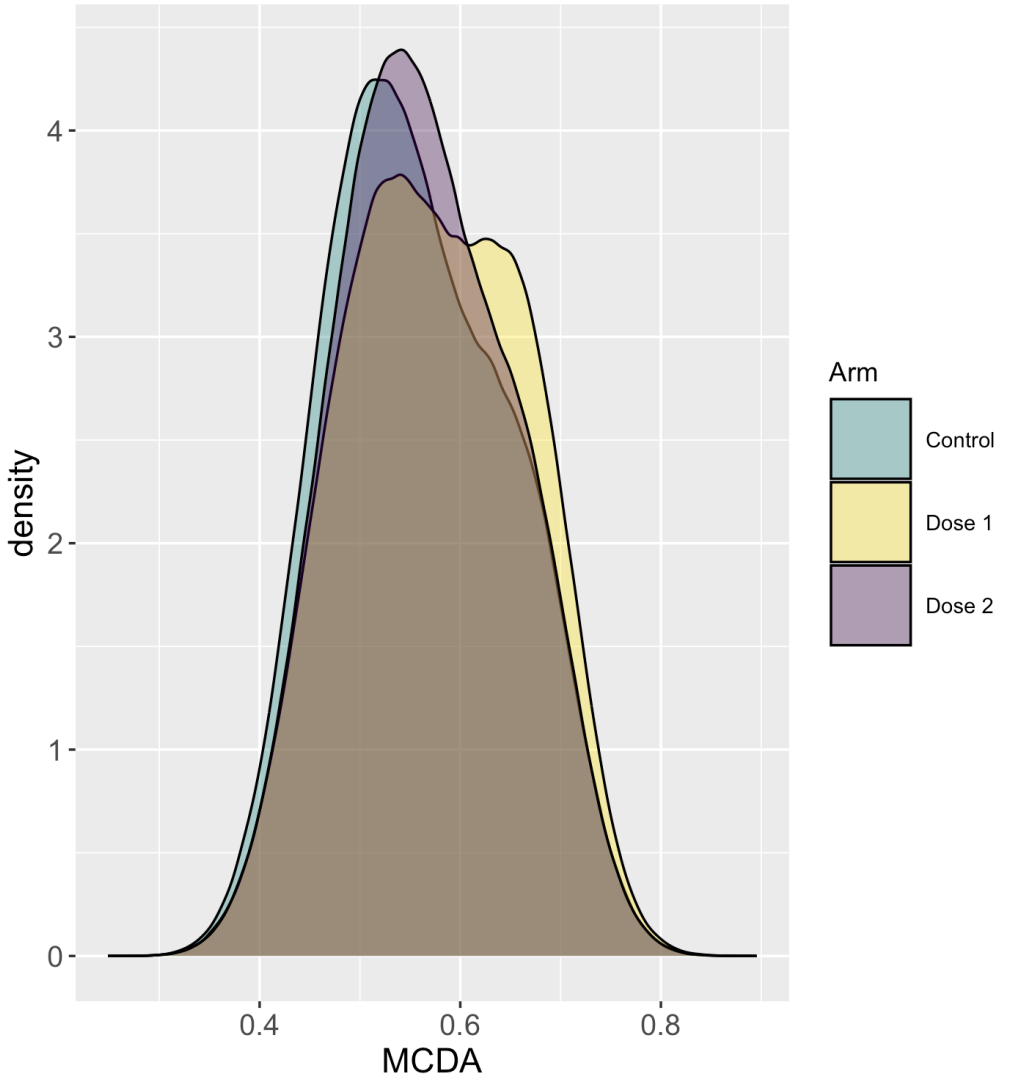
In order to account for the **variability in the parameters estimates**, we can work in a Bayesian framework, following this procedure:

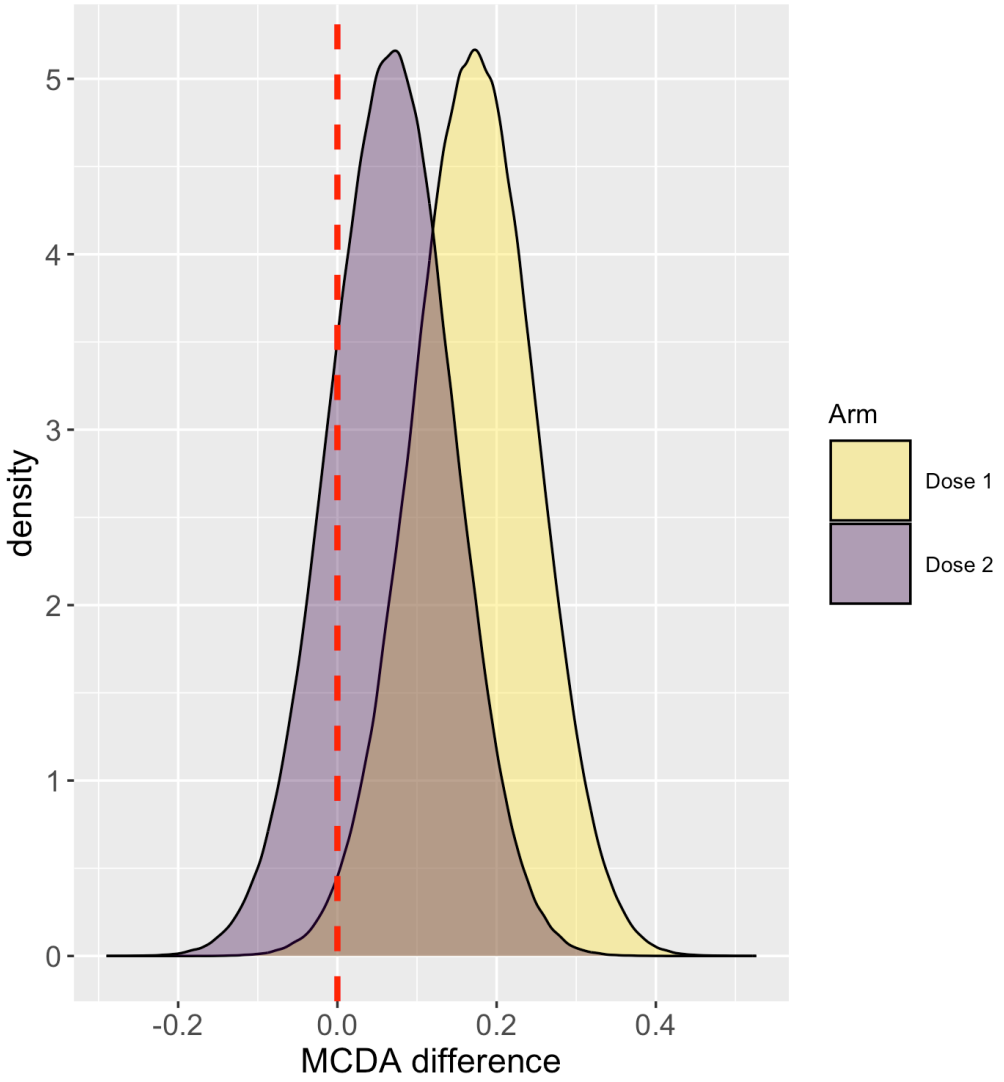
- Non informative **prior distributions** are assigned to the parameters, namely θ_{ji}^{prior}
- Once data are observed **posterior distributions** θ_{ji}^{post} are obtained via Bayesian rule
- The MCDA score is found transforming θ_{ji}^{post} as follows

$$MCDA_j = \sum_{j=1}^{J} w_j u\left(\theta_{ji}^{post}\right)$$

- For each active dose, the **posterior probability that its MCDA score is better than control** is found and the dose with higher probability is selected

$$P_j = \mathbb{P}\left(MCDA_j > MCDA_0\right) \qquad S = \underset{j=1,\dots,J}{\operatorname{argmax}} P_j$$





$P_1 = 0.99$
$P_2 = 0.81$

Dose 1 is selected

Distribution of the Z statistic (an idea..)

The interim test statistics Z_{S1}^{IA} can be written as

$$f_{Z_{S1}^{FA}}(x) = \sum_{j=1}^{J} \int_{-\infty}^{+\infty} f_{Z_{j1}^{FA} \mid Z_{j1}^{IA}}\left(z \mid Z_{j1}^{IA} = x\right) f_{Z_{j1}^{IA} \mid S}(x \mid S = j)\, f_S(j)\, dx\, dz$$

KEY ISSUE

The distribution of the selection random variable $S = \underset{j=1,\ldots,J}{\operatorname{argmax}} P_j$, has no analytical form, because:

- It is based on a **probabilistic criterion** (based on Bayesian posterior probabilities)
- The posterior distribution of the MCDA scores is **discontinuous** due to the truncation introduced by the linear partial value function $u(\cdot)$

Approximation of the selection criterion

Hypothesis:

The upper and lower bounds of the linear partial value function $u(\cdot)$, namely θ_i^U and θ_i^L are chosen so that the posterior probability $P(\theta_i^L < \theta_i < \theta_i^U) \approx 1$

Equivalent selection rule:

An equivalent selection rule is:

$$S = \underset{j=1,\ldots,J}{\operatorname{argmax}}\, \gamma_j$$

$$\gamma_j = \frac{\sum_{I=1}^{I} \omega_i \left[\prod_{k\neq i}\left(\theta_k^U - \theta_k^L\right)\right]\left(\hat{\theta}_{ji} - \hat{\theta}_{0i}\right)}{\sqrt{\sum_{p,q} \rho_{pq}\omega_p\omega_q\left[\prod_{k\neq p}(\theta_k^U - \theta_k^L)\right]\left[\prod_{k\neq q}(\theta_k^U - \theta_k^L)\right]\left(\sigma_{jq}\sigma_{jp} + \sigma_{0q}\sigma_{0p}\right)}}$$

- More **practical**, as does not need for Monte Carlo simulation
- An **analytical expression for the Z statistic** at final analysis can be derived

Strong control of type I Error control

Since the hypothesis testing at final analysis is only on the primary endpoint, the null hypothesis is

$$H_0\colon\ \theta_{01} = \theta_{11} = \theta_{21} = \cdots = \theta_{I1},$$
$$\theta_{ji} \in \mathbb{R}, \forall j, \forall i > 1$$

INFINITE MANY NULL CONFIGURATIONS !

It can be proven that The distribution of Z_{S1}^{FA} is

- Stochastically increasing with $\theta_{ji} - \theta_{01}, \forall i > 1$
- Stochastically increasing with $\sigma_{ji}^2, \forall j, \forall i$

Worst Case Configuration

$$\mathcal{C}\colon\quad \theta_{ji} = \theta_{0i} = \underset{\theta_{ji}}{\operatorname{argmax}}\, \sigma_{ji}^2 \quad \forall j > 0, \forall i$$

Strong control of type I error is achieved if

$$\eta = \left| \underset{q}{\operatorname{argmin}}\, P\left(Z_{S1}^{FA} > q\right) - \alpha \right| \quad \text{under} \quad \mathcal{C}$$

Power

Power is defined as the joint probability of these two events:

- Select a treatment which is effective on the primary endpoint
- Reject the null hypothesis for the selected treatment on the primary endpoint

However, as per the «null configurations», we have also **many alternative configurations**:

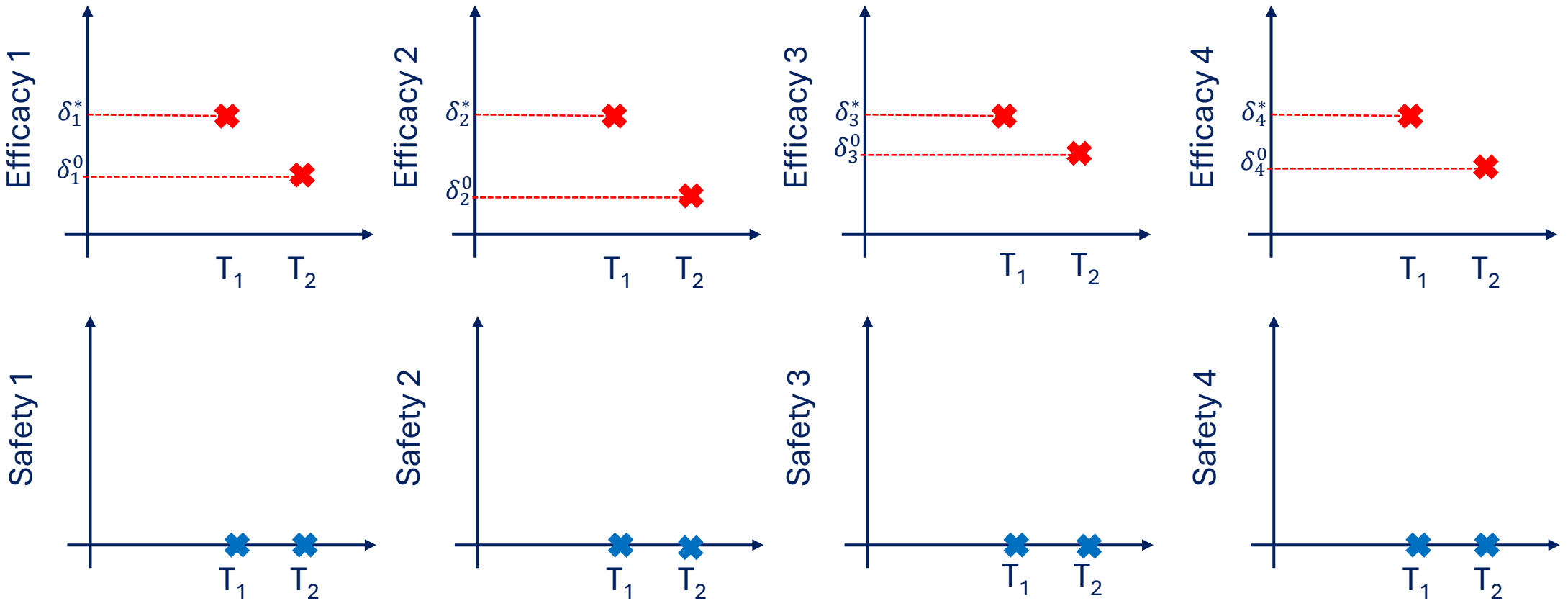
$$H_A\colon\ \theta_{j1} > \theta_{01} \text{ for at least one } j = 1, \dots, J$$
$$\theta_{ji} \in \mathbb{R}, \forall j, \forall i > 1$$

HOW DO WE CHOOSE THE CONFIGURATION FOR POWER ?

1. Assume that there exists **one single dose** which is superior in all efficacy endpoints at a level δ_i^*
2. Assume that the efficacy of all the other active doses is at the maximum non relevant level δ_i^0
3. All the doses are as safe as the control

Least Favorable Configuration

Least Favorable Configuration (LFC)



The LFC represents the **best possible configuration** that the stakeholder would not be willing to select at the time of the interim analysis.

Sample Size determination

- Make some assumptions on the **control parameters** θ_{0i}
- Choose **the target treatment effects** on all efficacy endpoints, namely $\delta_1^*, \delta_2^*, \delta_3^*, \ldots$
- Choose the **maximum non inteteresting treatment effects** on all efficacy endpoints, namely $\delta_1^0, \delta_2^0, \delta_3^0, \ldots$
- Target the **information fraction of the interim analysis** on the primary endpoint (or expected information fraction if the timing is nor driven by the primary endpoint)
- Target a **nominal level $1 - \boldsymbol{\beta}$ for the power** under the Least Favorable Configuration (LFC)
- Find numerically the **minimum sample size** so that

$$\mathrm{P}\left(Z_{S1}^{FA} > \eta\right) > 1 - \beta \qquad \text{under LFC}$$

Simulation Study

Design used in the simulations

- Two experimental doses, one common control arm
- 500 patients enrolled, with accrual rate 20 patients per arm per month
- Primary endpoint is OS
- For the MCDA we use:
- Two efficacy endpoints: Overall Survival (OS) – primary endpoint
  Overall Response Rate (ORR)
  Two safety endpoints: Serious Adverse Events (SerAE)
  Severe Adverse Events (SevAE)
- Weights $\omega = (0.1, 0.4, 0.25, 0.25)$ used in the probabilistic MCDA approach
- Interim Analysis after 30 patients per arm (total 90 patients) patients are evaluable on ORR (20% IF)
- Final analysis after 160 OS events are observed across the selected arm and the control arm → 80% Power under the following Least Favorable Configuration (LFC)

LFC	Haz	ORR	SerAE	SevAE
Control	0.10	0.3	0.3	0.3
Dose 1	0.08	0.4	0.3	0.3
Dose 2	0.06	0.6	0.3	0.3

Stallard & Todd (2003) – competing approach

STATISTICS IN MEDICINE
Statist. Med. 2003; **22**:689–703 (DOI: 10.1002/sim.1362)

Sequential designs for phase III clinical trials incorporating treatment selection

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- The best performing treatment **on the primary endpoint** is selected
- Only primary endpoint is tested at the time of the final analysis
- Critical value η is computed in order to control type I error at the nominal level under the least favorable configuration (**expressed only in terms of primary endpoint**)

Operating characteristics used in the simulation study

- Probability that **dose 2 is selected** and continued until final analysis.
- **Type I Error**: probability to reject the null hypothesis that the selected treatment is effective on the primary endpoint, when none of the active treatment is effective on the primary endpoint.
- **Power**: probability to jointly make the «right selection» and reject the null hypothesis for the selected treatment when the best treatment has a treatment effect of HR(OS)=0.5
- **Uninteresting Success**: probability to jointly make the «wrong selection» and reject the null hypothesis for the selected treatment when the best treatment has a treatment effect of HR(OS)=0.5
- **Average Toxicity**: average toxicity (on the probability scale) for the selected dose for each safety endpoint considered

Type I Error analysis

- Dose 1 is equivalent to control
- Varying characteristics of dose 2
- Selection based on probabilistic MCDA.
- FA after **160 OS events**, IF after **90 patients on ORR**.

Characteristics of dose 2

	Haz	ORR	Tox 1	Tox 2
S1	0.1	0.3	0.3	0.3
S2	0.1	0.5	0.3	0.3
S3	0.1	0.7	0.3	0.3
S4	0.1	0.3	0.45	0.4
S5	0.1	0.7	0.6	0.5

			Our Approach		Stallard & Todd	
	γ_1	γ_2	P(sel. T2)	t1e	P(sel. T2)	t1e
S1	0	0	50.3	2.2	50.2	2.2
S2	0	1.56	94.1	2.2	49.6	2.5
S3	0	3.14	99.9	2.0	48.7	2.5
S4	0	-1.25	10.6	2.2	50.7	2.4
S5	0	0.74	76.5	2.3	50.2	2.5

- Type I Error is strictly controlled below 2.5%, while it is controlled exactly at 2.5% for Stallard & Todd
- Probability of selecting dose 2 depends on $\gamma_2 - \gamma_1$

Power analysis

- FA after **160 events** are observed (control + selected arm)
- IA after **90 responses** on secondary efficacy endpoint
- Almost **20% IF** on primary endpoint

Characteristics of control arm

Haz	ORR	Tox1	Tox2
0.10	0.3	0.3	0.3

Characteristics of dose 1

Haz	ORR	Tox1	Tox2	γ_1
0.08	0.4	0.3	0.3	0.57

Characteristics of dose 2

					Our Approach					Stallard & Todd				
Haz	ORR	Tox1	Tox2	γ_2	Avg Tox 1	Avg Tox 2	Sel T2	Unint. Success	Pow	Avg Tox 1	Avg Tox 2	Sel T2	Unint. Success	Pow
0.06	0.6	0.3	0.3	2.83	0.30	0.30	95.9	1.7	79.2	0.30	0.30	67.9	11.7	57.7
0.06	0.7	0.3	0.3	3.64	0.30	0.30	99.4	0.2	82.2	0.30	0.30	67.7	12.2	57.4
0.06	0.6	0.5	0.5	0.92	0.38	0.38	39.2	20.9	33.5	0.44	0.44	66.9	12.5	57.3
0.06	0.7	0.55	0.55	1.29	0.44	0.44	54.5	15.9	46.5	0.48	0.48	68.3	12.2	57.9
0.06	0.3	0.4	0.4	-0.5	0.31	0.31	16.6	30.7	3.5	0.37	0.37	68.1	11.8	57.9

✓ Power may be lower of higher wrt Stallard & Todd depending on the benefit-risk profile

✓ Arms with high level of toxicity are reccomended less on average with our approach

Final remarks

- We constructed a seamless phase 2/3 design where:
  - Selection at IA is based on **probabilistic linear MCDA**
  - Final hypothesis testing is based on **primary endpoint**

- An **analytical expression** for the distribution of the test statistic at the final analysis is not available, but can be approximated under reasonable assumptions

- **Strong control of type I error** at the nominal level α is achieved computing the critical value of the final test under a «worst case configuration»

- The concept of *least favorable configuration* (LFC) has been extended to the context of multiple endpoints in order to compute sample size

- Results show that including MCDA in the selection step of the design effectively helps in **limiting the probability to select potentially toxic doses**, with a substantial loss in power only under extreme scenarios

Conclusion

The proposed trial design combines

- **Time efficiency**
  Because the phase 2 and phase 3 are run within the same trial in a seamless way

- **Resource efficiency**
  Because the multi-arm nature of the design allows for the control patients to be shared across all experimental arms

- **Adherence with regulatory guidelines**
  Because selection of the optimal dose at the end of phase 2 is made based on a comprehensive benefit-risk assessment

- **Statistical integrity**
  Because critical value at the end of the trial are specifically design to accomodate for the dose selection criterion

Thanks for the attention