Data & Statistical Sciences

Comparison of Adaptive Seamless Phase 2/3 Designs with Dose Selection and Multiple Endpoints

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Outline

- FDA Guidance:
  - Adaptive Designs for Clinical Trials of Drugs and Biologics
  - Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases
- Adaptive Seamless Design with Dose Selection
  - A seamless design which can allow for the mid-Term modification
  - Adaptive Graph-based Multiple Testing Procedure (agMTP) Based on Conditional Error Rate
  - Dunnett-adjusted Adaptive Test based On Ranked Dose Responses
- Q&A

Advantage of Adaptive Design

- An Adaptive Design uses accumulating data to decide how to modify aspects of the study design based on pre-specified criteria

- Advantages of Adaptive Design:
  - Decrease development time
  - Decrease sample sizes (costs)
  - Reduce patient burden

- Assessment of Adaptive Design:
  - Power gain/total sample size saving
  - Type I error
  - Less operation challenges
  - More ……

FDA Guidance: Adaptive Designs for Clinical Trials of Drugs and Biologics (FDA 2019)

- Four key principals:
  - Chance of erroneous conclusions should be adequately controlled
  - Estimation of treatment effects should be sufficiently reliable
  - Details of the design should be completely prespecified
  - Trial integrity should be appropriately maintained

Types of Adaptive Designs (Included in FDA Guidance)

- Group sequential designs
- Adaptations to the patient population
- Adaptations to endpoint selection
- Adaptations to the sample size
- Adaptations to patient allocation
- Adaptations to treatment arm selection (e.g., seamless design)

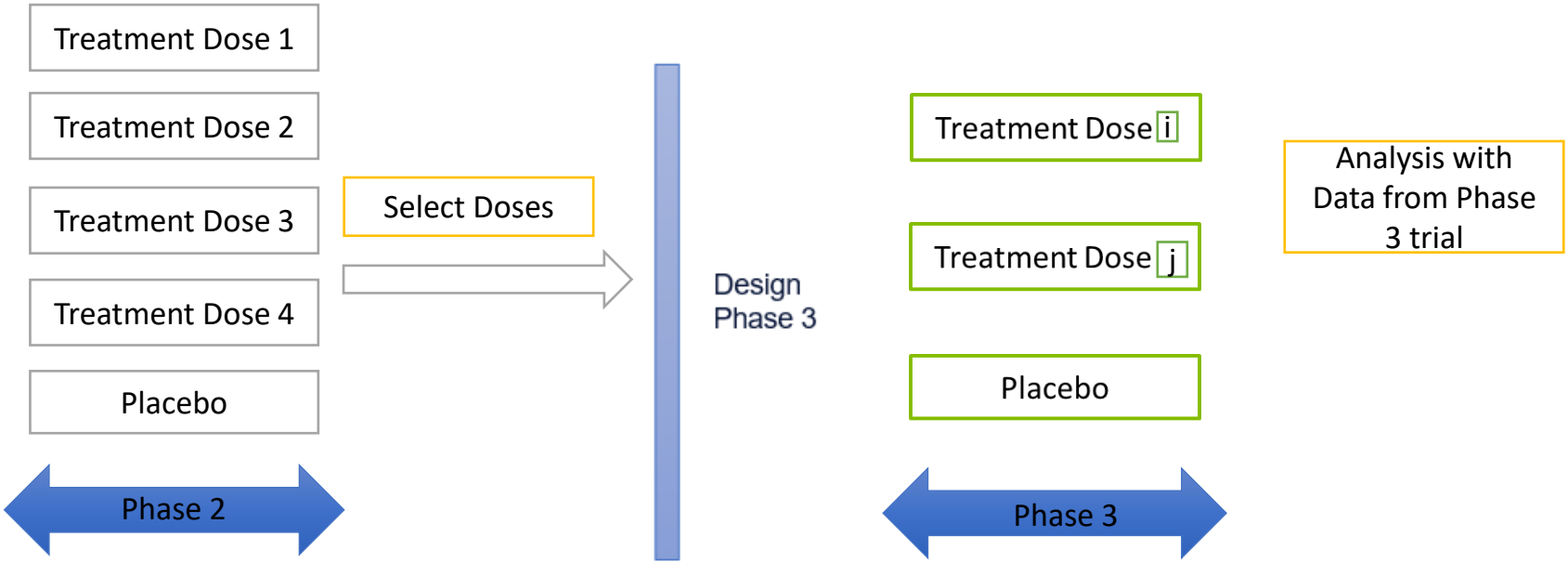
FDA Guidance: Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases (FDA 2023)

- Moves away from selecting the maximum tolerated dose (MTD)
- An optimal dose with similar efficacy and better safety profile based on comprehensive benefit risk assessment
- Should be applied to Adaptive Desing with Dose Selection too

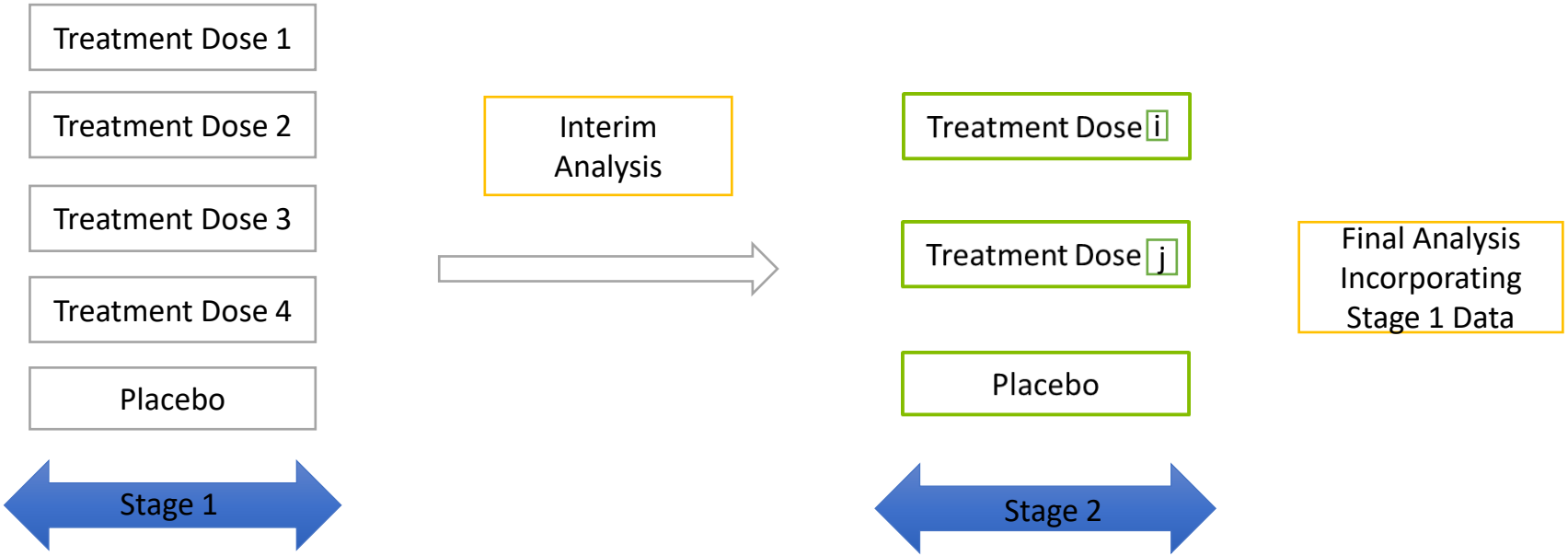
Seamless Adaptive Seamless Phase 2/3 Designs with Dose Selection

- Starts as a Phase 2, and select doses based on pre-specified criteria to expand to a confirmatory stage seamlessly
- Can incorporate both dose selection and confirmation of efficacy of a selected dose in one trial
- Proceeds in the same trial, but uses data from subjects enrolled in both stages in the final analysis
- Can expedite drug development compared to the conventional approach with conducting Phase 2 and Phase 3 trials sequentially

Traditional Approach of Conducting Phase 2 and Phase 3 Trials Sequentially



Adaptive Design with Dose Selection (Select One or Multiple Doses in Stage 2/Confirmatory Stage)



Criteria for dose selection should be based on efficacy and safety, and not necessary the dose with maximum efficacy.

Inferential Adaptive Seamless Design with Dose Selection

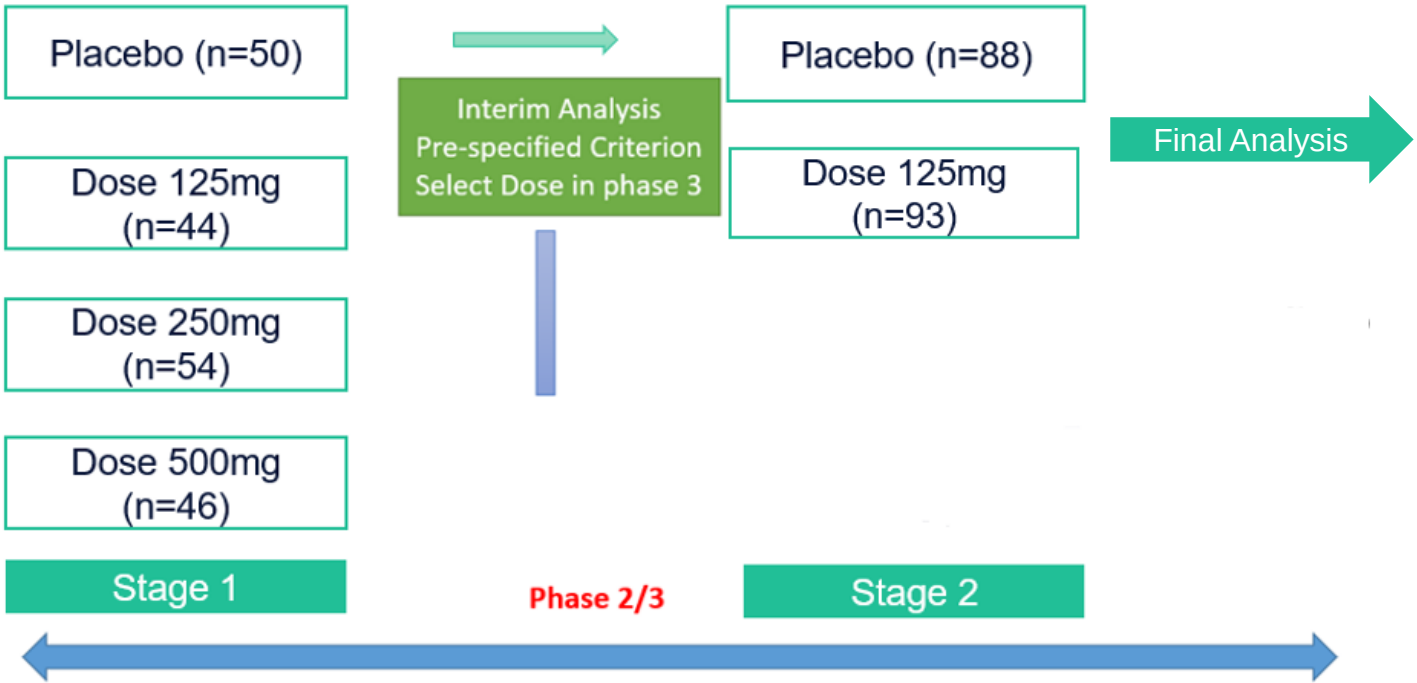
- An inferential seamless design combines the data from the Phase 2 component with the data from the Phase 3 component
- Requires control of Type I Error
- The Phase 2 component serves for dose selection, with typically one or two dose moving to Phase 3
- Dose selection can be based on surrogate endpoints which shows early efficacy signal, if long term endpoints are not mature
- Multiplicity adjustment should be applied if there are multiple hypotheses in the final analysis (multiple doses and/or multiple endpoints)

Case Studies

Case Study 1: ADVENT Trial- An Anti-Diarrhea Therapy in Patients with HIV Disease

- Chaturvedi, Antonijevic, and Mehta, 2014
- A two-stage seamless adaptive design
- Assess the efficacy and safety of three doses of crofelemer (125, 250, 500 mg) taken orally twice daily against placebo
- Dose selected at interim analysis with the pre-specified criteria based on efficacy and safety evaluations
- The first trial using this type of seamless adaptive clinical trial design that led to an FDA approval

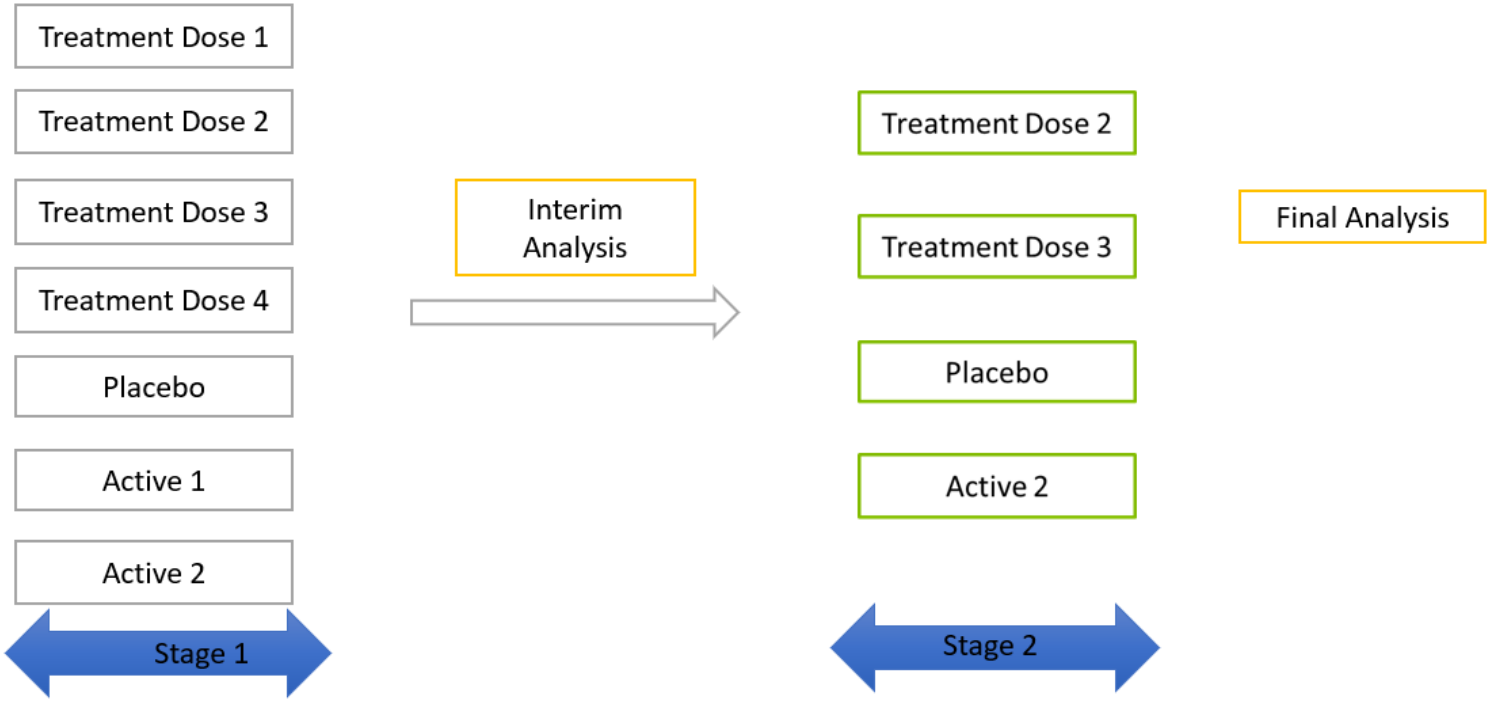
ADVENT Trial



Case Study 2: INHANCE Study for COPD

- A seamless adaptive Phase 2/3 : Sugitani and Bretz, 2016
- Multiple arms in Stage 1 (Phase 2), select 2 doses of indacaterol, active control, placebo in Stage 2 (Phase 3)
- Dose selected at interim analysis with the pre-specified criteria for efficacy and safety
- Mentioned in an earlier example

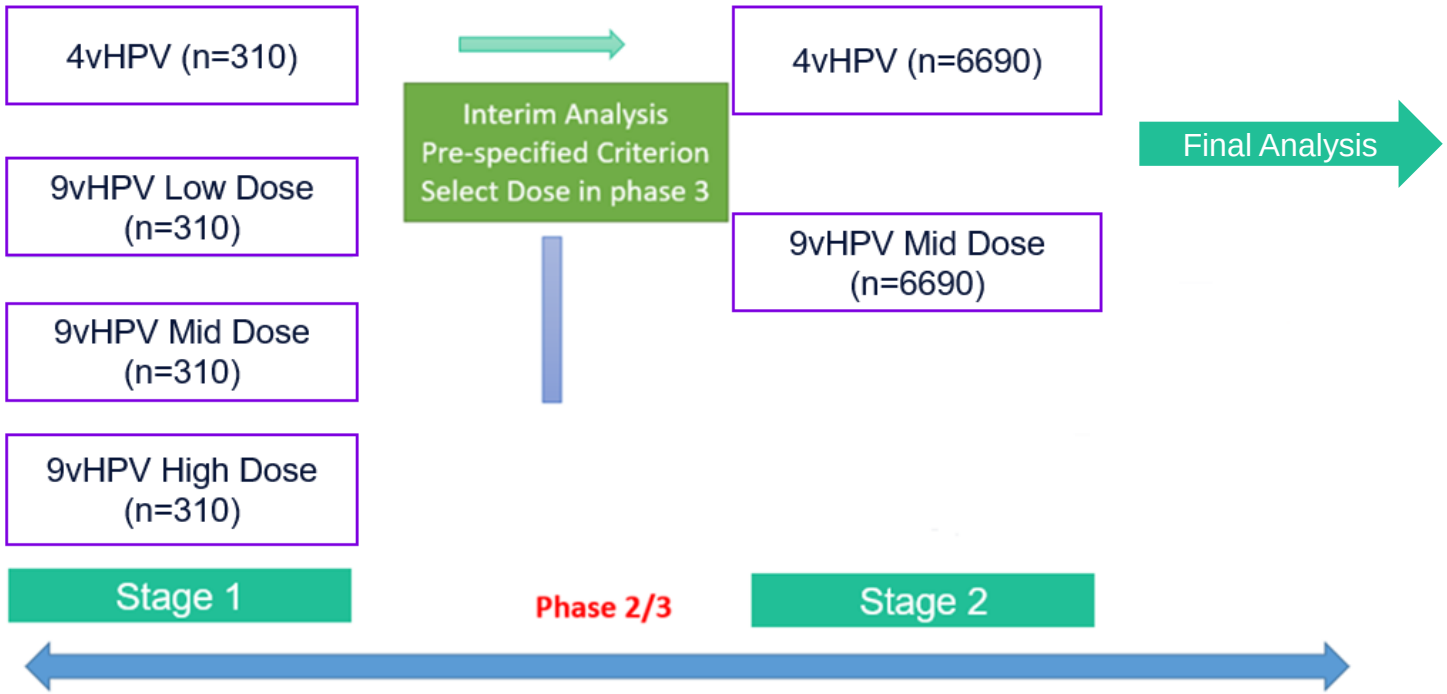
INHANCE Study



Case Study 3: The 9-valent HPV Vaccine Trial (An Example in FDA Guidance)

- Chen, Gesser, and Luxembourg, 2015
- A seamless Phase 2b/3 design
- In Phase 2b stage, subjects randomized to three doses of the 9vHPV vaccine or the 4vHPV (active control)
- 9vHPV Mid dose was selected at interim analysis based on phase 2b data for comparative immunogenicity and safety data

9-valent HPV Vaccine Trial



Test Procedure in Adaptive Design with Dose Selection

- In many-to-one comparison: $H_i: \mu_i = \mu_0, i = 1, \ldots, m\ doses, I = \{1, \ldots, m\}$
- Global hypothesis: $H_I = \cap_{i \in I} H_i$
- After IA, select doses J $\subset I$, final tested hypotheses is $H_J = \cap_{j \in J} H_j$
- Multiple testing procedure or adjustment should be applied to H_J in the adaptive design setting with dose selection

Design 1: A Seamless Design with Mid-Term Modification

- A seamless design by Sugitani and Bretz, 2016
- A multi-stage design (T≥ 2 stages) with m doses (m hypotheses: $H_1 \ldots H_{m,}$ $\mathrm{I} = \{\mathrm{i} \leq \mathrm{m}\}$)
- Example for a 2-stage design, at stage t $\leq 2, p_{j,t},\ H_j, j \leq m$
  - Inverse normal combination test for hypothesis j is:
  - $Z_{j,t} = \left[\sqrt{\eta_1}\phi^{-1}\left(1 - p_{j,1}\right) + \cdots + \sqrt{\eta_t}\phi^{-1}\left(1 - p_{j,t}\right)\right]/\sqrt{E_t}$ $(E_t = \eta_1 + \cdots + \eta_t)$
  - Drop a set of doses $D_t \subset I$ (e.g., drop some doses, and select doses $I\backslash \mathrm{D}_t$)
  - Inverse normal combination test: $q_{j,t} = 1 - \phi(Z_{j,t})$ for $j \in I\backslash \mathrm{D}_t$
  - At Stage t, $q_{j,t}$ is compared with incremental spent level $\alpha^*_{j,t}(\alpha w_j(J))$ for H_j
  - Remove unselected doses from the Graph-based multiple testing procedure, keep the original weights and transition fractions
- The design controls Type I error

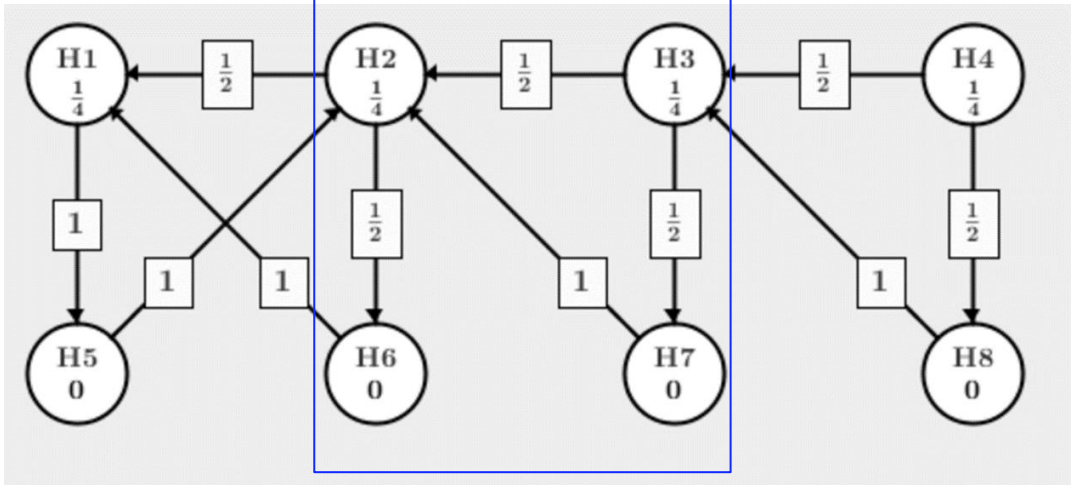
Testing Strategy in Sugitani and Bretz 2016

Selected for Stage 2

Dose 1 Dose 2 Dose 3 Dose 4

Superiority vs Placebo

Noninferiority vs Active 2



Design 2: Adaptive Graph-based Multiple Testing Procedure (agMTP) Based on Conditional Error Rate

- Conditional Error rate: Koenig, Brannath, Bretz, Posch, 2008
- Corresponding conditional error function of ϕ conditioning on the first-stage data ($\boldsymbol{\chi}_1$) for each treatment group is given by

$$A(\boldsymbol{\chi}_1) = E_H(\phi = 1|\boldsymbol{\chi}_1)$$

$$\phi = 0 \; or \; 1: accept \; or \; reject \; H$$

- After IA, option to
  - Complete the trial as initially planned, or select doses based on pre-specified criteria
  - Choose any other test for H at level $A(\boldsymbol{\chi}_1)$ for the second-stage
- If adaptations are performed, the null hypothesis H is rejected based on the second-stage p-value q whenever $q \leq A(\boldsymbol{\chi}_1)$

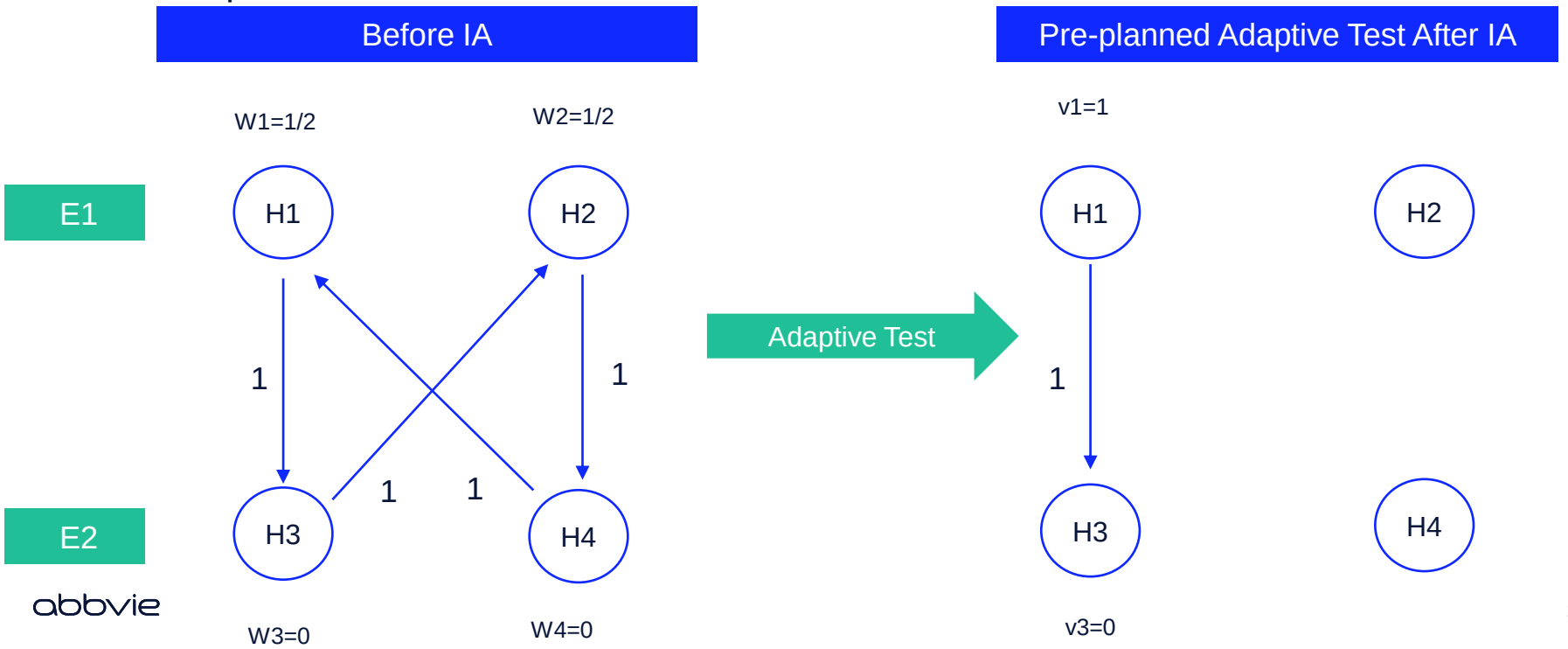
Design 2: agMTP Based on Conditional Error Rate

- agMTP: Klinglmueller, Posch, and Koenig, 2014
- A multi-stage design (T≥ 2 stages) with m doses (hypotheses: $H_1 \dots H_m, \mathrm{I} = \{\mathrm{i} \leq \mathrm{m}\}$)
- Example for a 2-stage design, at stage $\mathrm{t} \leq 2, p_{j,t},\ H_j, j \leq m$
  - Conditional Error Rate for each intersection hypothesis $H_J, J \subset I$,. for all $j \in J$

    $A_{j,J}(w_{j,J}\alpha) = E_{H_J}[\mathbf{1}\{p_{j,1} \leq w_{j,J}\alpha\}|\boldsymbol{\chi}_1]$, $B_J(\alpha) = \sum_{j\in J} A_{j,J}(w_{j,J}\alpha)$; ($\boldsymbol{\chi}_1$ denoted Stage 1 data)
  - Second stage p-values $\mathbf{q} = (\mathrm{q}_1, \dots, \mathrm{q}_m)$
    - ✓ Dose j selected, $q_j = p_{j,2}$
    - ✓ Dose k not selected, $q_k = 1$
  - Define $v_J = (v_{1,J}, \dots, v_{m,J})$ $with\ v_{i,J} = 0$ *for all* $i \notin J$ and $\sum_{j\in J} v_{j,J} \leq 1$ (v_J may be chosen arbitrarily for each $J \subset I$ but the choice of weights will have an impact on the power of the procedure)
  - Adaptive test: $\tilde{\phi}_J(q, B_J) = \begin{cases} \max_{j\in J} \mathbf{1}(q_j < v_{j,J}B_J), if\ B_J \leq 1 \\ 1, otherwise \end{cases}$
  - Closed test procedure that rejects H_i $(i \in J)$: $\tilde{\psi}_i = \min_{J\subset I, j\in J} \tilde{\phi}_J(\boldsymbol{q}, B_J)$
  - The design strongly controls FWER

An Example in Klinglmueller, Posch, and Koenig, 2014

- Dose 1, 2 and Control
- Two endpoints E1 and E2



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Design 3: Dunnett-adjusted Adaptive Test based On Ranked Dose Responses

- Dunnett-adjusted Adaptive Test based On Ranked Doses: Wang et al. 2023
- Extend Wang et al. 2023 to a design which can select multiple doses
- A multi-stage design (T ≥ 2 stages) with m doses (m hypotheses: $H_1 \ldots H_m$)
- Example for a 2-stage design, at stage t $\leq 2, p_{j,t},\ H_j, j \leq m$, ranked Stage 1 data
  - $X_{(1),1} \leq X_{(2),1} \leq \cdots \leq X_{(m),1}$

Design 3: Dunnett-adjusted Adaptive Test based On Ranked Dose Responses

- Dose s is selected based on the ranked response $X_{(r),1}$ based on Stage 1 data, $s \in J \subset I$
  - $X_{(r),1} = X_{s,1}$
  - r is not necessarily the highest rank or highest dose performance
  - Since $X_{(r),1}$ on the selected dose s does not follow standard normal distribution, Dunnett adjustment to adjusted statistics following standard normal distribution

$$p^1_{s,adj} = \text{Addjust\_Dunnett}(1 - \Phi(X_{s,1}))$$
$$X^1_{s,adj} = \Phi^{-1}(1 - p^1_{s,adj}) \sim N(0,1)$$

  - Wang et al (2023) improved the efficiency using Dunnett adjustment based on selected rank r
  - $X_{s,adj} = \sqrt{w_1} X^1_{s,adj} + \sqrt{w_2} X_{s,2}$ ($X_{s,2}$ is the Stage 2 data for Dose $s \in J$)
  - Plan a graph-based multiple testing procedure on doses in J
- The design by Wang et al. (2023) can be extended to a design which selects more than one doses and testing multiple endpoints
- The design with all the possible modifications controls Type I error

Extensions to Adaptive Design with Dose Selection and Multiple Endpoints

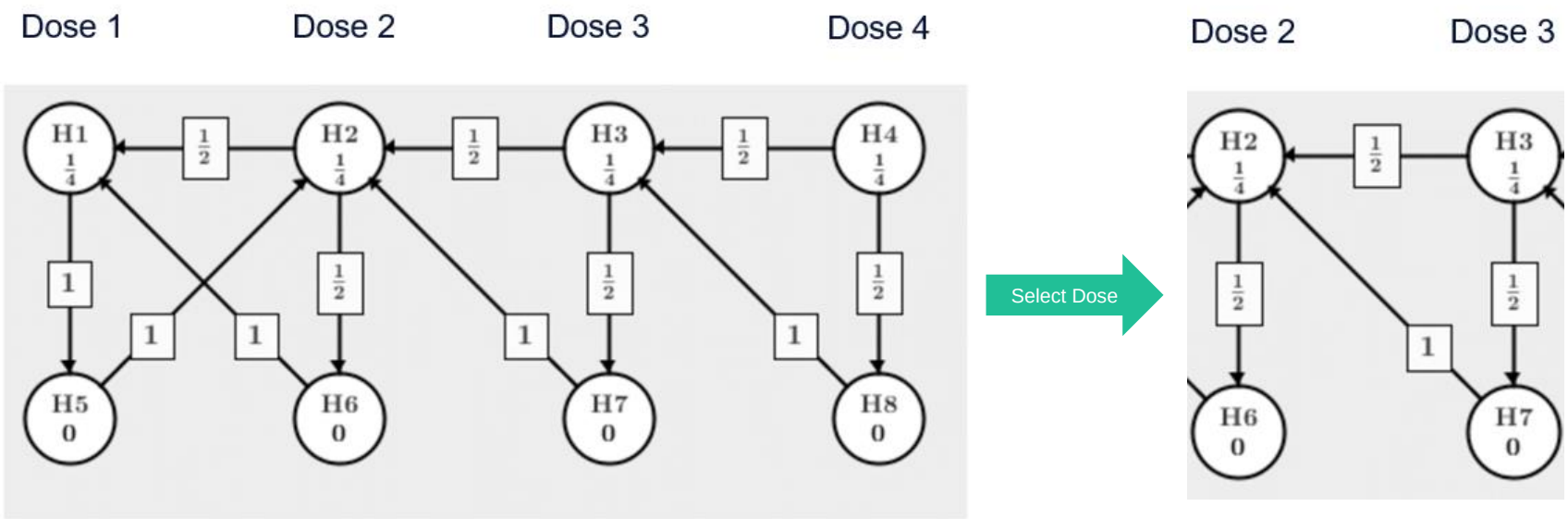
- The design can be extended to multiple doses and multiple endpoints
- Dose is selected based on Primary or *Surrogate Endpoint E1*, which shows short-term efficacy
- Advantage is that the endpoint with long term effect is not mature at IA
- E1 is usually correlated with another Endpoint E2 (such as clinical outcome)
- At the final analysis, plan a multiple testing procedure on the selected doses with Endpoints E1, E2, …
- Design 1, 2, and 3 can be easily extended to a design for this goal

Adaptive Design with Dose Selection Based on Primary Endpoint (For Simulation Purpose)

- Dose 1, 2, 3, 4, and Control
- Two endpoints E1 and E2, select 2 doses at IA (40% info) based on F^1

Design 1

Selected for Stage 2



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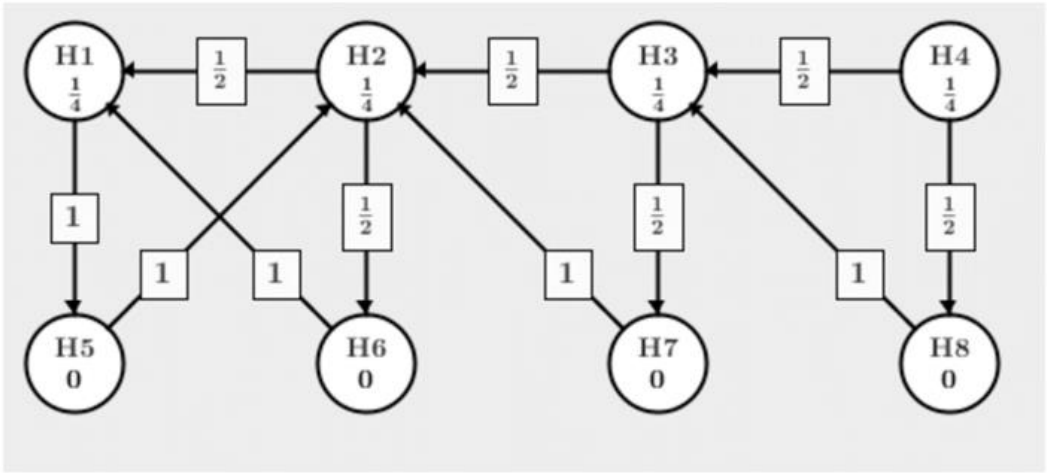
Adaptive Design with Dose Selection Based on Primary Endpoint (For Simulation Purpose)

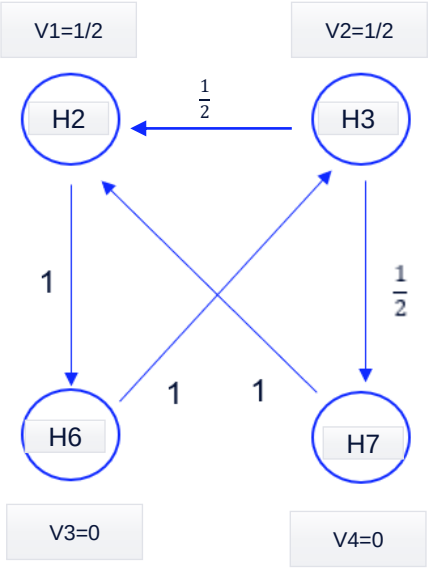
- Dose 1, 2, 3, 4, and Control
- Two endpoints E1 and E2, select 2 doses at IA (40% info) based on E1
- Calculate Conditional Error based on E1 and E2 using original planned graph
- Adaptive graph-based Multiple Test Procedure test after IA

Dose 1 Dose 2 Dose 3 Dose 4



Adaptive test after IA

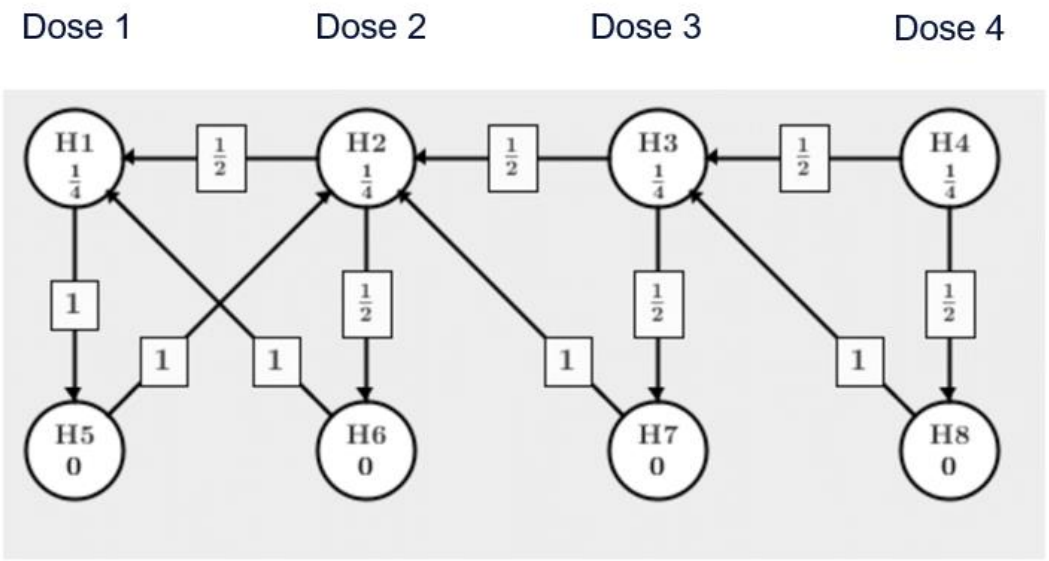
Design 2



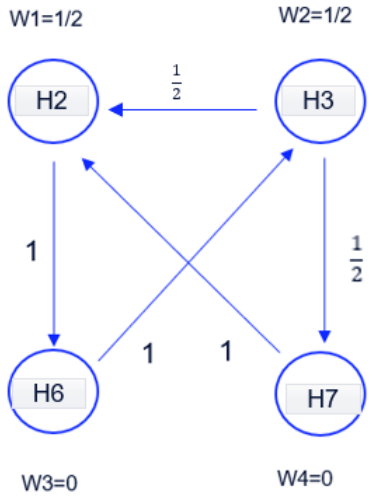
Adaptive Design with Dose Selection Based on Primary Endpoint (For Simulation Purpose)

- Dose 1, 2, 3, 4, and Control
- Two endpoints E1 and E2, select 2 doses at IA (40% info) based on E1
- Dunnett-adjusted test statistics from IA

Design 3



Select dose With Rank based Dunnett Adjustment



Notes to the Simulation Setting

- The selected doses can be any 2 doses, not necessarily the highest ranked doses
- Since the selected dose may or may not have the highest efficacy signal, multiplicity adjustment is required
- More simulation scenarios are considered to select 1 dose
- Another simulation setting with 3 doses are considered

Type I Error and Power with 4 Doses

	Method	Select 2 Doses (Ranks)			Select 1 Dose (Rank)			
		(3,4)	(2,3)	(1,2)	4	3	2	1
Type I (%)	Design 1	2.0	0.8	0.4	1.6	0.8	0.3	0.1
	Design 2	2.3	0.88	0.58	2.0	1.0	0.7	0.2
	Design 3	1.9	0.5	0.2	1.8	0.9	0.3	0.1
Power (%)	Design 1	90.5	82.6	73.1	84.8	74.7	64.9	51.9
	Design 2	91.1	86.6	81.9	89.6	83.2	78.7	71.8
	Design 3	90.4	82.5	73.2	89.2	82.6	77.5	73.2

Design 1: Design 1: A Seamless Design with Mid-Term Modification
Design 2: Adaptive Graph-based Multiple Testing Procedure (agMTP) Based on Conditional Error Rate
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Type I Error and Power with 3 Doses

	Method	Select 2 Doses (Ranks)		Select 1 Dose (Rank)		
		(2,3)	(1,2)	3	2	1
Type I (%)	Design 1	2.1	0.6	1.4	0.5	0.18
	Design 2	2.3	1.1	2.3	0.9	0.5
	Design 3	1.9	0.3	2.4	0.82	0.2
Power (%)	Design 1	89.9	80.3	85.5	74.7	59.1
	Design 2	91.3	84.8	88.5	81.6	74.5
	Design 3	86.6	79.3	87.8	81.3	76.7

Design 1: Design 1: A Seamless Design with Mid-Term Modification
Design 2: Adaptive Graph-based Multiple Testing Procedure (agMTP) Based on Conditional Error Rate
Design 3: Dunnett-adjusted Adaptive Test based On Ranked Dose Responses

Reference

- FDA Guidance, 2019: Adaptive Designs for Clinical Trials of Drugs and Biologics.
- FDA Guidance, 2023. Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases.
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Thank You!

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