Novel multiple testing procedures for structured study objectives and families of hypotheses – a case study

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Acknowledgement: Frank Bretz, Bjoern Holzhauer, Willi Maurer

Outline

- Introduction of graphical approaches to multiple testing
- Case study
  - Background and clinical considerations
  - Resulting multiple testing procedure
  - Interim analysis
- Summary and conclusions

Graphical approaches to multiple testing

Motivation

Increasing complexity of confirmatory trial designs

- Multiple treatment arms, multiple primary and secondary endpoints, interim analyses
- Designing a valid multiple testing strategy with desired properties is a cross-functional exercise and may involve several iterations
- Clinical, regulatory and business requirements need to be translated into a statistical testing procedure in a transparent and understandable way

Graphical approaches to multiple testing

Motivation (cont'd)

Graphical approaches provide a framework to

- Tailor advanced multiple test procedures to structured families of hypotheses
- Visualize complex decision strategies in an efficient and easily communicable way, and
- Ensure strong Type I error rate control (Bretz et al., 2009; Burman et al., 2009)

Notation

- Null hypotheses $H_1, \ldots, H_k$
- Initial allocation of the significance level $\alpha = \alpha_1 + \ldots + \alpha_k$.
- Unadjusted p-values $p_1, \ldots, p_k$

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"α propagation"

If a hypothesis H_i can be rejected at level α_i (i.e. $p_i \leq \alpha_i$), reallocate its level α_i to the remaining, not yet rejected hypotheses (according to a prefixed rule) and continue testing with the resulting α levels.

Graphical approaches to multiple testing

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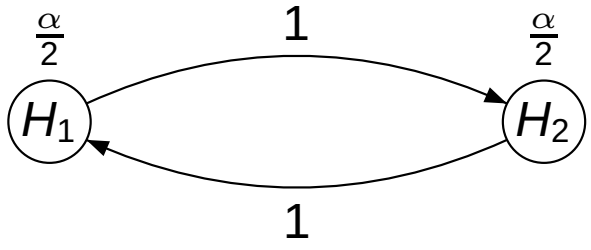
2. Split of significance level α as weights $\alpha_1, \ldots, \alpha_k$

3. "α propagation" through weighted, directed edges



Case study

Introduction and background

- Randomized double-blind event driven outcome trial in stable post myocardial infarction (MI) patients
- Three doses of a new therapy vs. placebo on top of standard of care
  - No validated surrogate available for dose-finding prior to Phase III
- Primary endpoint is composite of CV death, MI or stroke
- Two key secondary endpoints targeting additional label claims, thus included in multiple testing procedure
  - Extended composite endpoint including hospitalization for unstable angina requiring urgent unplanned revascularizations
  - New onset Type 2 diabetes among patients with pre-diabetes at baseline
- Additional multiplicity due to efficacy interim analyses

Case study

Clinical considerations

- Primary endpoint is essential to establish efficacy of the respective dose group. Key secondary objectives target additional label claims for doses that have established efficacy based on the primary endpoint.
  - Successiveness: Do not reject a secondary hypothesis without having rejected the associated primary hypothesis. (Maurer et al., 2011)
- Benefit risk considerations: Higher doses potentially more efficacious and lower doses generally safer
  - Allow testing of lower doses regardless of efficacy at higher doses.
  - Unequal split of significance level.

Case study

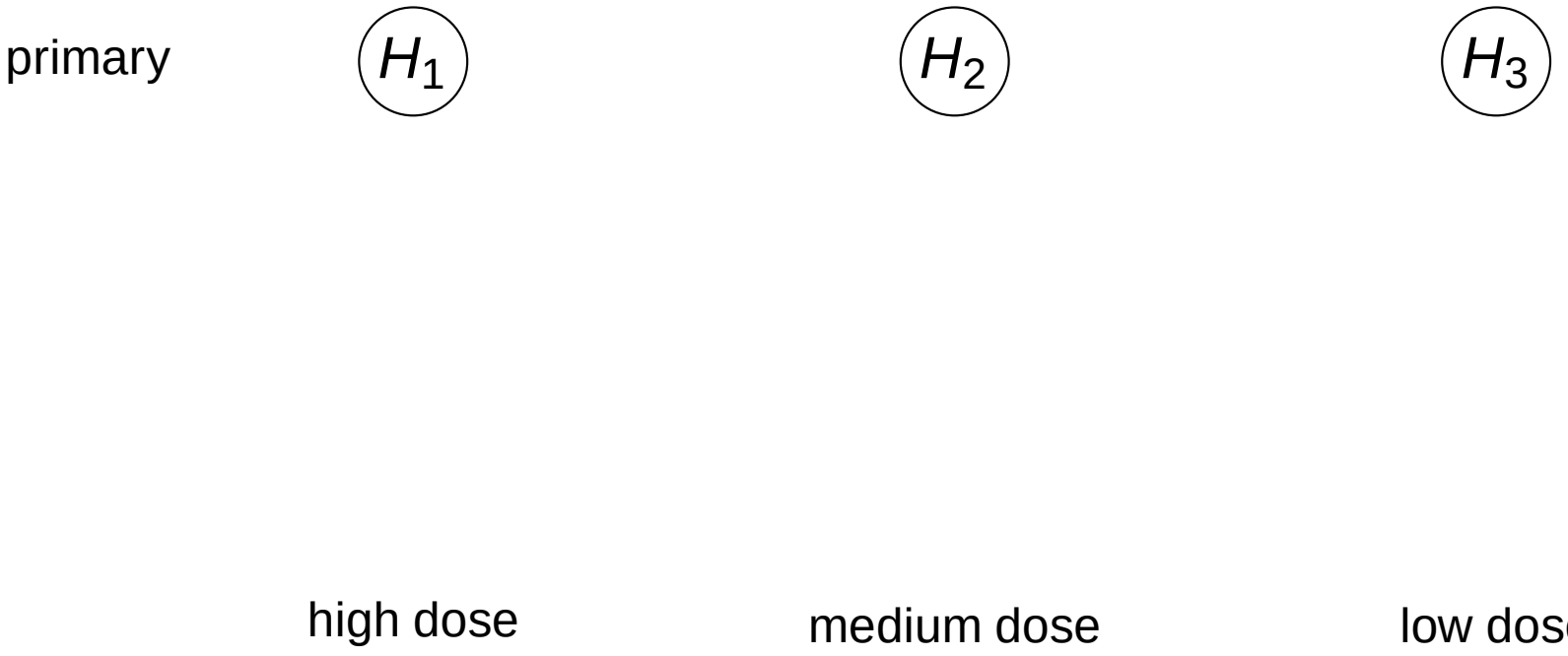
Structured family of hypotheses

- Four-armed trial comparing
  - Three dose levels $+$ standard of care
  - Placebo $+$ standard-of-care
- Three endpoints
  - Primary endpoint: composite of CV death, MI or stroke
  - Two key secondary endpoints

$\Rightarrow$ Nine hypotheses

- Three doses (low, medium, high)
- Three endpoints per dose

Tailored multiple test procedure



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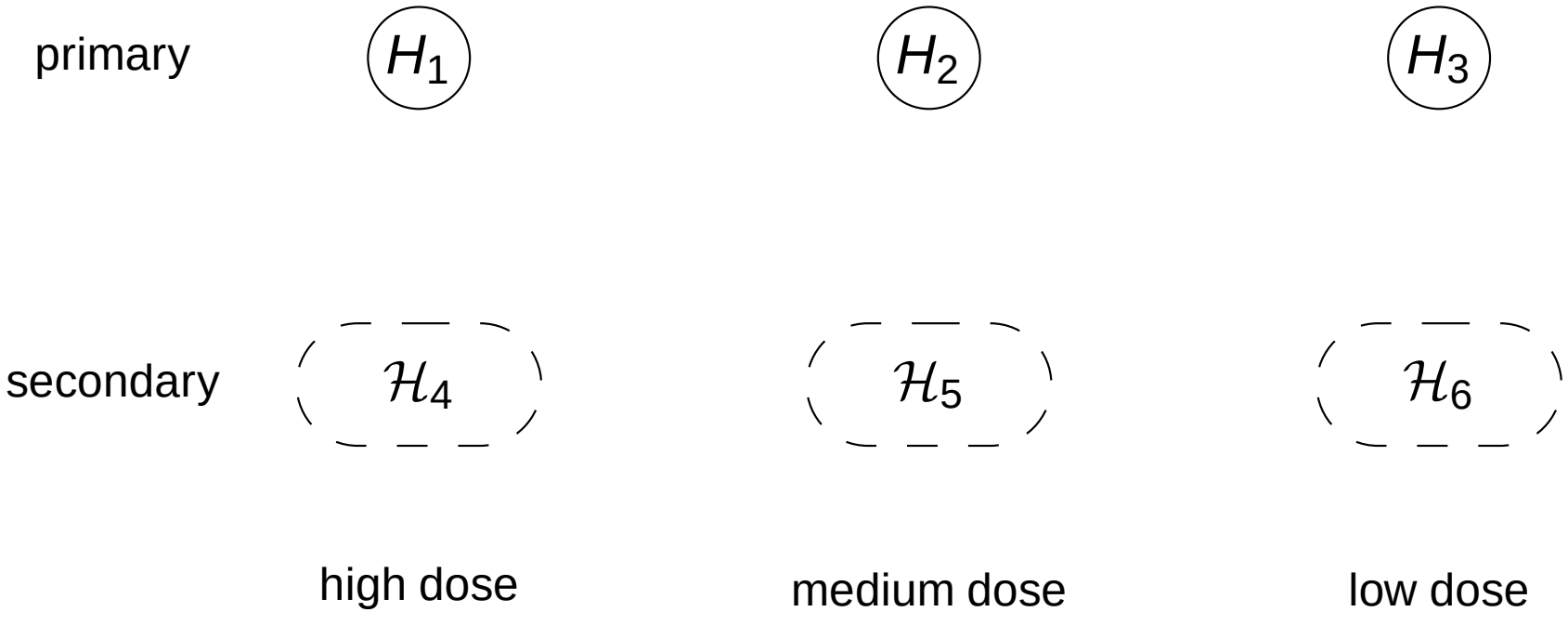

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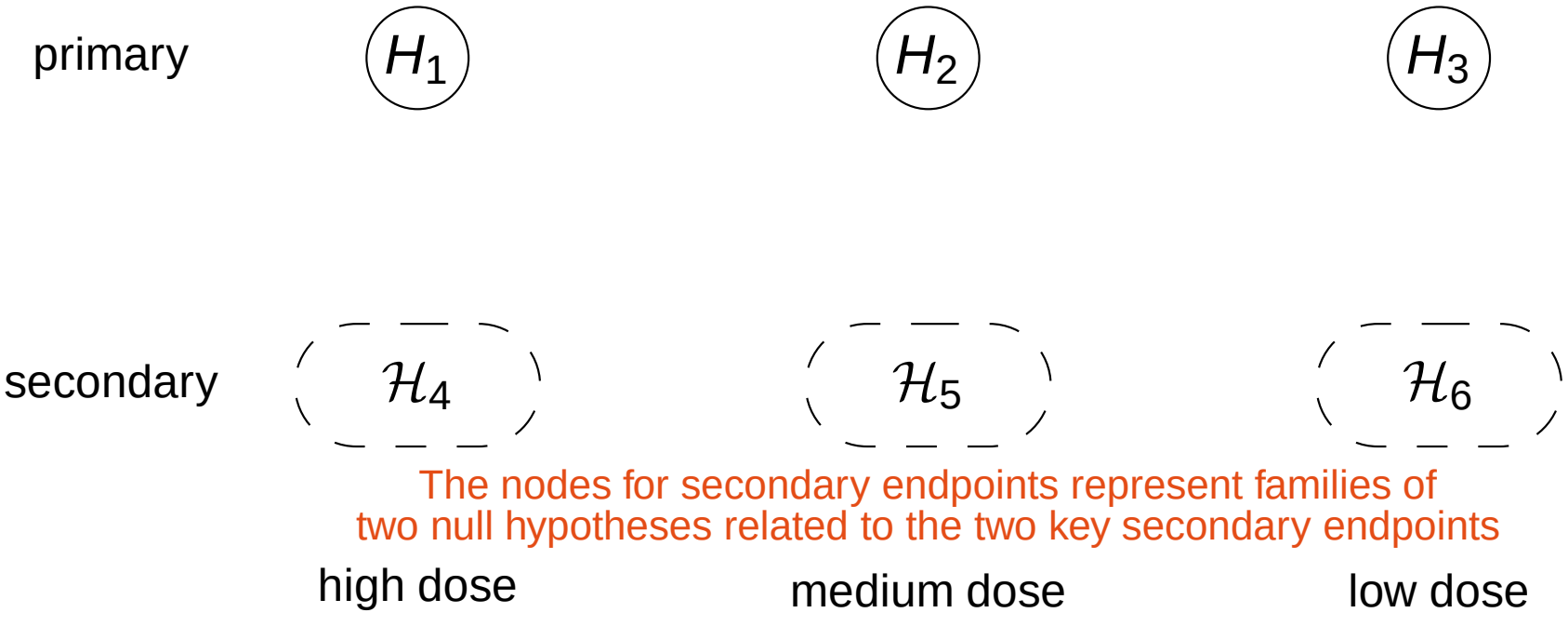

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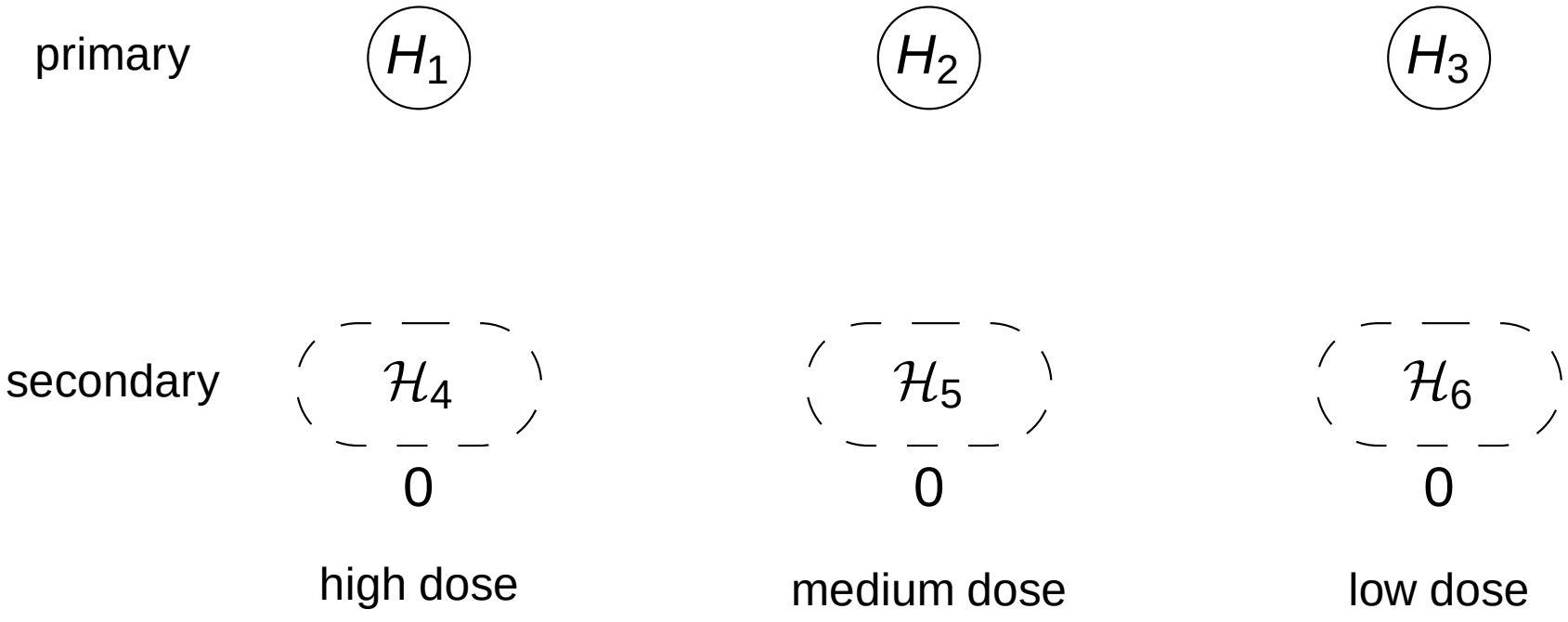

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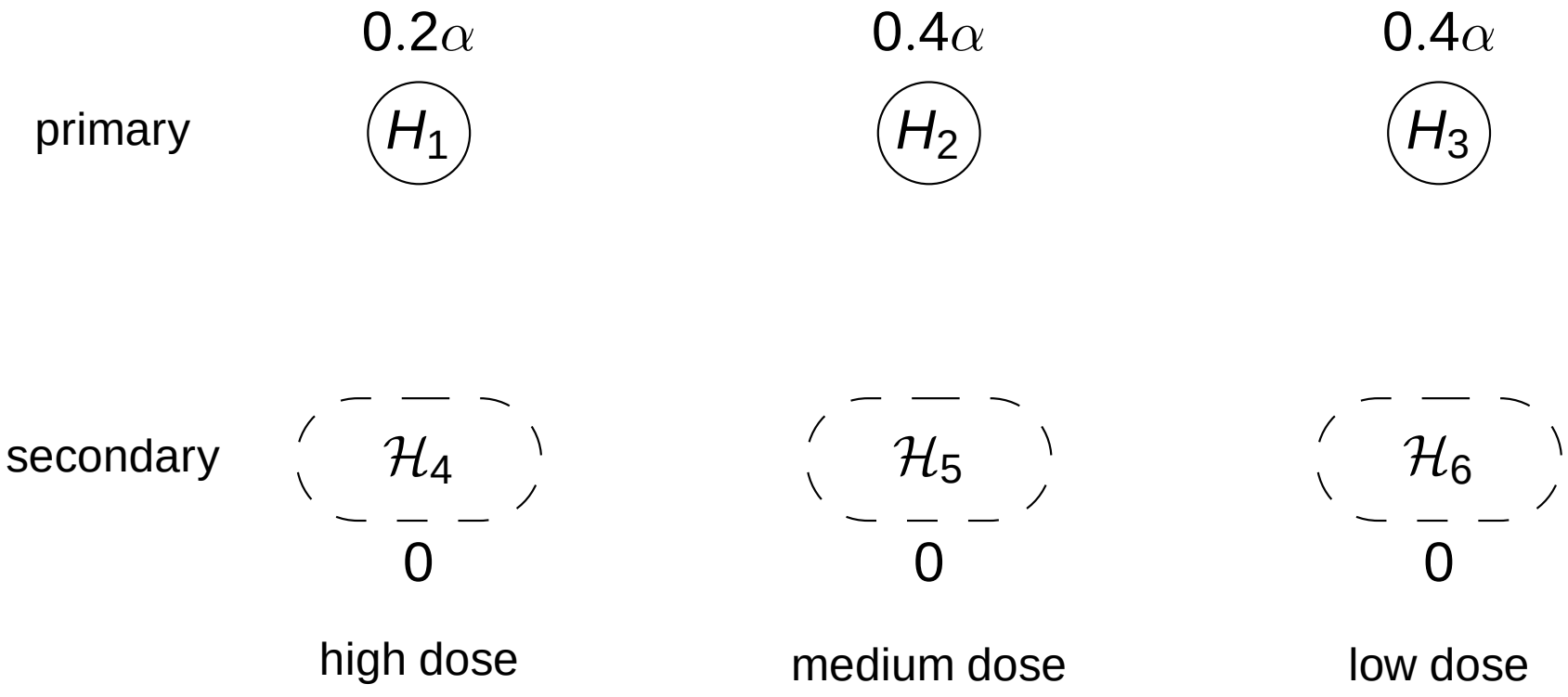

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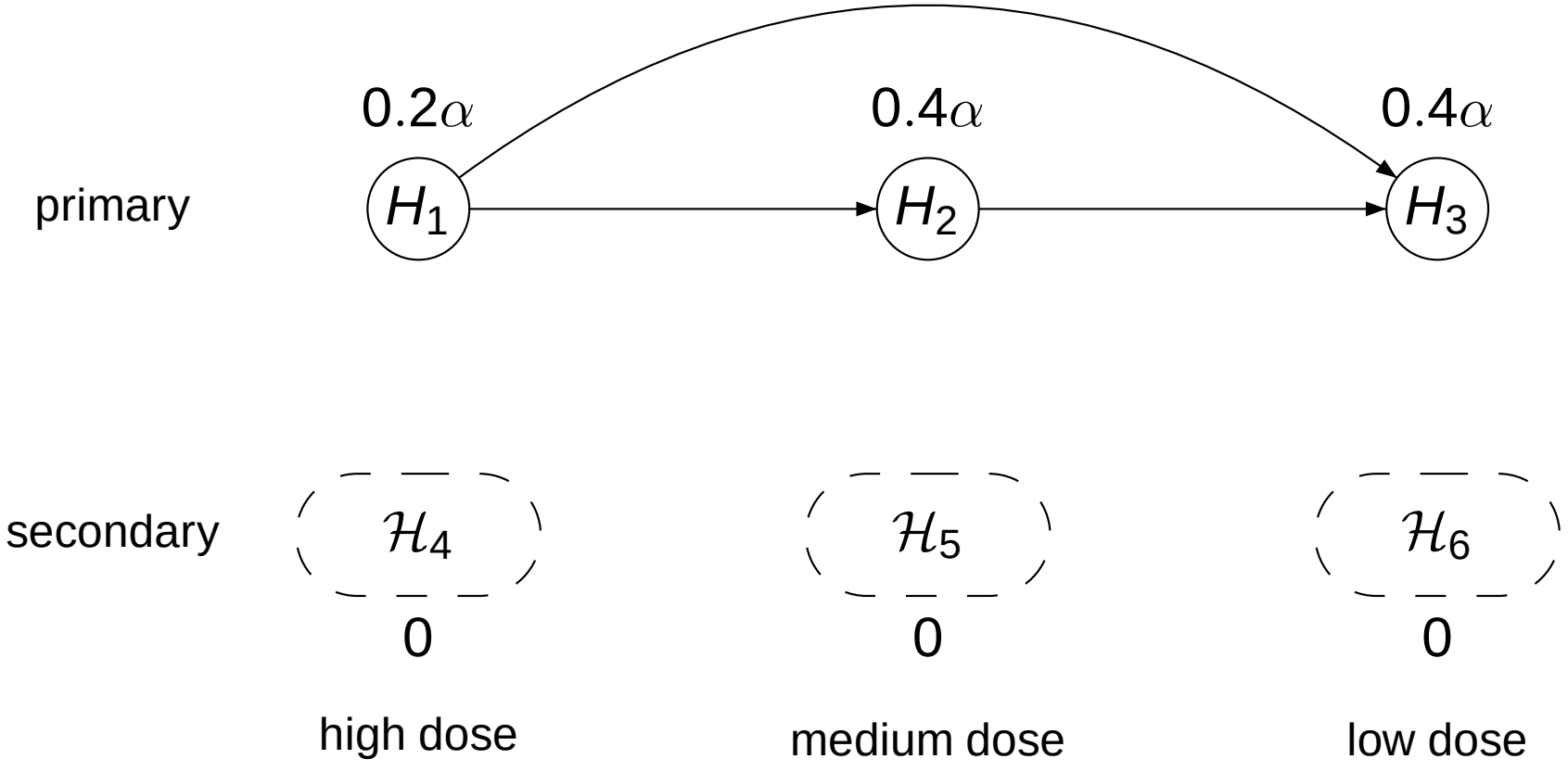

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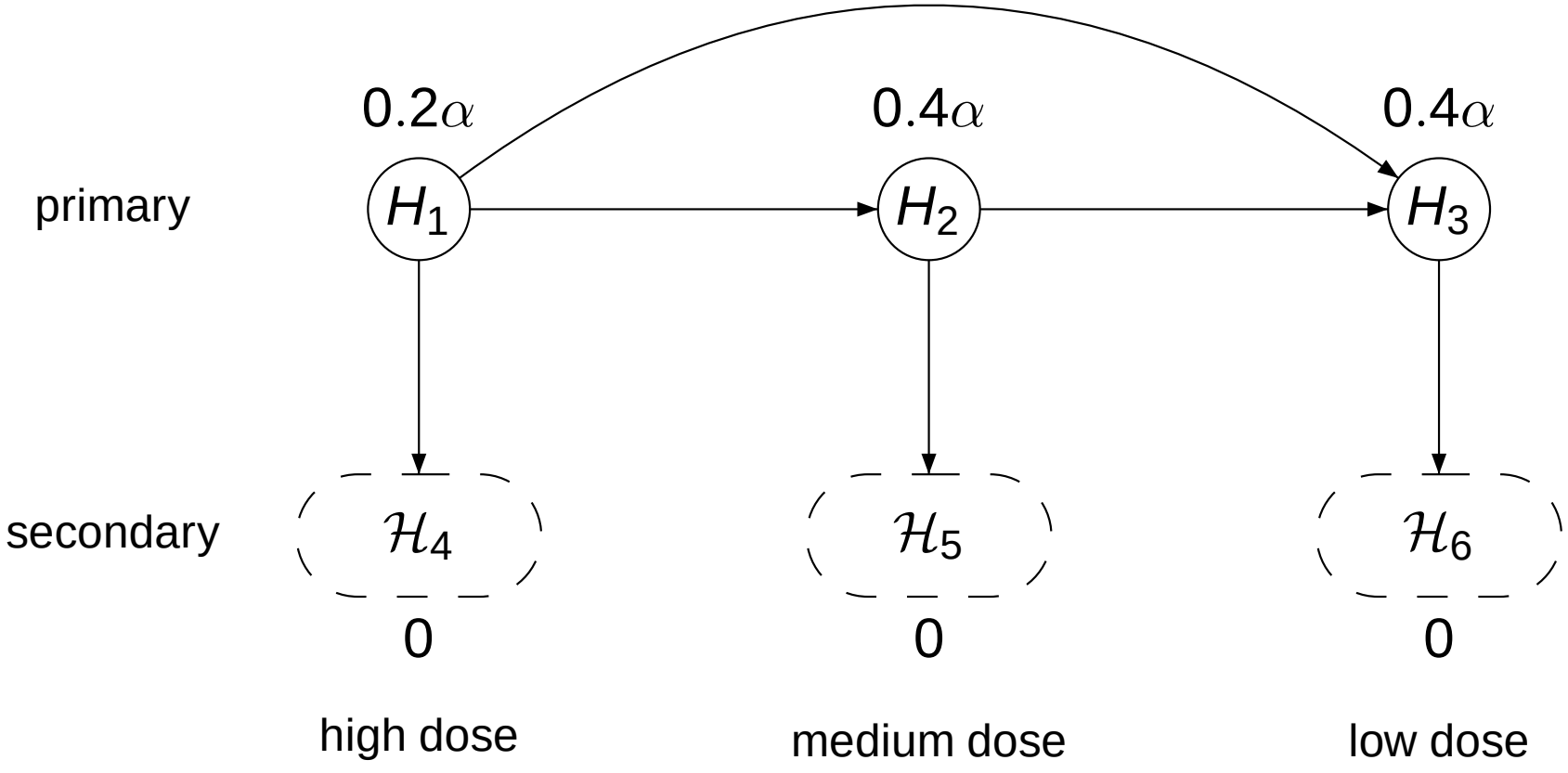

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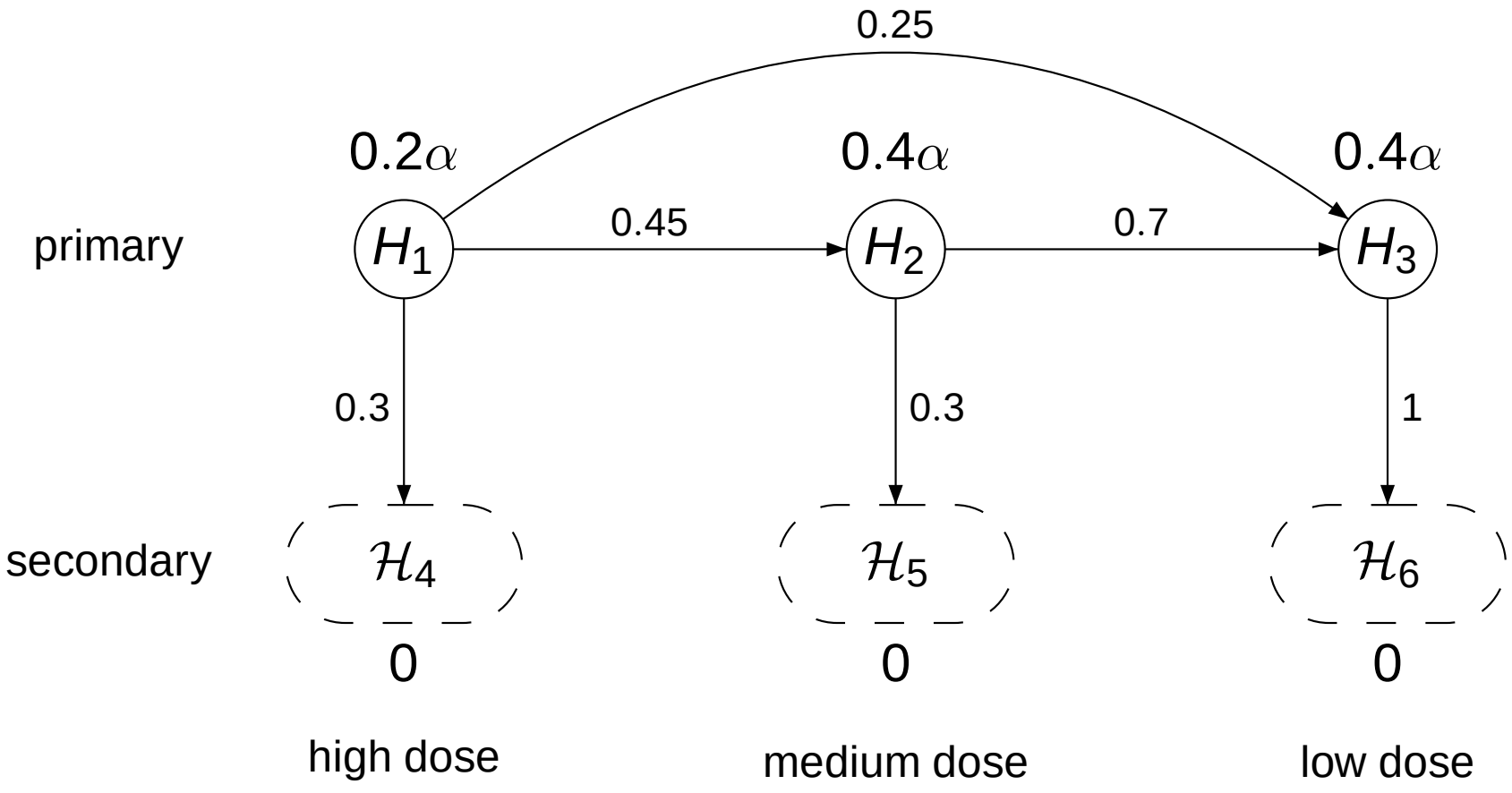

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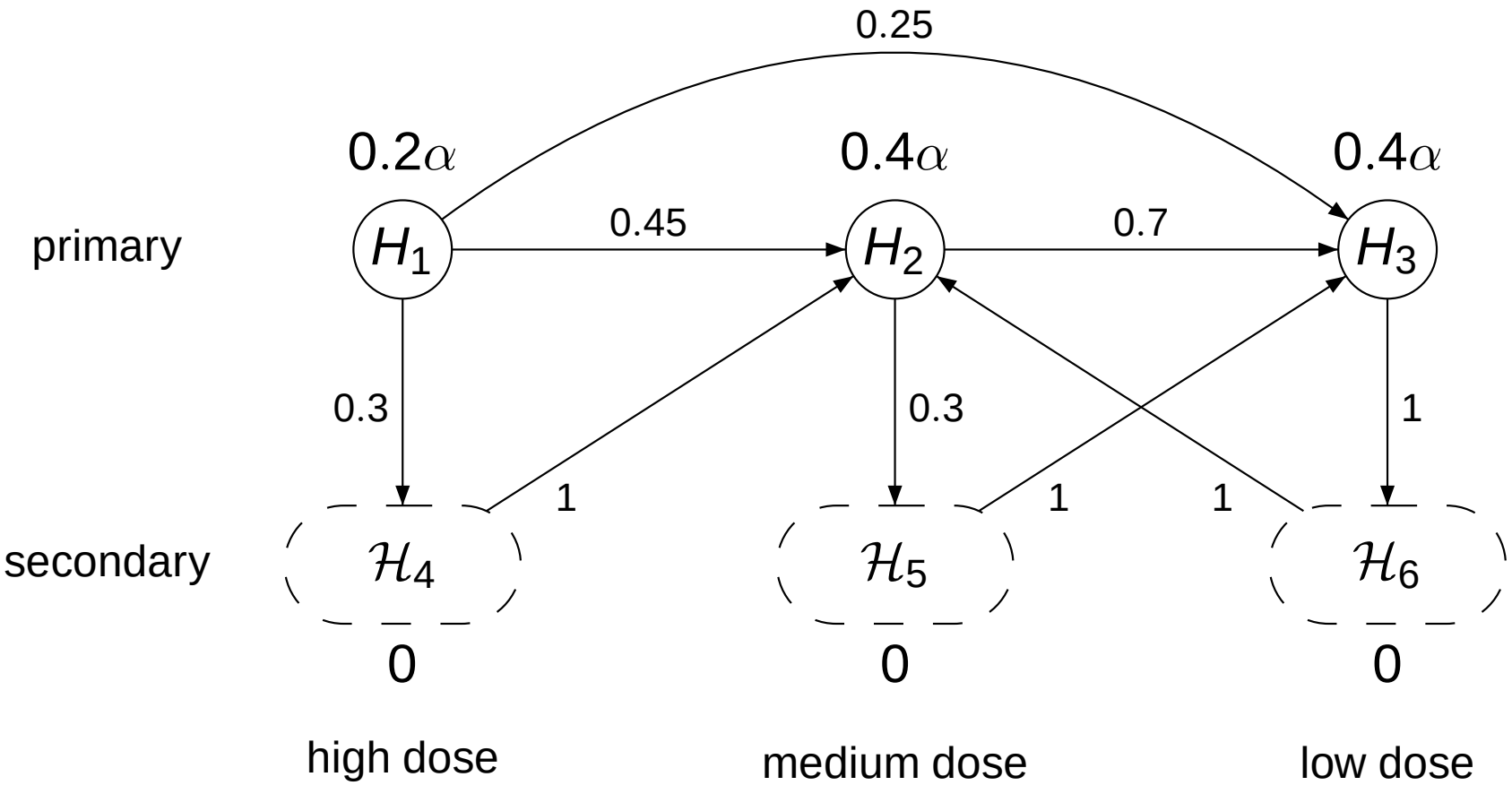

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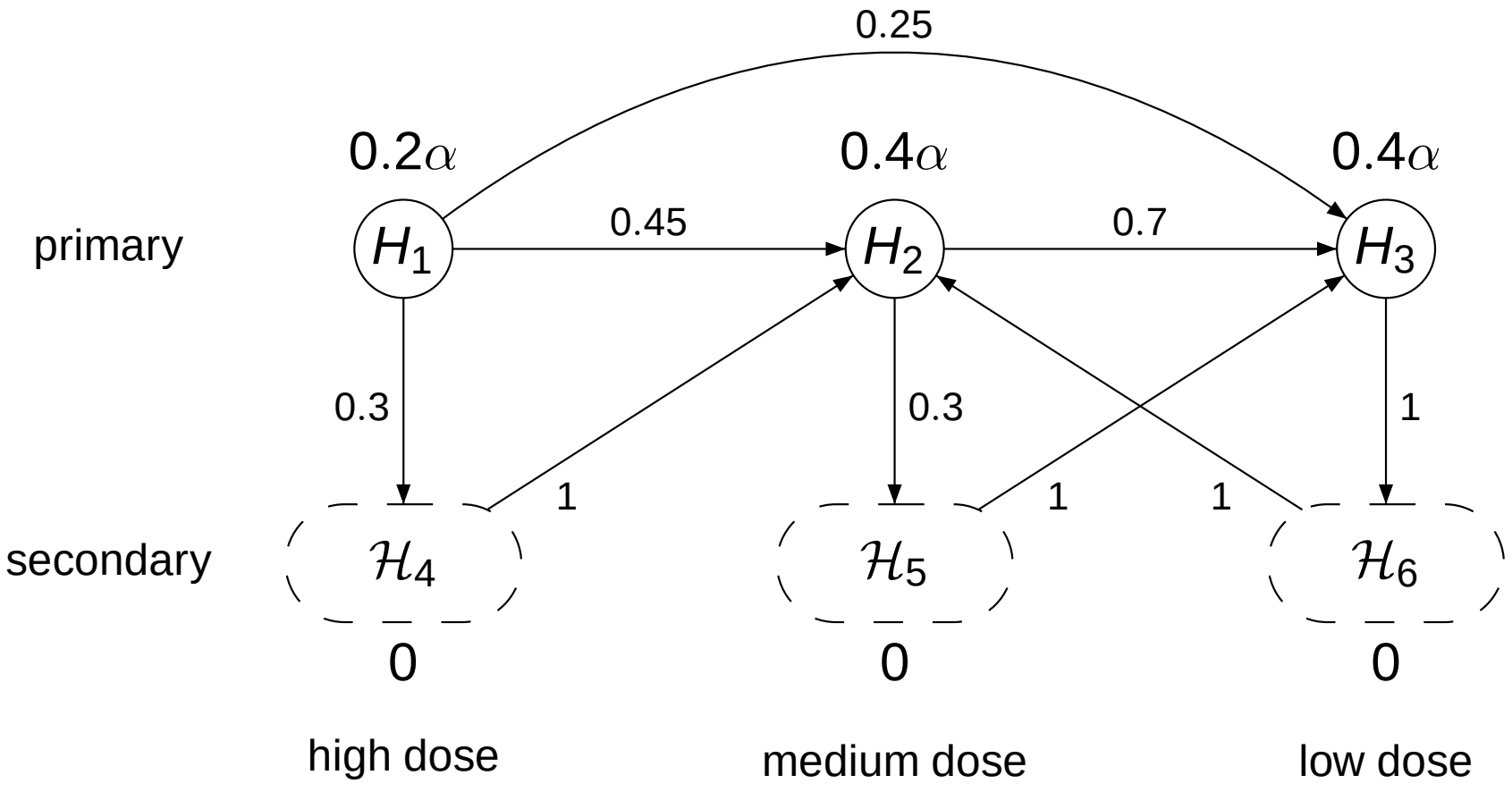
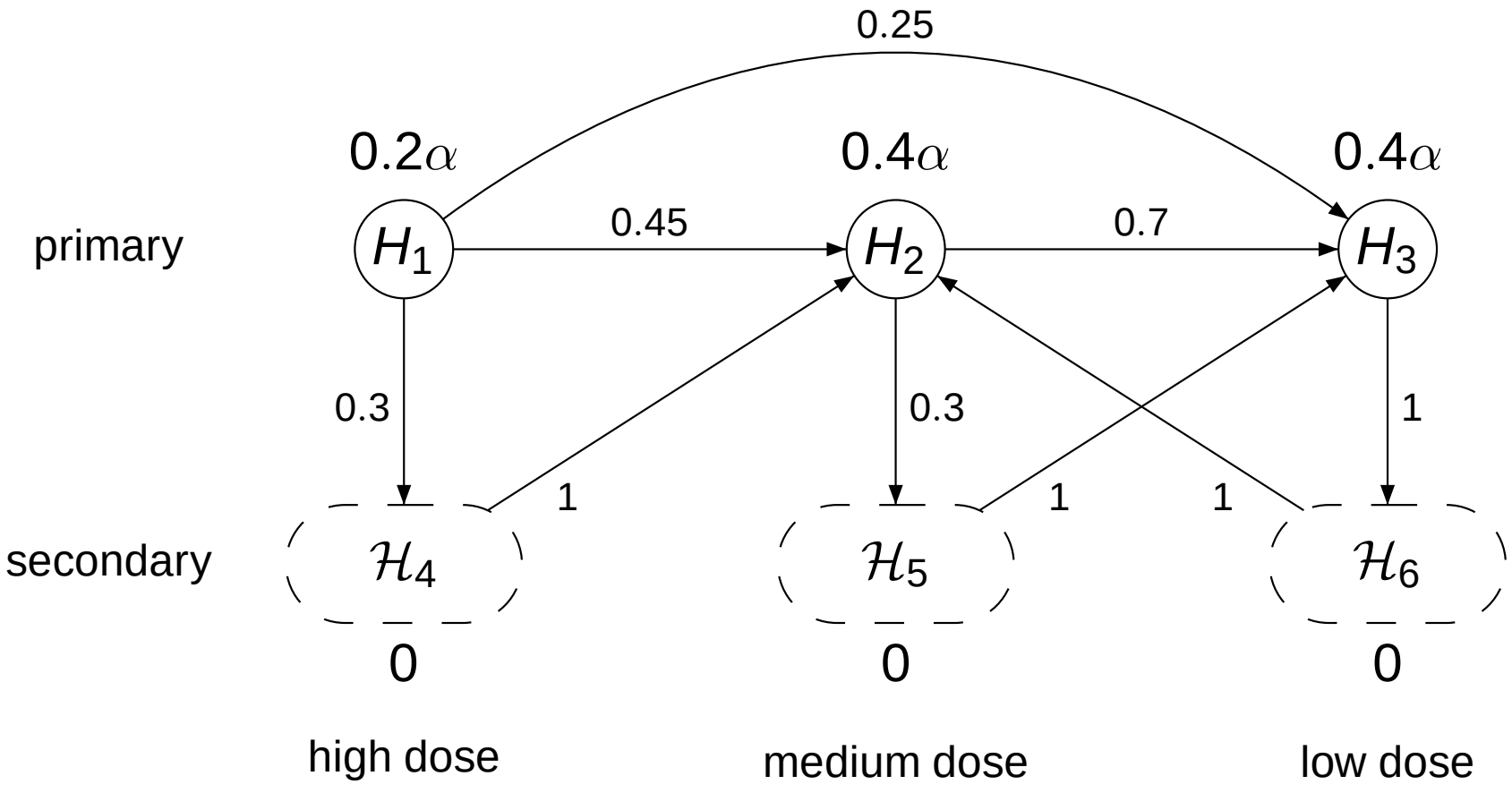


Key secondary endpoints within each dose group will be tested with a weighted Bonferroni-Holm test at the available local significance level

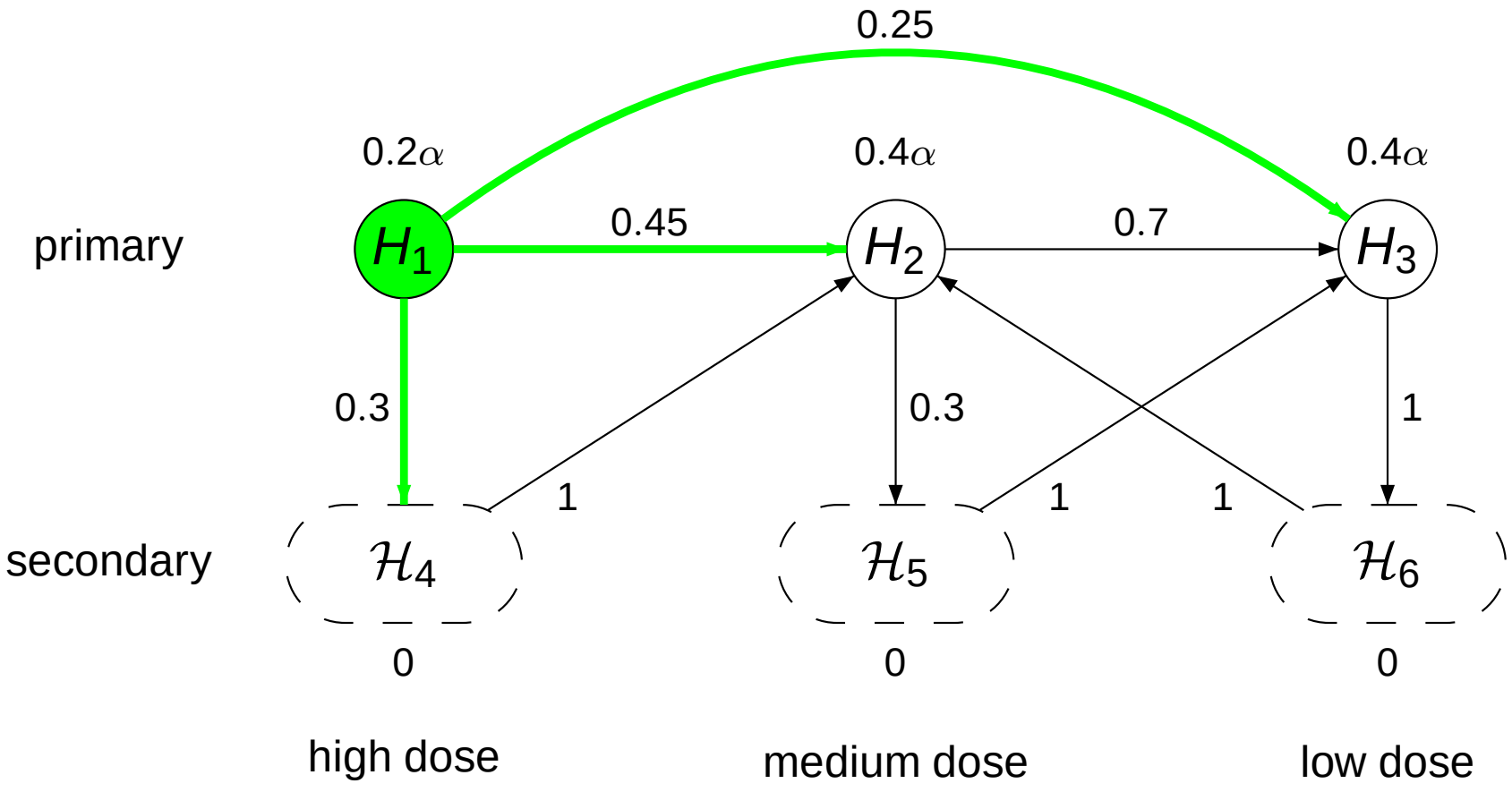
Tailored multiple test procedure



Key secondary endpoints within each dose group will be tested with a weighted Bonferroni-Holm test at the available local significance level

Improvement of the multiple testing procedure by using weighted Dunnett's test for all intersection hypotheses that contain at least two of H_1, H_2 and H_3 for the same endpoint

Example rejection sequence



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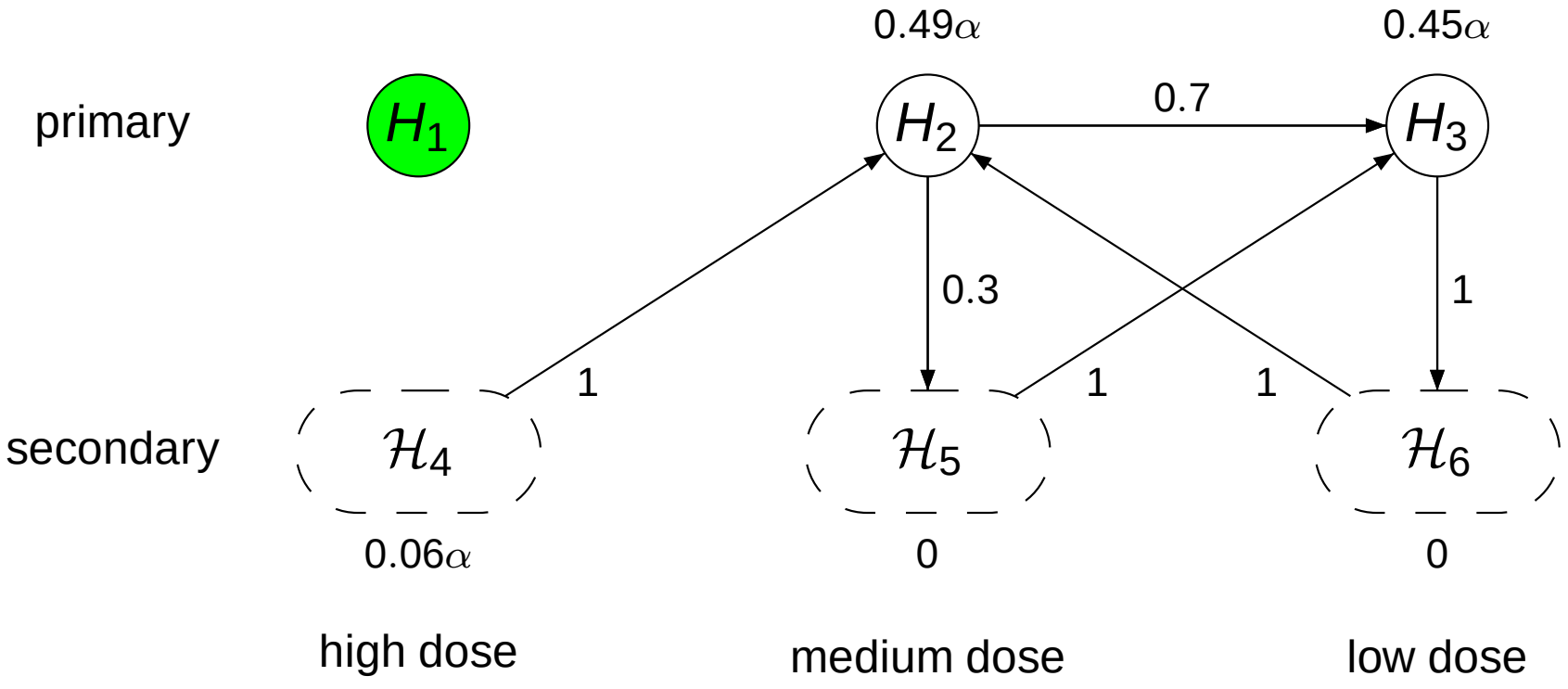
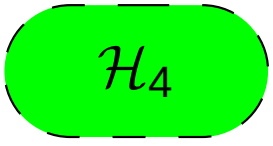


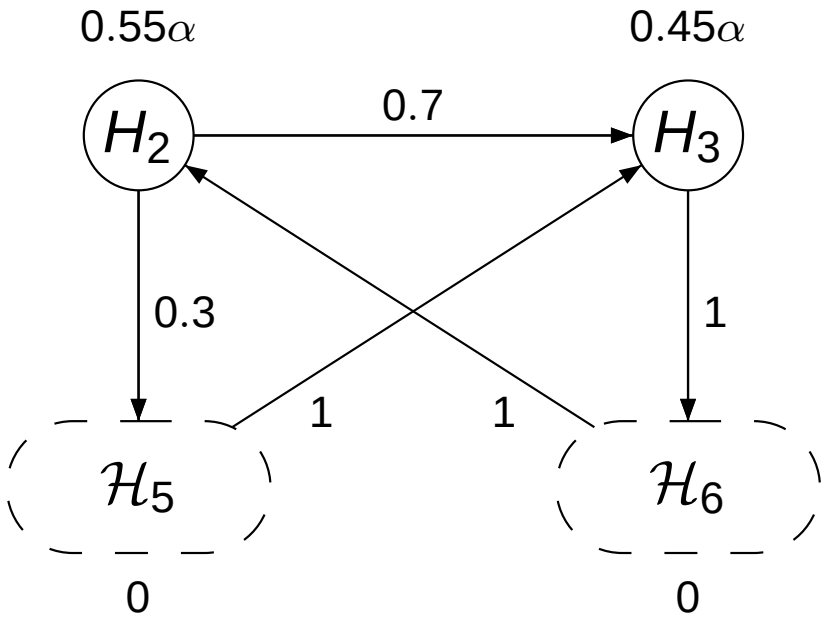
Example rejection sequence

primary

secondary



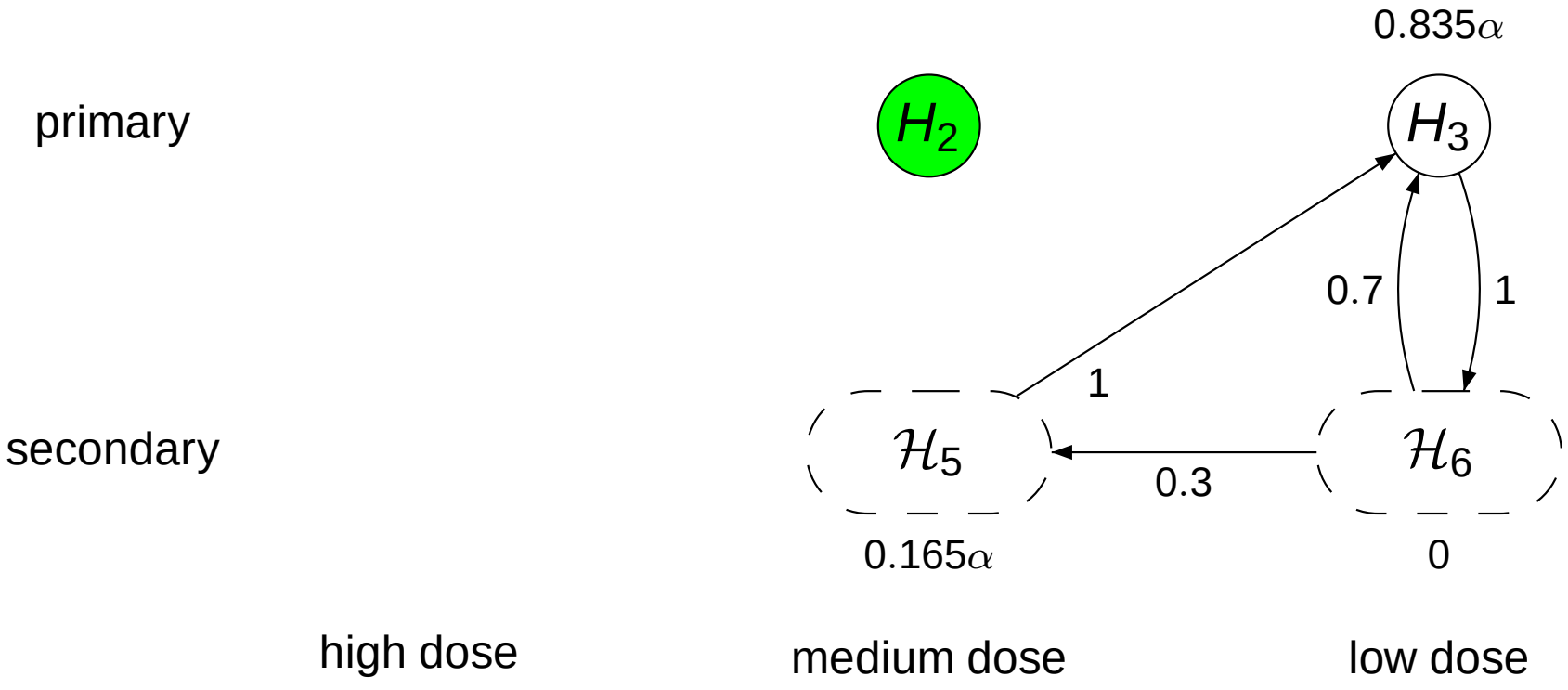
high dose



medium dose

low dose

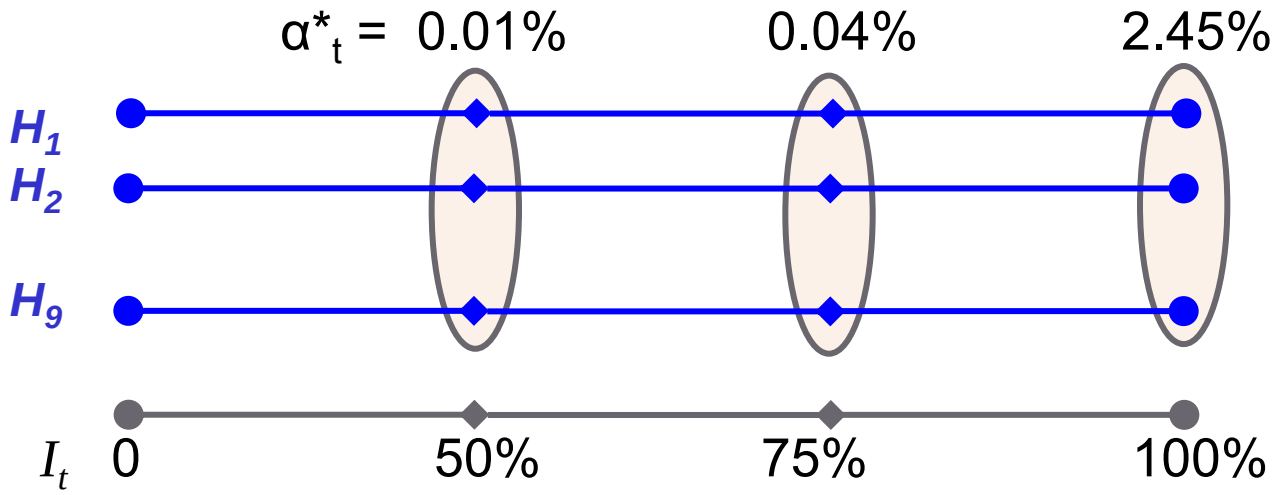
Example rejection sequence



Case study

Interim analyses: Bonferroni inequality for the repeated hypothesis testing

- Interim analyses at 50% and 75% information fraction I_t
  - A fixed Bonferroni split is used, with nominal overall significance levels α^*_t, t = 1, 2, 3, of 0.01% and 0.04% for the first and second efficacy interim analysis, leaving 2.45% for the final analysis.
  - At each of the 3 analyses, the graphical testing procedure exploiting correlations between test statistics will be performed at the respective nominal level α^*_t, controlling the familywise type I error rate at the overall (one-sided) significance level α = 2.5%.



Note: If a primary hypothesis is rejected, the respective secondary hypothesis cannot be tested at the full level α, even if the trial is stopped !

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Summary and conclusions

- Confirmatory clinical trials are becoming increasingly more complex, often comparing multiple doses or treatments with a control for several primary and secondary endpoints.
- The multiple study objectives are reflected by structured families of hypotheses that are characterized by multiple groups of “parent” primary hypotheses and “descendant” secondary hypotheses.
- Novel graphical approaches for constructing and visualizing complex multiple test procedures with a focus on structured families of hypotheses are well suited to facilitate communication in clinical teams and to provide transparent decision strategies.
- Graphical procedures ensure strong control of the overall Type I error rate across all primary and secondary hypotheses.
- Multiple test procedure should be customized based on operating characteristics obtained via clinical scenario simulation.
- Ideally, EMA could provide in its new guidance a harmonized terminology and framework categorizing study objectives and endpoints with respect to their impact on approval and labeling and respective need for type 1 error control.

References

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Back-up

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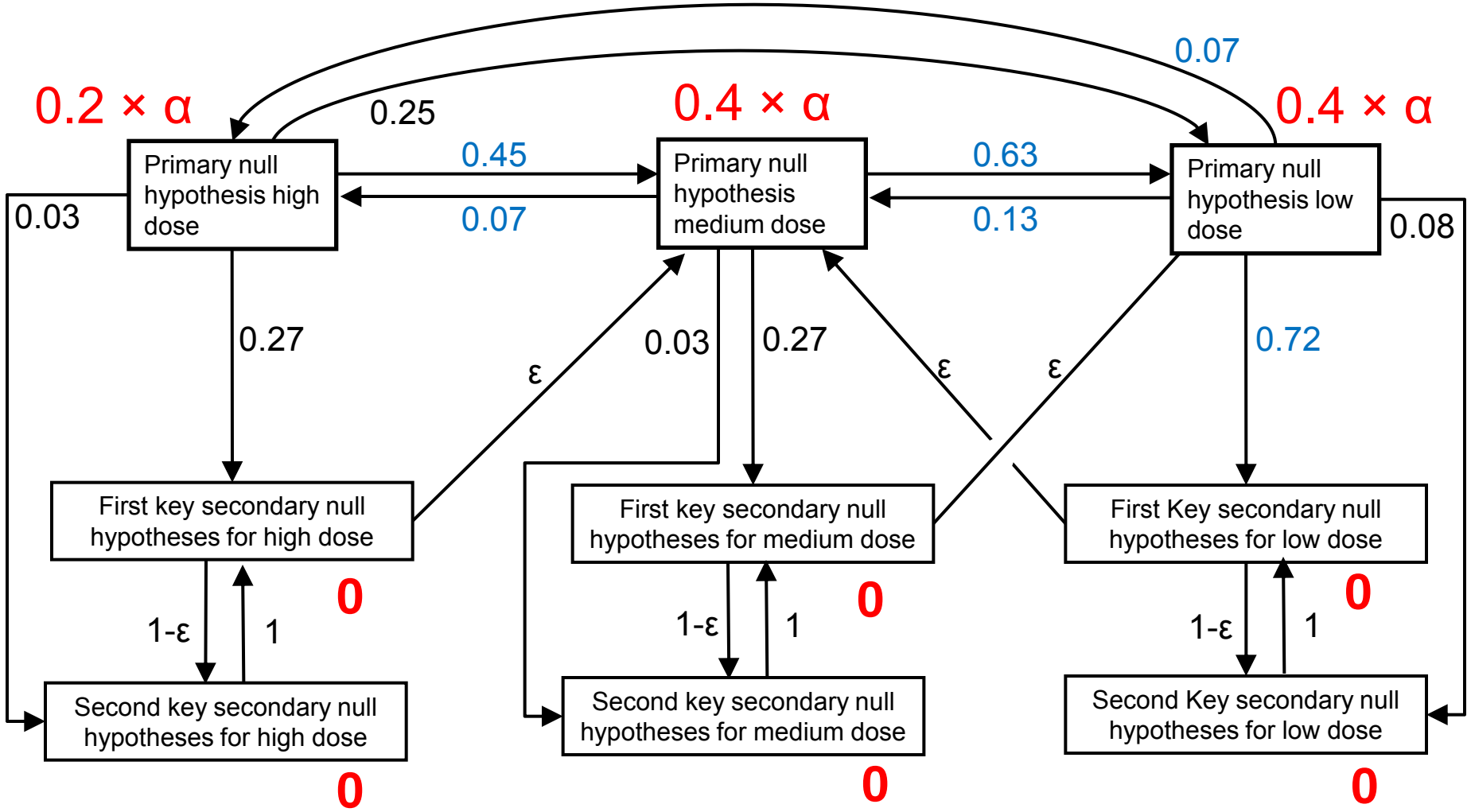
Case study

Improvement of the multiple testing procedure by using weighted Dunnett's test for all intersection hypotheses that contain at least two of H_1, H_2 and H_3 for the same endpoint



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