Discussion of Case study 3: a phase 3 study with 2 doses and secondary endpoints (Vincent Haddad)

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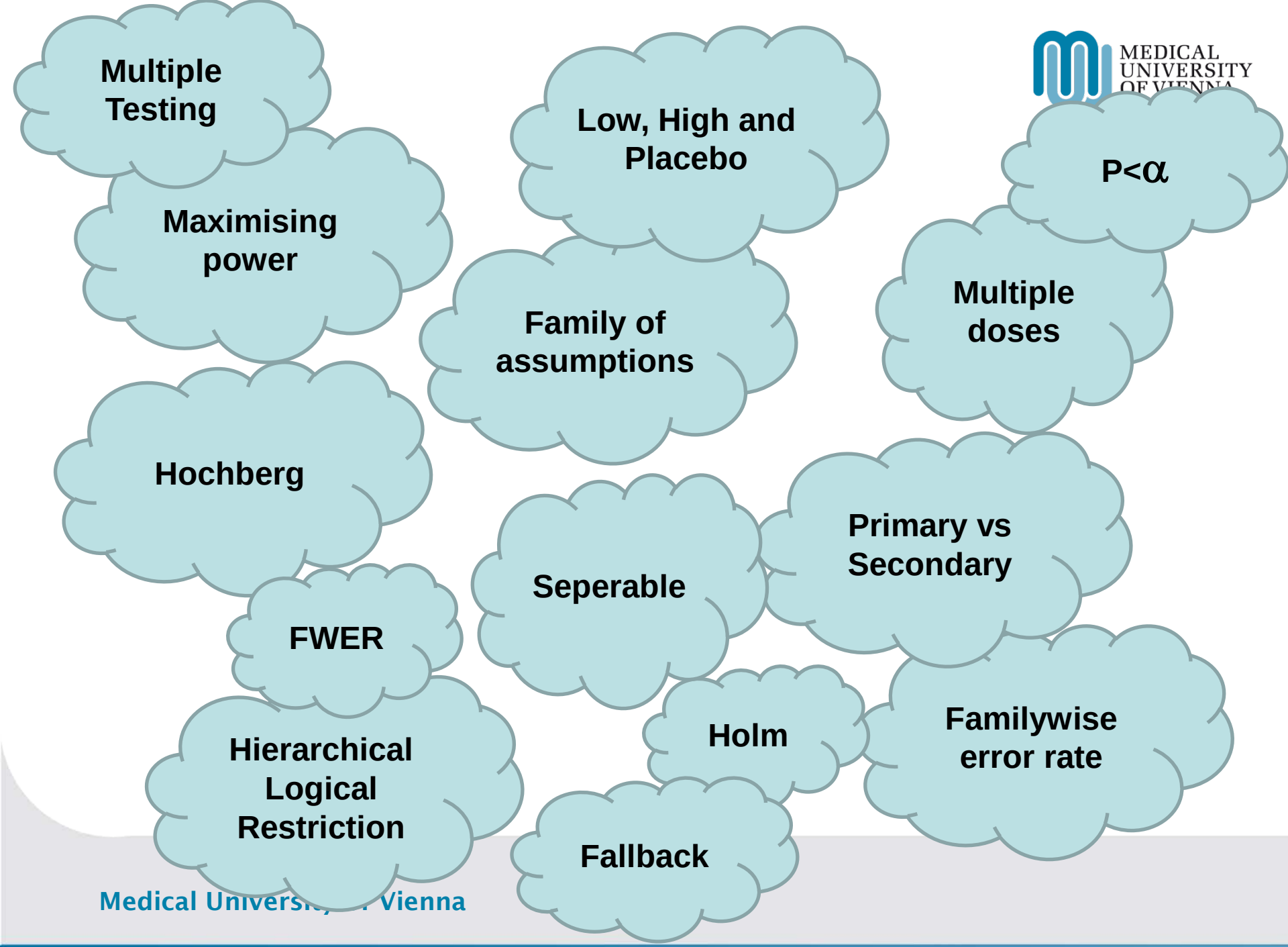

Multiple Testing
Low, High and Placebo
P<α
Maximising power
Family of assumptions
Multiple doses
Hochberg
Seperable
Primary vs Secondary
FWER
Holm
Familywise error rate
Hierarchical Logical Restriction
Fallback

Multiple Testing

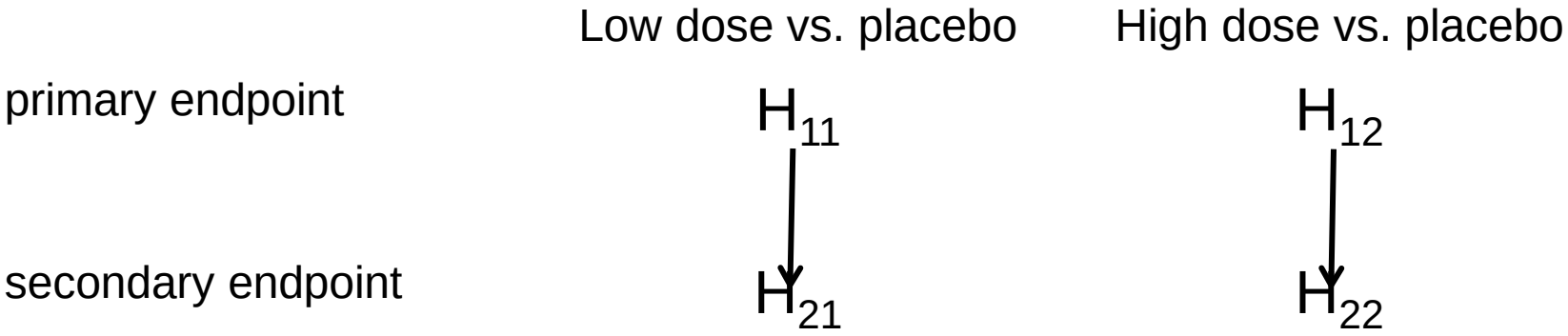
P<α

CONTROL OF PATIENT RISK:

PROB OF AT LEAST ONE FALSE POSITIVE CLAIM < α (2.5%)

Resti

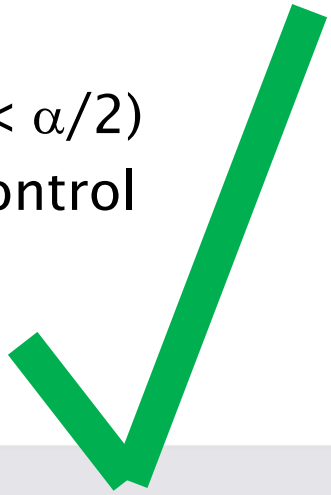
Visualize Testing Strategy



What if only primary endpoints were tested

	Low dose vs. placebo	High dose vs. placebo
primary endpoint	H_{11}	H_{12}

- Hochberg (either both p-values < α or one p-value < $\alpha/2$)
- Positive correlated test statistics due to common control group



Under global null (for all hypotheses the null is true)

	Low dose vs. placebo	High dose vs. placebo
primary endpoint	H_{11}	H_{12}
secondary endpoint	H_{21}	H_{22}

Weak type I error control

Some Hi are true and some Hi are false (=alternative is true)

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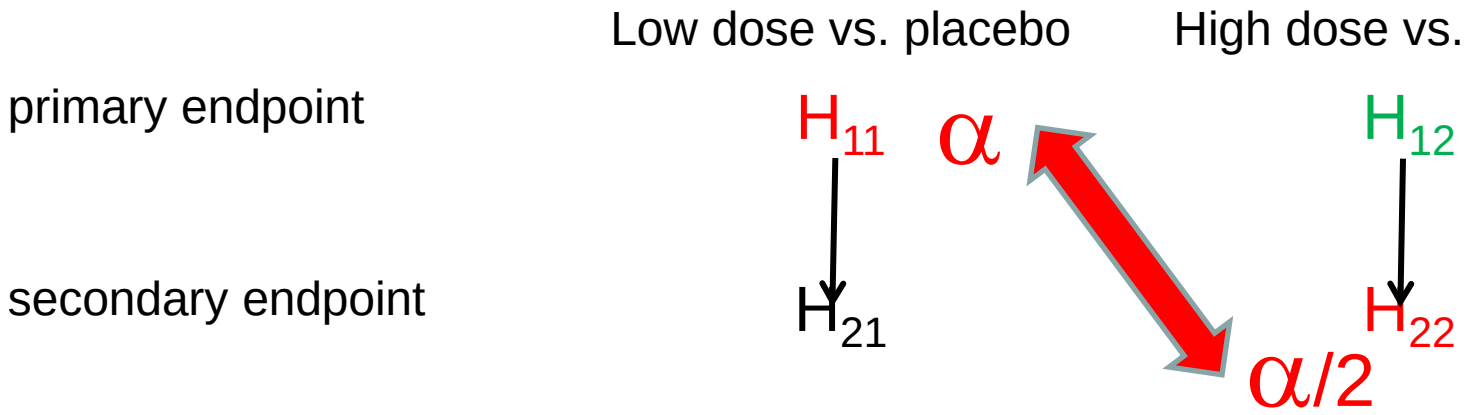
The true effect of the high dose is extremly large causing always very small p



e.g. assuming independence multiple type I error rate inflated up to 0.038 (>0.025)!!!

No strong type I error control =no FWER, no multiple T1E control

Summary

- No (regulatory) problem if successful primary endpoint while no secondary endpoint testing is allowed
- BUT: regulators should care on strict type I error control (for all important variables)

- Current PtC outlines all import principles (sufficient to discuss this case-study)
- A guideline will never be able to include all up-to-date methods
- Better of with a Q&A document to support PtC
- Indication specific guidance for which family of variables multiple type I error control is needed.
- Really curious to see what we will see within the next hours, days, months, years, …