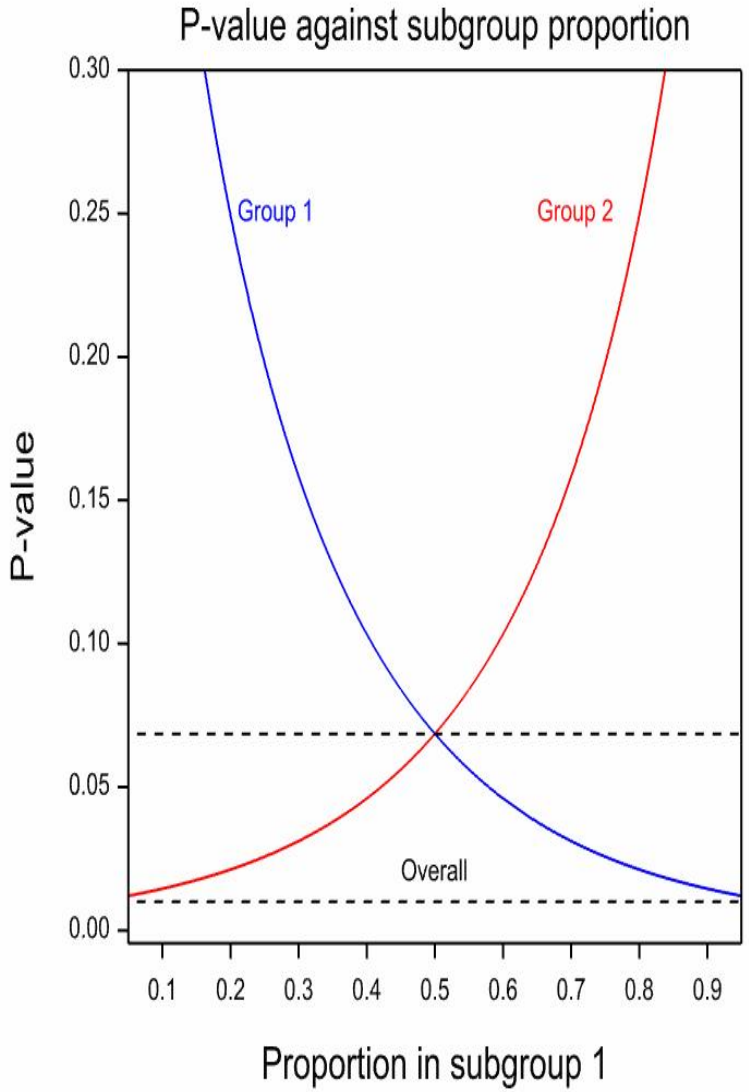
Subgroup analysis: trying to get more from less?

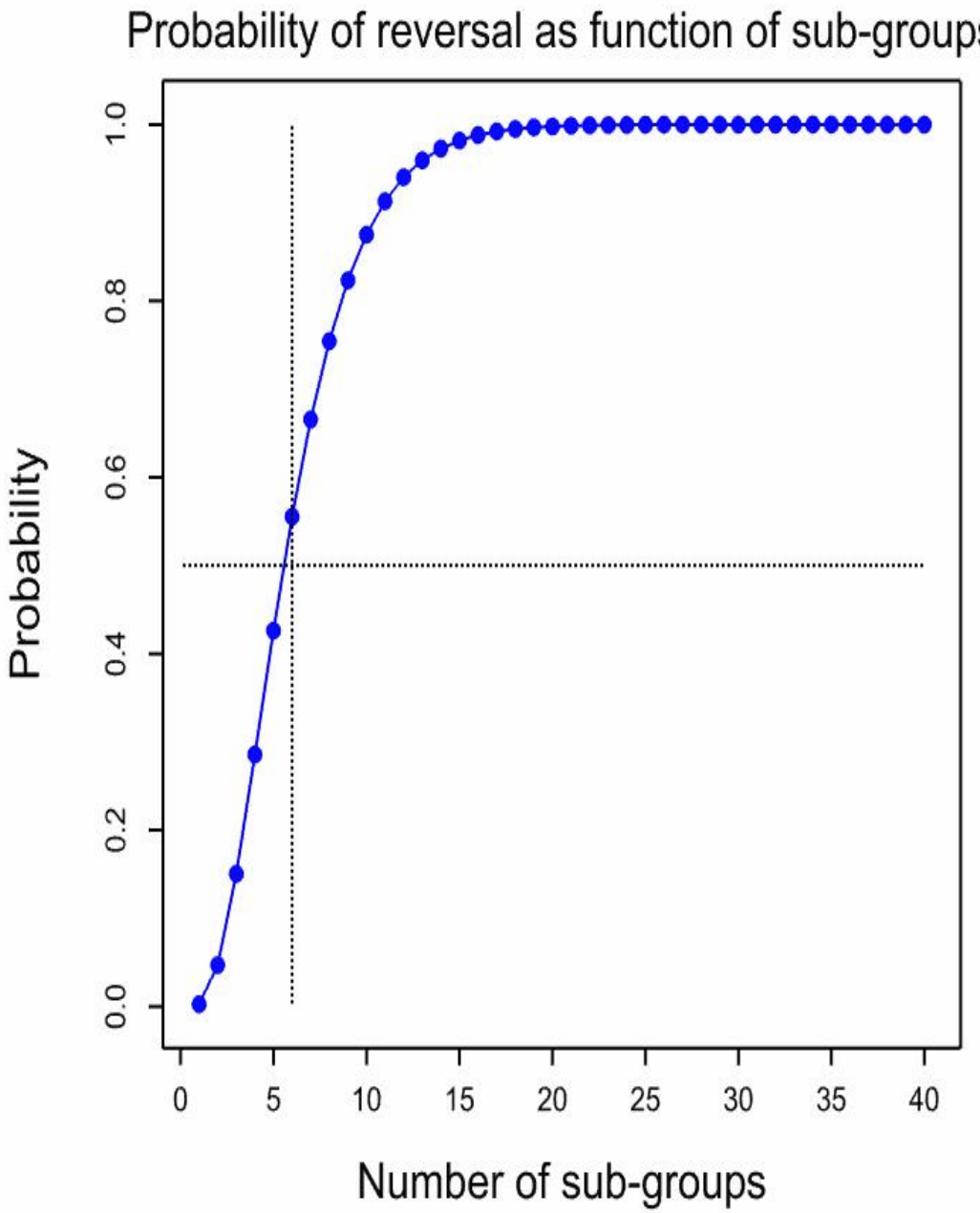
Stephen Senn
Geert Molenberghs*
Franz Koenig
Ralf-Dieter Hilgers

Consider this trial



This is a perfectly behaved trial. The point estimate is identical for the two groups and the overall P-value is 0.01.

Despite that, it is impossible for the P-value in both groups to be less than 0.05.



80% power overall

In each sub-group the *true* treatment effect is identically equal to the clinically relevant difference

Practical Considerations

- There is an opportunity cost in pursuing proof of sub-group benefit
- Trials would have to larger
- Proving effects in subgroups would then compete for patients and finance with other drug development programmes
- The question is as to whether this is a sensible use of resources
- In many cases the priorities, for society, patients and sponsors would be to research new treatments rather than dot the “i”s and cross the “t”s of existing ones

Two extreme different sub-group cases

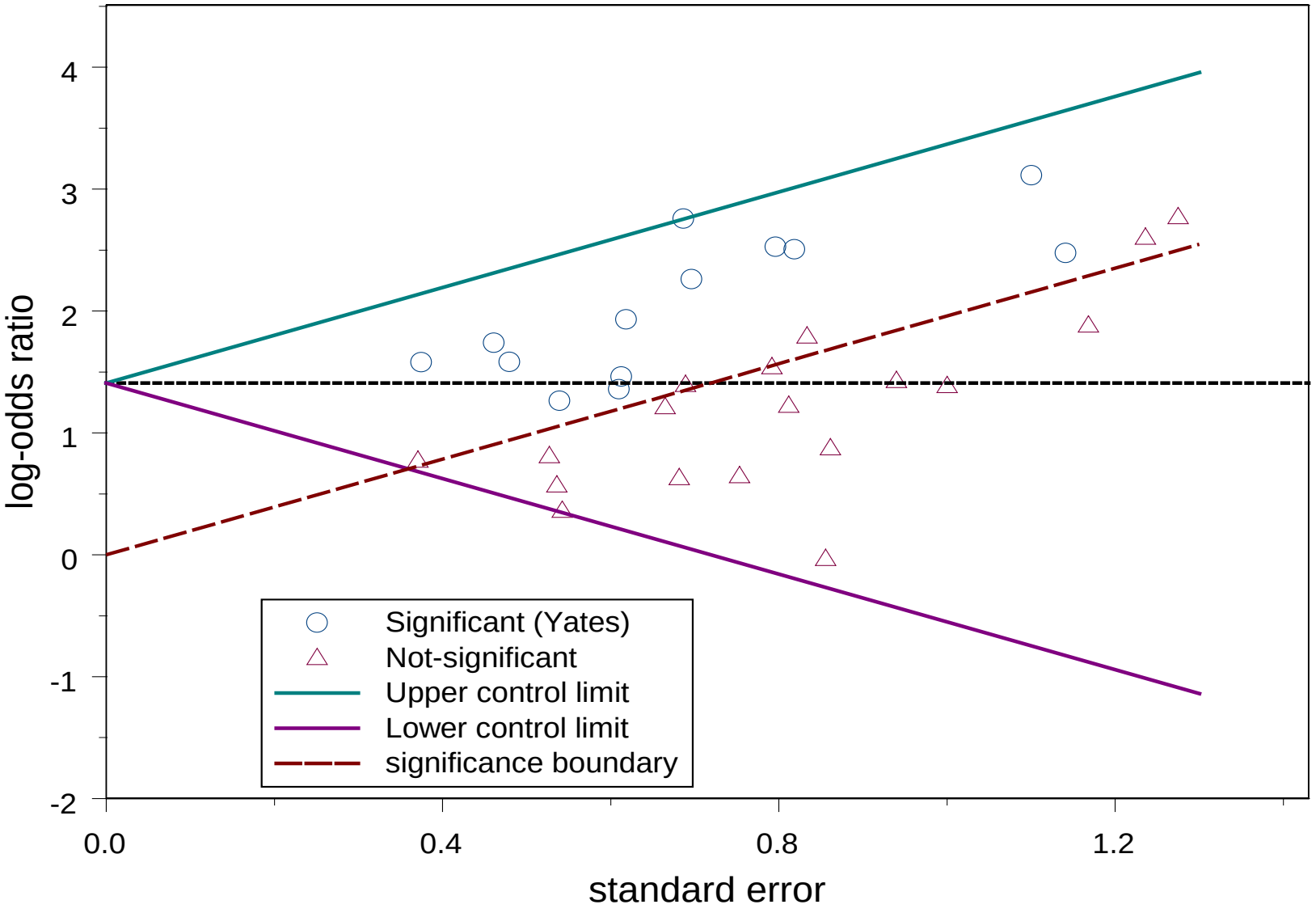
- **A few large subgroups**

- Fixed effect approaches would be the norm
  - For example, testing treatment by sub-group interaction
- However, expectations, of what can be shown should be small
- Proof of efficacy by subgroup not realistic

- **Many small subgroups**

- It may be possible to analyse these using a random effects model
- Some general impression of variability between subgroups may be obtained
- Does this exceed chance levels?

31 Placebo-Controlled Trials of Cimetidine



Two different cases in drug development

- **<u>A substantial average benefit is proven</u>**
- It would be illogical to require efficacy in subgroups for registration
- To do so would require future patients to take an existing treatment that was on average worse, simply because the new treatment had not been shown to be of benefit to all

- **<u>Non-inferiority (only) is shown</u>**
- Here there is not necessarily any great loss in patients continuing to use existing therapy
- Further regulatory assurance that certain groups of patients would not lose by switching might be reasonable

Conclusion

- Failure to provide convincing proof of efficacy in subgroups is the norm
- Clinical trials would have to be much larger for this not to be the case
- Furthermore, as the number of possible sub-groups increases the probability of a spurious ‘effect-reversal’ increases
- It is necessary to be realistic and modest in one’s ambitions
- Regulators should not demand and should not generally expect proof of efficacy in sub-groups
- The priorities in drug-development lie elsewhere

This project has received funding from the European Union’s 7th Framework Programme for research, technological development and demonstration under Grant Agreement no 602552