

Adaptive clinical trials with subgroup selection

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Setting

Definitive comparison of experimental treatment with control

Single predefined subgroup of interest

Research questions: is treatment effective in whole population
is treatment effective in subgroup

For confirmatory study wish to control risk of any false positive
Control familywise error rate in strong sense at specified level

(Wang et al 2007, Song & Chi 2007, Brannath et al 2009, Spiessens & Debois 2010, Jenkins et al 2011)

Adaptive design – idea

We are testing hypotheses in full population and subgroup

Controlling false positives means it is harder to show efficacy

If we knew which hypothesis to test, could focus on that

Adaptive design idea:

- use interim data to guide hypothesis to test in remainder of trial

Adaptive design – details

Stage 1: Recruit from full population

On basis of interim data decide to continue to

(i) test full and sub-populations at final analysis

(ii) test full population only final analysis

(iii) test sub-population only final analysis

(possibly include interim data on short-term endpoint)

Stage 2: Cases (i) or (ii): continue to recruit from full population

Case (iii): recruit from subgroup only

Final analysis: Conduct selected tests

Control error rate allowing for test selection

(Song & Chi 2007, Brannath et al 2009, Jenkins et al 2011)

Test statistics

Test $H_0^{\{F\}}$ (full population) and $H_0^{\{S\}}$ (sub population)

At stage i , let

$p_i^{\{F\}}$ and $p_i^{\{S\}}$ be p-values for full and sub-population

$Z_i^{\{F\}}$ and $Z_i^{\{S\}}$ be test statistics for full and sub-population

$$p_i^{\{F\}} = 1 - \Phi(Z_i^{\{F\}}), p_i^{\{S\}} = 1 - \Phi(Z_i^{\{S\}})$$

Assume $Z_i^{\{F\}}$ and $Z_i^{\{S\}}$ normal with
unit variance

correlation $\sqrt{\tau}$ where τ is proportion in subgroup

(Spiessens and Debois 2010)

Controlling the overall error rate

Bonferroni test

$$p_i^{\{F,S\}} = 2 \min\{p_i^{\{F\}}, p_i^{\{S\}}\}$$

Simes test

$$p_i^{\{F,S\}} = \min\{2 \min\{p_i^{\{F\}}, p_i^{\{S\}}\}, \max\{p_i^{\{F\}}, p_i^{\{S\}}\}\}$$

(Simes 1986)

These tests ignore correlation between $p^{\{F\}}$ and $p^{\{S\}}$

Spiessens and Debois test

Obtain p-value based on distribution of $\max\{Z_i^{\{S\}}, Z_i^{\{F\}}\}$
(Spiessens and Debois 2010)

Combining stages 1 and 2

Combination test

Obtain overall p-value for each hypothesis using
pre-specified combination function

(Bretz et al 2006)

Conditional error function approach

Obtain design assuming testing both hypotheses
At interim analysis obtain error rate for second stage
conditional on stage 1 data

Can redesign stage 2 so long as conditional
error rate is controlled

e.g. restrict testing to full population or subgroup alone
(Müller and Schäfer 2001, Friede et al 2011)

Simulation study

Based on Brannath et al. (2009) and Jenkins et al. (2011)

Model: Normal approximation for logrank test statistics

Standardised effects based on

haz. ratio: 0.77 in subgroup, 1 outside subgroup

$n_1 = 170$, $n_2 = 748$ (if recruit from full population)

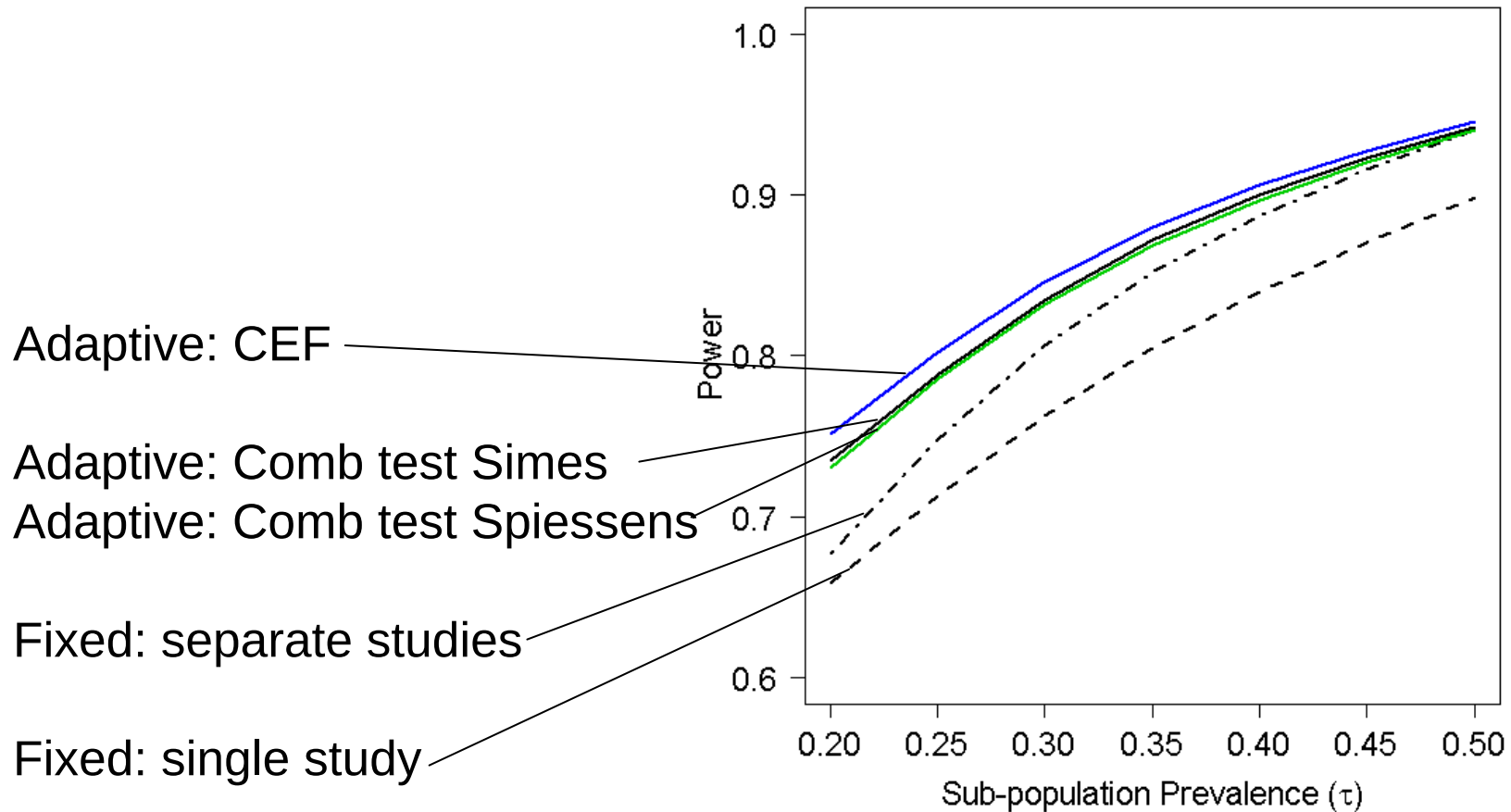
470 (if recruit from subgroup)

Subgroup prevalence: 20% to 50%

Fixed designs: single study testing both hypotheses
two separate studies

Adaptive designs: CEF test with Spiessens and Debois test
combination test with Spiessens test
combination test with Simes test

Simulation study results



Conclusions

We may want to test treatment in a subgroup in addition to full population

In confirmatory test need to control overall error rate

Adaptive design allows us to use interim analysis data to select hypothesis(hypotheses) for final analysis

Appropriate methodology exists to control overall error rate

Adaptive design appears more powerful than either:
fixed single stage design adjusting for multiple testing
selection of hypotheses in separate study

We have assumed a pre-defined subgroup. Allowing for use of interim data to select subgroup is harder!

References

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