

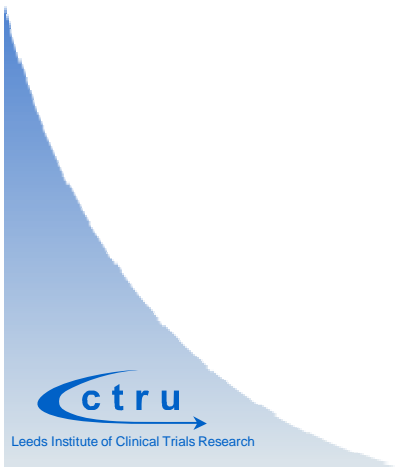
Futility analysis considerations for a phase II trial with short term non-inferiority and long term superiority co-primary endpoints

Samantha Hinsley, Sarah Brown

Leeds Institute of Clinical Trials Research, University of Leeds, UK

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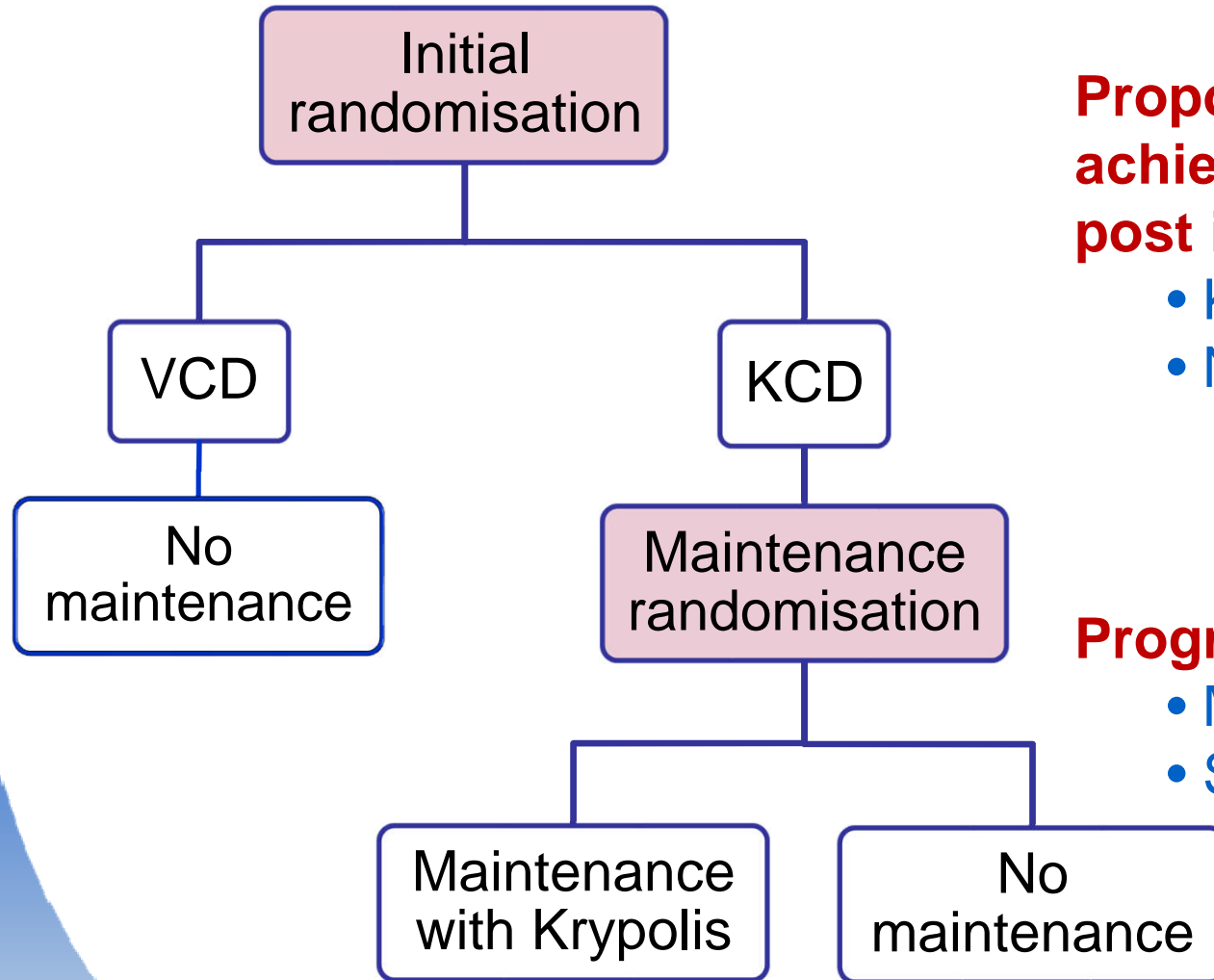
15th – 18th May 2016



Futility analyses

- Stop if, based on the current data, we are unlikely to observe a significant result at the end of the trial
- Improve efficiency
- Reduce number of patients recruited
- Reduce number treated with ineffective regimens

MUK five trial design



Co-primary endpoints:

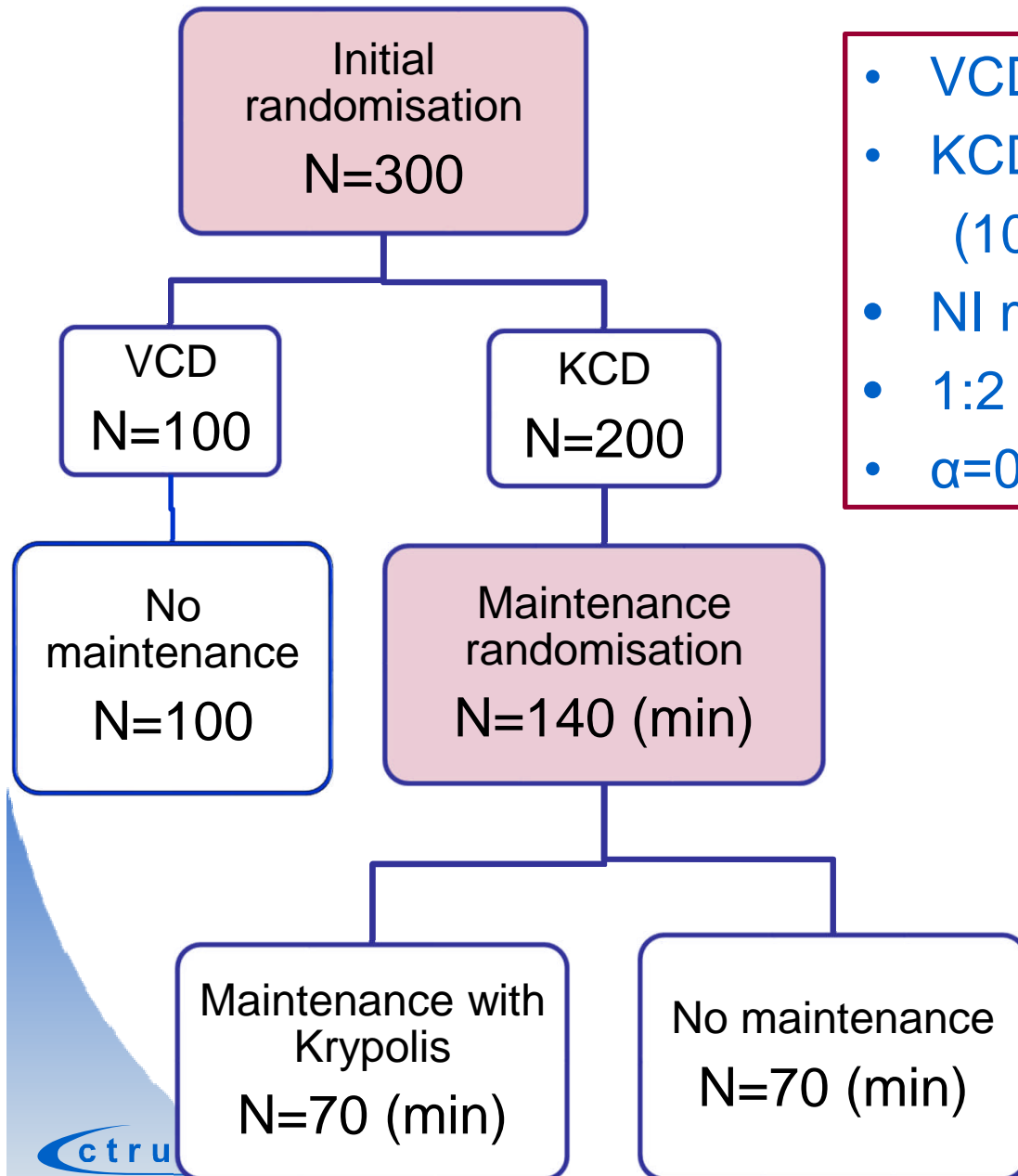
Proportion of patients achieving \geq VGPR 24-weeks post initial randomisation

- KCD vs. VCD
- Non-inferiority

Progression-free survival

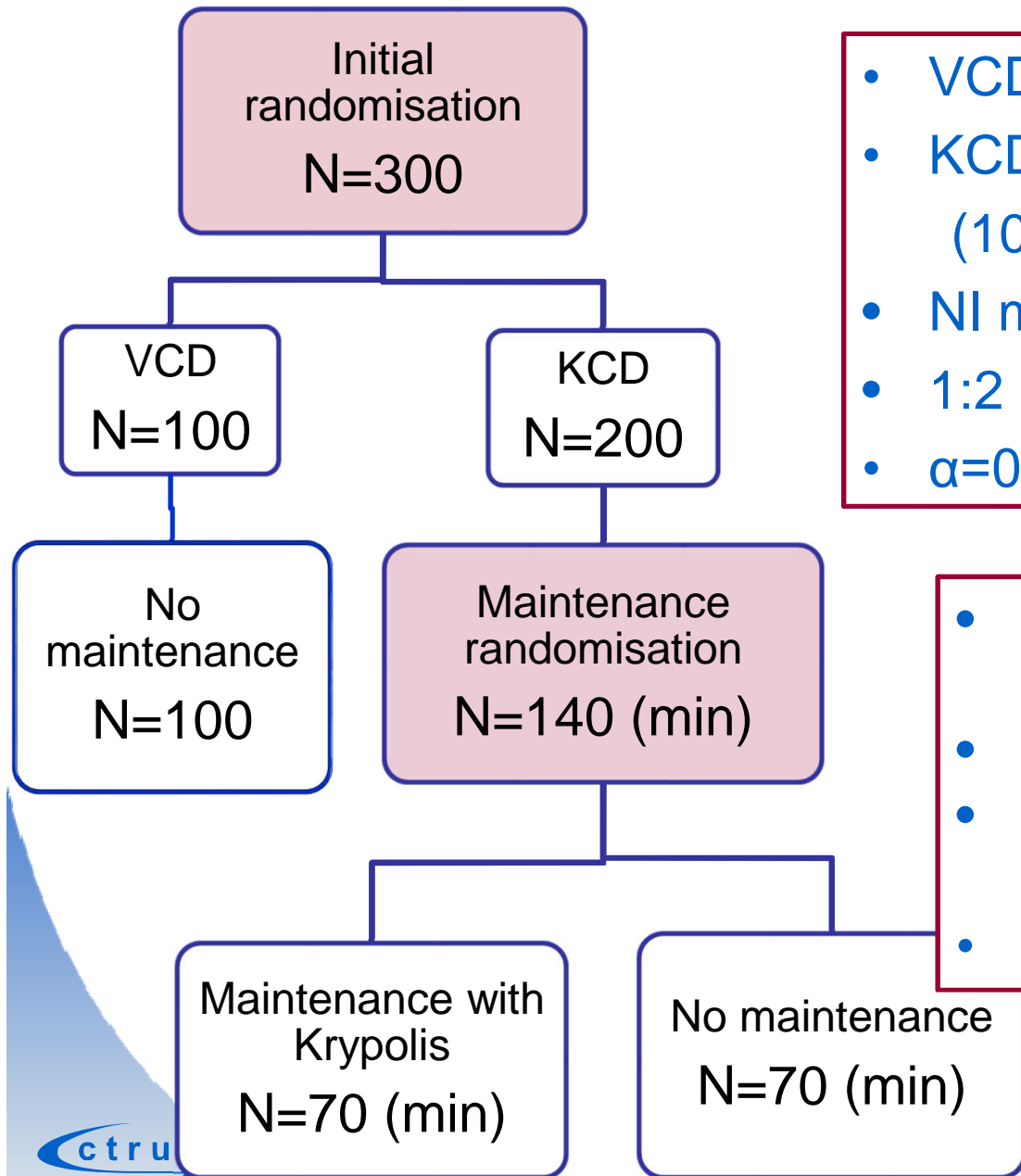
- Maint vs. no maint
- Superiority

Sample size



- VCD: \geq VGPR rate of 35%
- KCD: \geq VGPR rate of 45% (10% improvement)
- NI margin of 5%
- 1:2 randomisation
- $\alpha=0.05$ (1 sided), power=80%

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- PFS measured from maint randomisation
- No maint: median PFS 12m
- HR=0.67 (increase 6m in median PFS)
- $\alpha=0.2$ (2 sided), power=80%

MUK five futility analysis considerations

- Analysis methods based on short term co-primary endpoint

**Proportion of patients achieving \geq VGPR
24-weeks post initial randomisation**

- After 50% of patients (150) have reached the time-point

Options considered:

- Conditional power
- Conditional power only if treatment difference $\leq 10\%$
(Difference of 10% anticipated / powered)
- No futility analysis, with the option of an inferiority analysis
(As safety is a key driver)

Conditional power

The power to show non-inferiority at the final analysis (under different assumptions on the remaining patients) given the current data.

Perform simulations to estimate the number of \geq VGPRs at the final analysis under different scenarios:

- Generate data to represent remaining patients
- Combine simulated patients with current 150 patients and calculate treatment difference and confidence interval

Repeat & combine results to find conditional power:

- Percentage of simulations that have demonstrated non-inferiority



Conditional power – simulation scenarios

NO TREATMENT DIFFERENCE

- \geq VGPR rate of 35% with both KCD and VCD

AS POWERED FOR

- 10% difference: \geq VGPR rate of 45% with KCD and 35% with VCD

OPTIMISTIC ('best case' scenario)

- Calculate 95% CI of difference seen in first 150 patients
- Use upper limit for difference to simulate under, assuming \geq VGPR rate for VCD as seen in first 150 patients

Conditional power – simulation scenarios

OPTIMISTIC – Example

- Calculate 95% CI of difference seen in first 150 patients

VCD: 36% (18/50 patients) \geq VGPR

KCD: 50% (50/100 patients) \geq VGPR

Difference: $50-36=14\%$, with 95% CI (-2.5%, 30.5%)

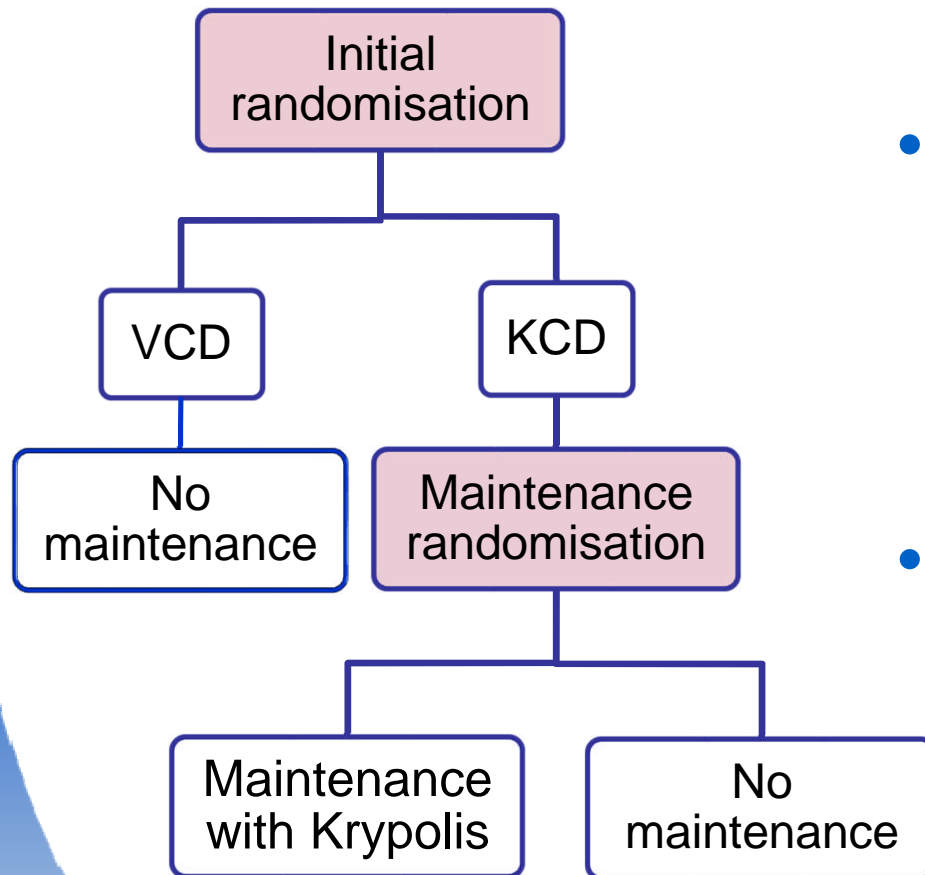
- Use upper limit for difference to simulate under, assuming \geq VGPR rate for VCD as seen in first 150 patients

Assumptions for simulations of remaining patients:

VCD: 36% as observed

KCD: $36+30.5=66.5\%$ using upper limit of 95% CI

Choosing a method



- Choice depends on how the two co-primary endpoints interact
- Maintenance question still relevant if KCD not non-inferior
 - No futility analysis to be performed
- Not relevant if KCD inferior
 - Inferiority interim analysis to be performed

Reminder: not non-inferior \neq inferior

Conclusions

- Conditional power provides a useful way to consider futility analyses for non-inferiority endpoints
- With co-primary endpoints, the use of a futility analysis requires more thought
- Depends on the interaction of the endpoints
- With a short-term and long-term endpoint combination, the relevance of the long-term endpoint needs to be considered