Adaptive decision making for cardiovascular outcomes in diabetes drug development

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Non-adaptive two stage CV trial design

Assuming group sequential design

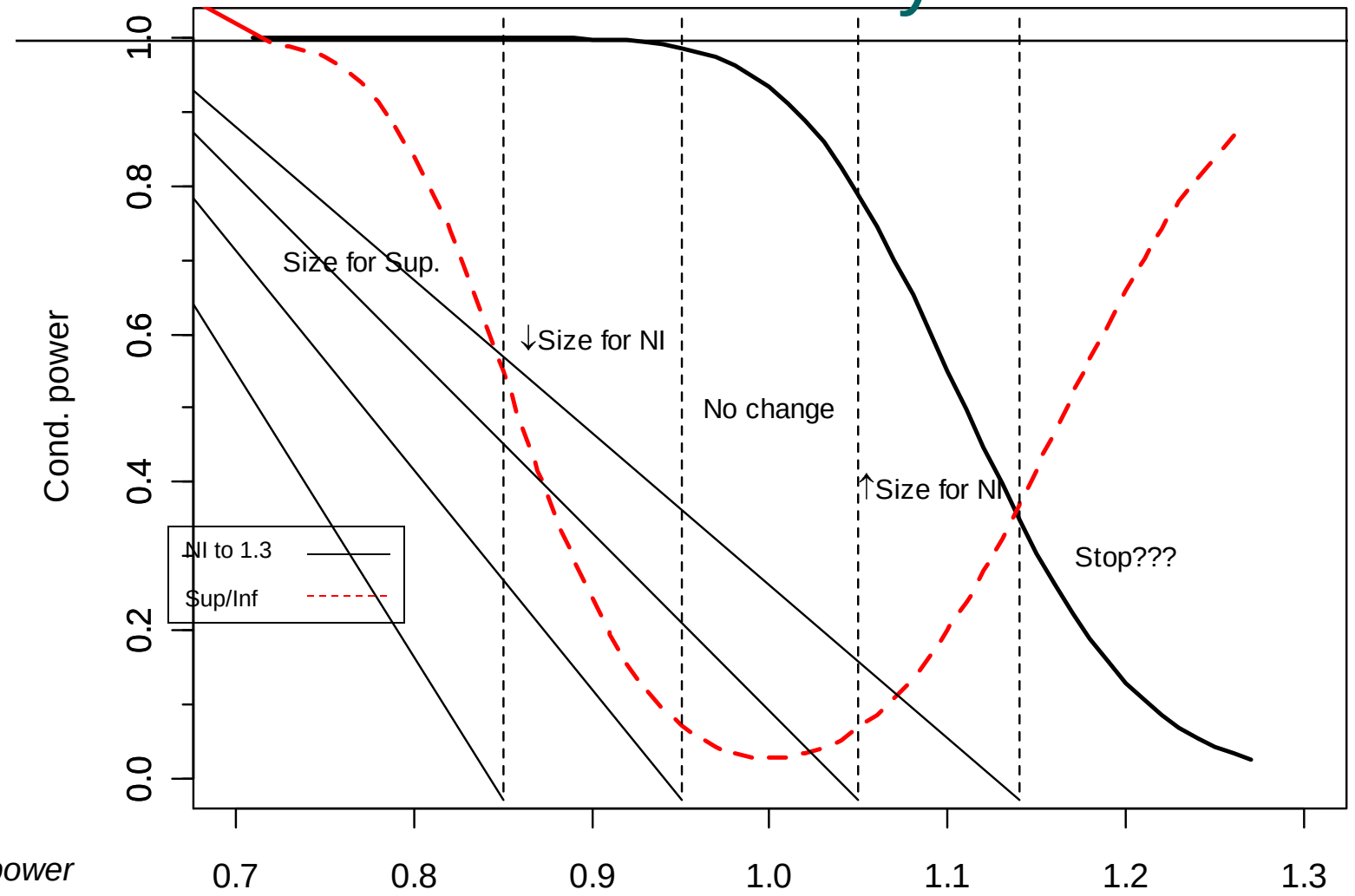
Stage	Cohort 1	Cohort 2
NI margin	1.8	1.3
# events	122	489
Sample Size	3000-4000 ‡	~4500‡
Duration	~2.5 years	~5 years
Largest obs HR	1.26	1.14

‡depending on event rate, enrollment, dropout, duration, alpha spending function

What do we do after the first cohort?

- FDA guidance – if make 1.8, can file
- Discussions generally center around "file" or "not file"
  - i.e. do we conduct, or not, the "confirmatory" trial
- But wide spectrum of possible results – what more can we do based on the first cohort besides this binary decision
  - Sample size
  - Hypothesis (non-inferiority vs superiority)
  - Spending functions

Conditional Power Analysis



NOTE: Cond. power evaluated assuming true HR=Obs. HR at final look for 1.8.

Additional # **EVENTS** required for cohort 2, based on results from cohort 1

	Add'l # events needed for NI to 1.3 with cond. Power of		Add'l # events needed for Superiority with cond. Power of	
Obs. HR at end of cohort 1	80%	90%	80%	90%
0.71	16	30	145	214
0.85	78	121	1040	1421
0.95	205	298	13202	17459
1.05	573	798	na	na
1.14	1822	2469	na	na
1.27	71308	93904	na	na

NOTE: Computed assuming true HR = observed HR at conclusion of cohort 1

A decision rule for an adaptive design strategy

Assuming group sequential design

Range of observed hazard ratio	Feasible action for cohort 2
<0.55*	Declare superiority after 1st cohort, 2nd cohort not needed
0.55-.85	Repower 2nd cohort for superiority (increase or decrease sample size based on observed HR)
0.85-0.95	Resize 2nd cohort for non-inferiority (decrease sample size since overpowered for non-inferiority to 1.3)
0.95-1.05	Keep original design
1.05-1.14	Increase sample size to meet non-inferiority
>1.14	Not feasible to conduct 2nd cohort

*Exact boundary depends on spending function

Conclusions

- Complex decision to be made at time of initial registration because it is possible to meet the 1.8 threshold but have <50% chance of success for 1.3
- Adaptive development program allows sponsor to respond to interim data
- Important that regulatory agencies support pragmatic issues to allow an adaptive program
  - Limited unblinding of sponsor personnel necessary for decision making
  - Re-use of patients and events in cumulative meta-analysis approach
  - Return of alpha for Cohort 2 analysis