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Design choice for small-scale phase II trials with non-inferiority (NI) intention

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Background

- NI intention for
  - Same drug/therapy with reduced dose
  - Different treatments with less toxicities and more convenience
  - Better strategies/drug combinations
- Mostly for phase III trials
- Practical issues, e.g. required large sample sizes, difficult to choose NI margin

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Raised questions

- Could it be too late if only evaluate NI in phase III setting?
- Can NI intention also be evaluated in phase II trials?
- Are phase II NI trials necessary and feasible?
- Are there any design choices for trials with NI intention in phase II setting?
- How large the sample sizes are needed?
- Anything should be paid more attention?

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Methods for NI in Phase II trials

- Frequentist hypothesis testing
  - Single-Arm
  - Two-Arm
- Confidence interval (C.I.) approach
  - Single-Arm
  - Two-Arm

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Designs for continuous&binary endpoints

- Confidence interval for one mean/proportion
- One-mean/one-proportion Non-inferiority
- Confidence interval for two means/proportions
- Phase II non-inferiority (two arms comparison with means/proportions)

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Case study

- P0=0.5, α=0.05, Margin(δ)=Width=P0-Pi (i=1,2,3)
- 12 random samples

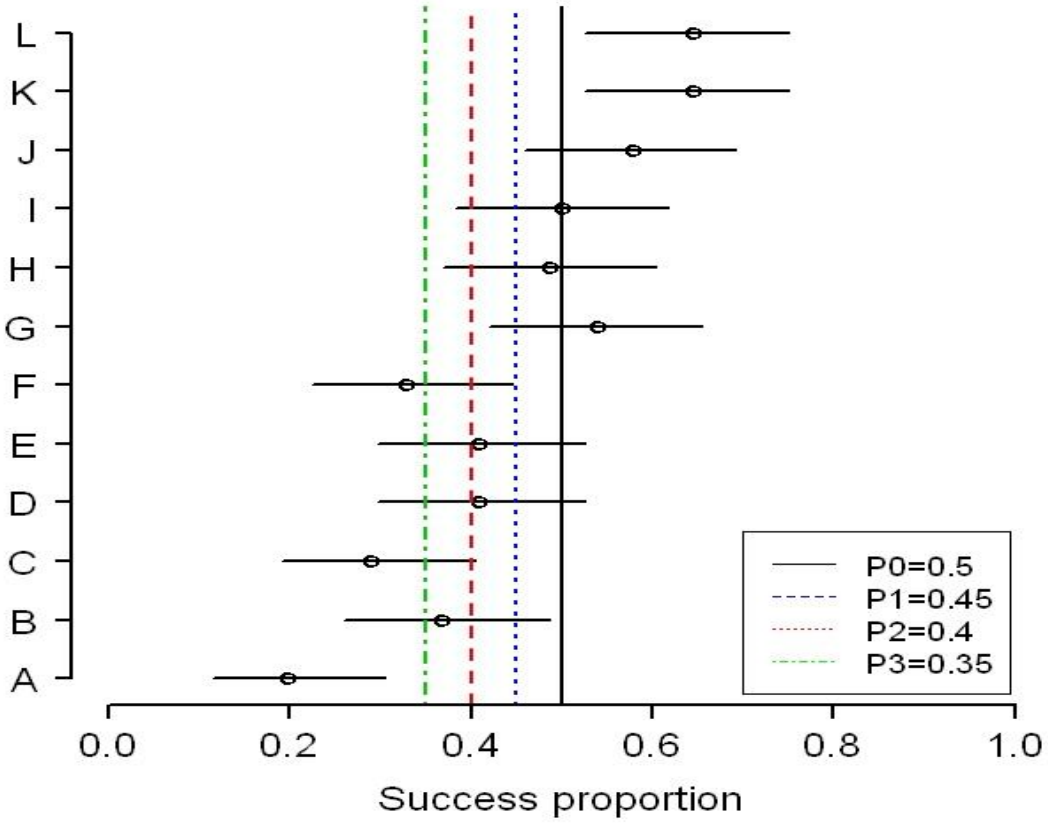

Figure 1: Proportions and confidence intervals for random samples

C.I. for one proportion

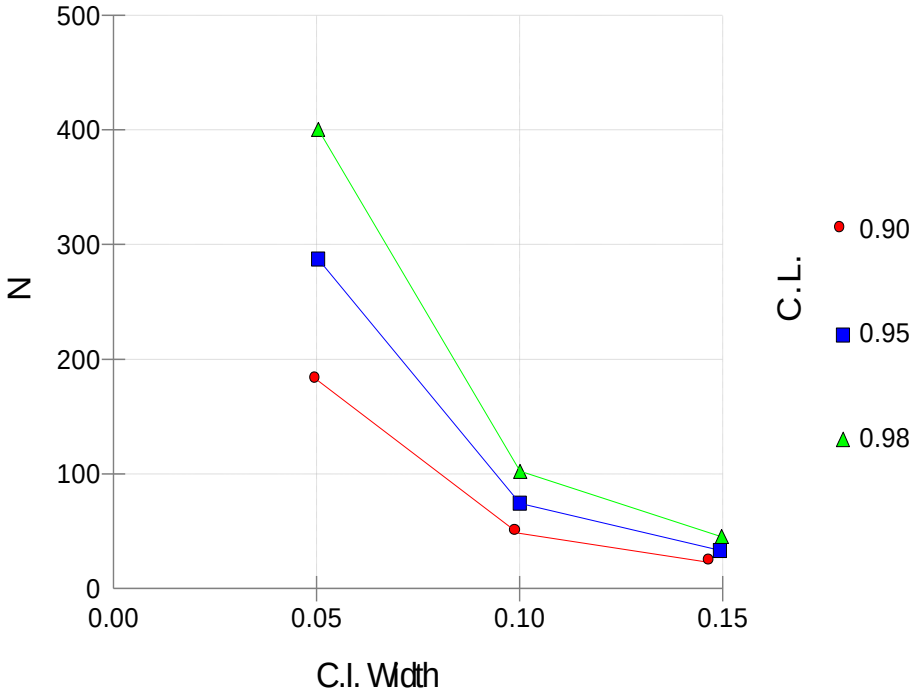

***Figure 2: Sample sizes (N) vs. confidence interval (C.I.) width by different confidence* levels (C.L.)**

Table 2: Sample sizes for single-arm confidence interval approach

Total Sample size	***Confidence level (1- α)%***		
C.I. Width	**97.5%**	**95%**	**90%**
D=0.05	402	289	183
D=0.1	104	76	50
D=0.15	47	35	24

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One-proportion Non-inferiority

Table 2: Sample size for One-proportion Non-inferiority approach

Total sample size (N)		Power (1-β)		
		90%	**80%**	**50%**
δ =0.05	***α =0.025***	1055	789	387
	α =0.05	861	618	269
	α =0.10	658	451	169
	α =0.20	461	294	73
δ =0.1	***α =0.025***	262	195	97
	α =0.05	214	158	69
	α =0.10	168	112	41
	α =0.20	115	77	21
δ=0.15	***α =0.025***	115	85	41
	α =0.05	96	86	29
	α =0.10	72	49	21
	α =0.20	53	32	9

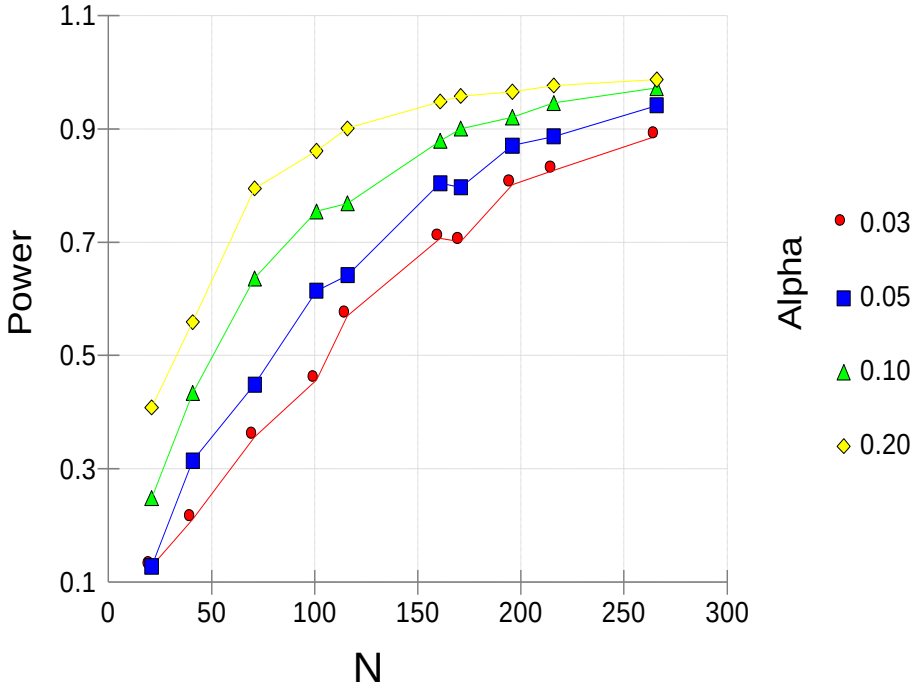

***Figure 3: Sample sizes (N) vs. power by different type one errors* (Alpha)**

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C.I. for two proportions

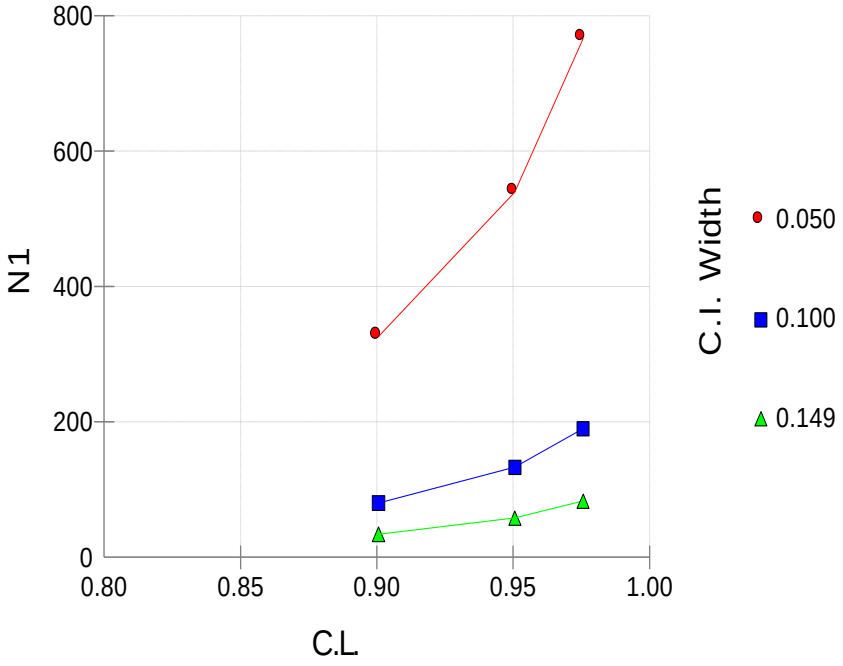

Figure 4: Sample sizes (N1) in one arm vs. different confidence* levels (C.L.) by *confidence interval (C.I.) width

Table 4: Sample sizes for two-arm confidence interval approach

Total Sample size (N=N1+N2)	***Confidence level (1- α)%***		
C.I. Width	**97.5%**	**95%**	**90%**
D=0.05	1538	1084	658
D=0.1	386	272	166
D=0.15	172	122	74

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Phase II NI (two-arm comparison)

Table 2: Sample size for two-arm Non-inferiority approach

Total sample size (N)		Power (1-β)		
		90%	**80%**	**50%**
δ =0.05	***α =0.025***	4204	3140	1538
	α =0.05	3426	2474	1084
	α =0.10	2628	1804	658
	α =0.20	1804	1134	284
δ =0.1	***α =0.025***	1052	786	186
	α =0.05	856	620	272
	α =0.10	658	452	164
	α =0.20	452	284	72
δ=0.15	***α =0.025***	468	350	172
	α =0.05	382	276	120
	α =0.10	292	202	74
	α =0.20	200	114	32

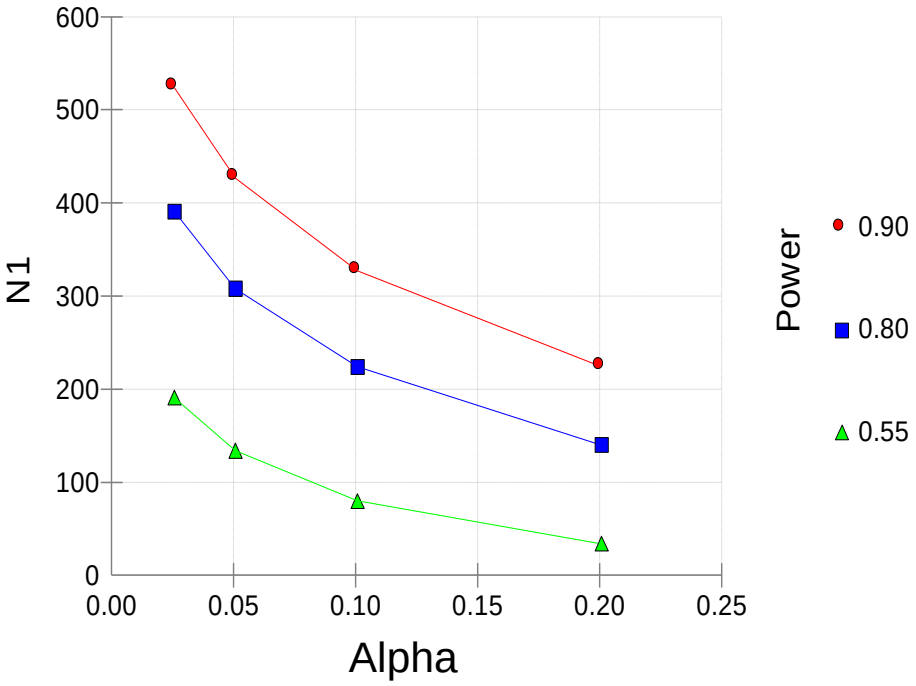

Figure 5: Sample sizes in one arm (N1) vs. type one errors* (Alpha) *by different power

Discussion for NI approach

- Phase II NI is the same as for phase III NI trials with a larger NI margin or alpha
- Larger power, larger sample size
- Smaller type I error, larger sample size
- Smaller margin, larger sample size
- Difficult to choose margin
- Strict decision rule from testing

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Discussion for C.I. approach

- Smaller width, larger sample size
- Smaller confidence level, smaller sample size
- Do not require margin and power
- No rigid go/no-go decision rule
- Other aspects can be considered

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Conclusion

- NI margin in the hypothesis testing approach equal to the width in the C.I. approach
- The sample size from the C.I. approach is always lower than that from NI approach under the same settings.
- Larger sample sizes are required for two-arm than single-arm in both approaches
- Reliable historical references are required for single-arm

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Reference

- Neuenschwander B, Rouyrre N, Holländer N, Zuber E, Branson M: **A proof of concept phase II non-inferiority criterion.** *Statist. Med.* 2011.
- Rubinstein L, Crowley J, Ivy P, LeBlanc M, Sargent D: **Randomized phase II designs.** *Clinical Cancer Research* 2009, 15:1883-1890.

Thank you for your attention

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