Sequential Parallel Comparison Design (SPCD):

Review of a Novel Trial Design

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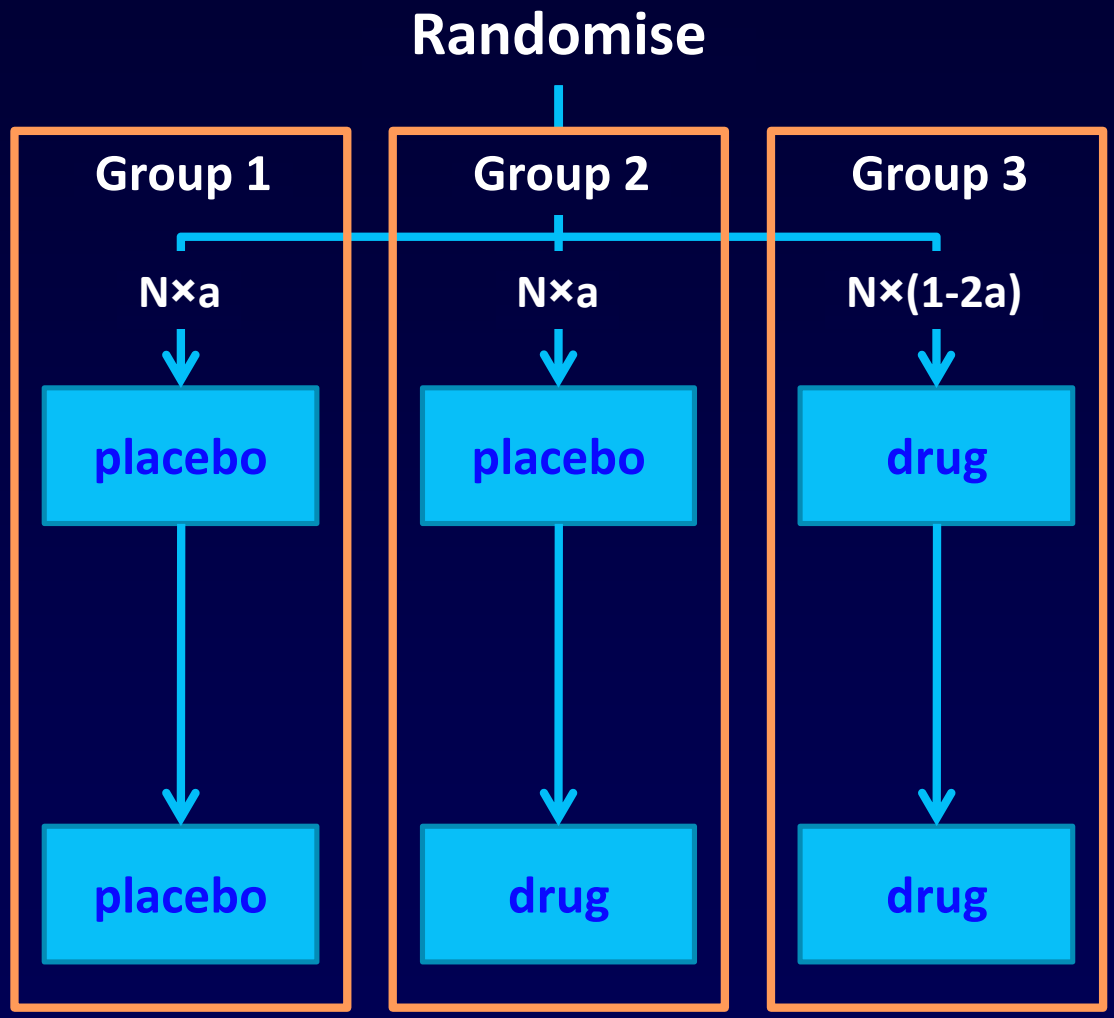
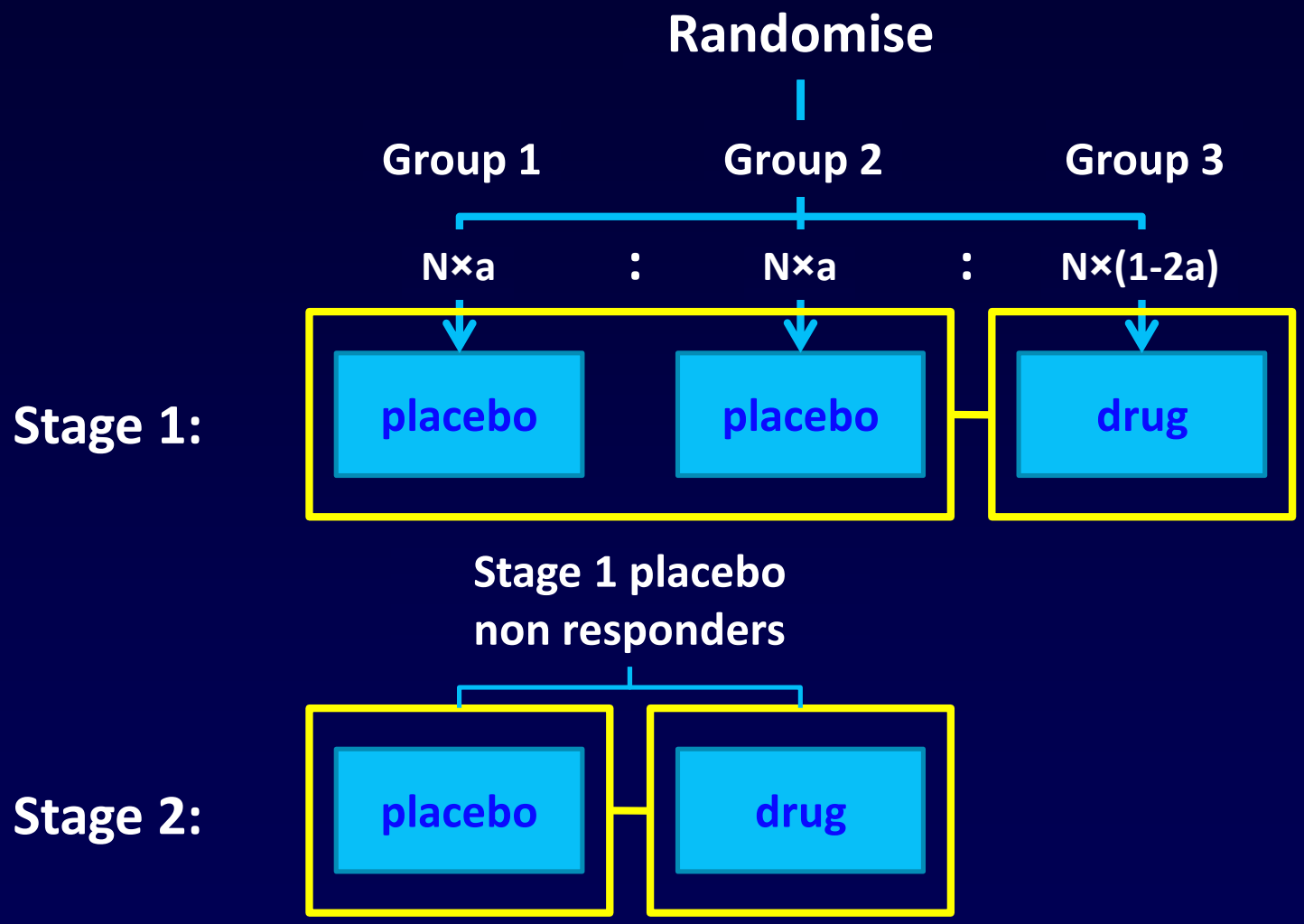
Source material

- Fava M et al. The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach. *Psychotherapy Psychosomastics.* 2003; 72:115-27.
- Tamura R and Huang X. An examination of the efficiency of the sequential parallel design in psychiatric clinical trials" *Clinical Trials*. 2007; 4:309-317
- Huang X and Tamura R. Comparison of Test Statistics for the Sequential Parallel Design. *Statistics in Biopharmaceutical Research*. 2010; Vol.2, No. 1:42-50.
- www.rctlogic.com

SPCD design


Randomise
Group 1
Group 2
Group 3
N×a
N×a
N×(1-2a)
Stage 1:
placebo
placebo
drug
Stage 2:
placebo
drug
drug

Comparisons



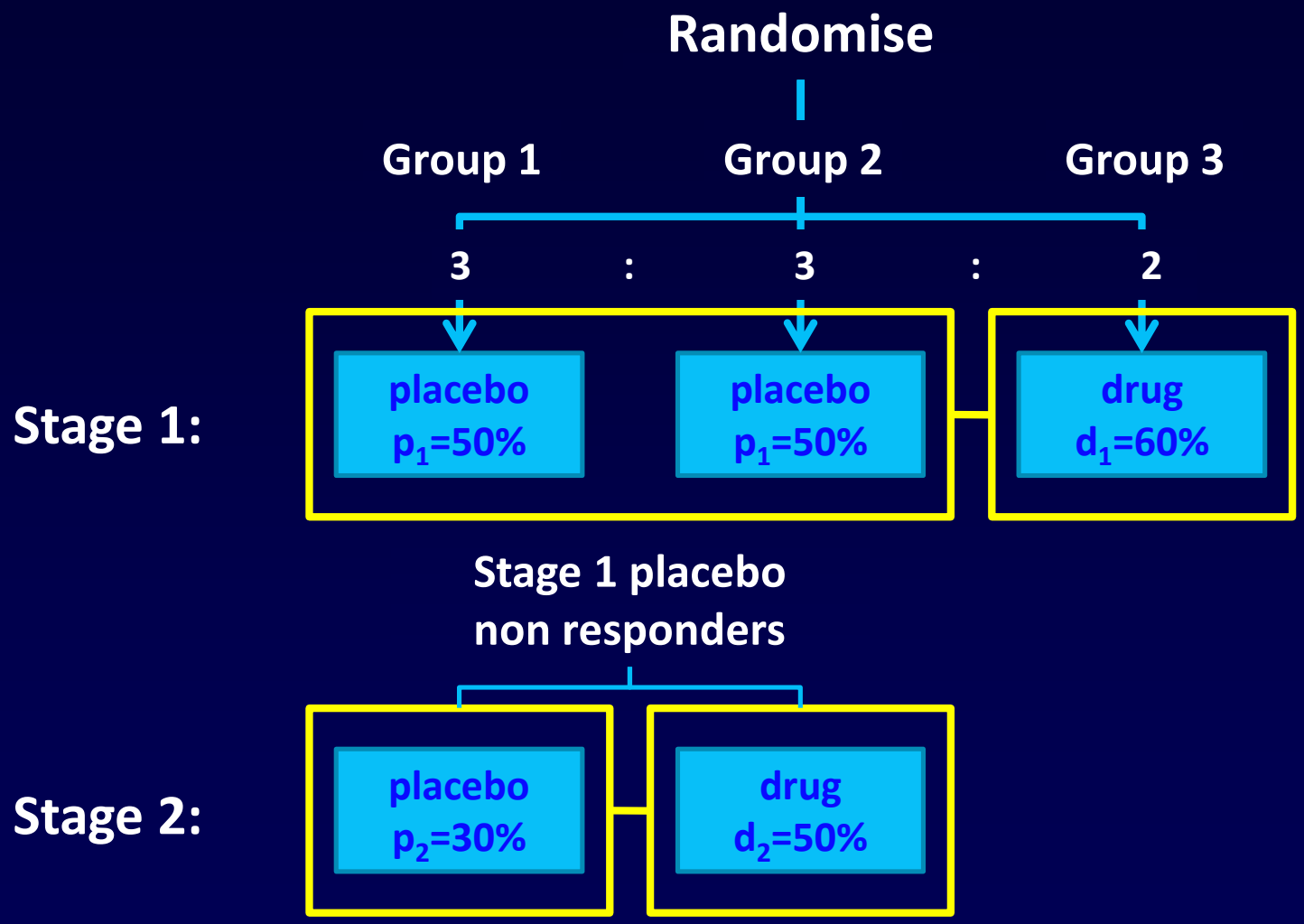
Comparisons and Treatment Effects

- Stage 1
  - Drug vs combined placebo
    - All randomised patients contribute
    - Treatment effect = d_1-p_1
- Stage 2
  - Drug vs placebo in Stage 1 placebo non-responders
    - Data in placebo non-responders do not contribute in Stage 2
    - Data in patients receiving drug in Stage 2 do not contribute
    - Treatment effect = d_2-p_2

Some issues

- Overall comparison based on weighted average of treatment effects in Stage 1 and Stage 2
  - $w \times (d_1-p_1) + (1-w) \times (d_2-p_2)$
- Does it make sense to combine the treatment effect in allcomers in Stage 1 with the treatment effect in non-responders in Stage 2? How is the result to be interpreted?
- And what value for 'w'?
  - $w = ½ \Rightarrow$ equal weight to Stage 1 and Stage 2 data?
  - $w = ¾ \Rightarrow$ more weight to Stage 2 than Stage 1?

Example #1


Randomise
Group 1
Group 2
Group 3
3 : 3 : 2
Stage 1:
placebo
p_1=50%
placebo
p_1=50%
drug
d_1=60%
Stage 1 placebo
non responders
Stage 2:
placebo
p_2=30%
drug
d_2=50%

Sample size (regular 1:1 design requires 770 patients)

P:P:D	w	N
	0.70	397
3:3:2		

Sample size (regular 1:1 design requires 770 patients)

P:P:D	w	N
3:3:2	0.70	397
	0.95	835
	0.50	327
	0.30	358

Sample size (regular 1:1 design requires 770 patients)

P:P:D	w	N
3:3:2	0.70	397
	0.95	835
	0.50	327
	0.30	358
1:1:1		
1:1:2		
1:1:4		

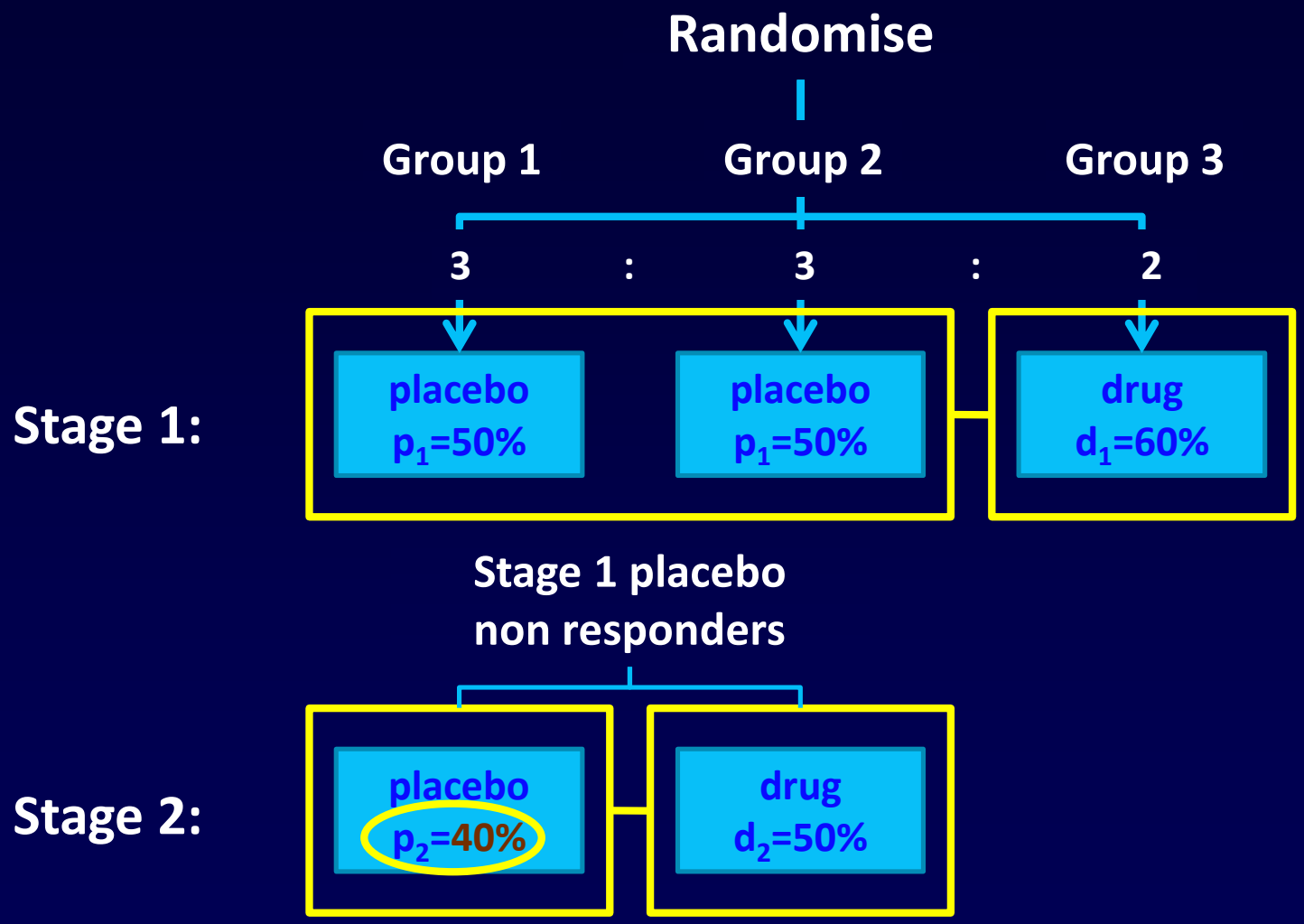
Sample size (regular 1:1 design requires 770 patients)

P:P:D	w	N
3:3:2	0.70	397
	0.95	835
	0.50	327
	0.30	358
1:1:1	0.70	365
	0.95	708
	0.50	336
	0.30	394
1:1:2	0.70	377
	0.95	636
	0.50	406
	0.30	514
1:1:4	0.70	483
	0.95	723
	0.50	578
	0.30	762

Issues

- What choice for randomisation? Design is based upon randomising more patients to placebo than drug in Stage 1.
- What choice for 'w'? How much weight to apply to Stage 1 data as compared to Stage 2?
  - Inherently not a statisitical choice – must be justified and rationalised clinically.
- Fundamentally, a 60% vs 50% drug vs placebo response in Stage 1, a 50% vs 30% drug vs placebo response in placebo non-responders in Stage 2 is impossible in practice.
  - If within patient correlation is 0.33 then :
    - Stage 2: drug response = 50%, placebo response = 40%.
  - If within patient correlation is 0.60 then :
    - Stage 2: drug response = 40%, placebo response = 30%.

Example #1 revisited



When corrected, advantage of the SPCD design is largely lost

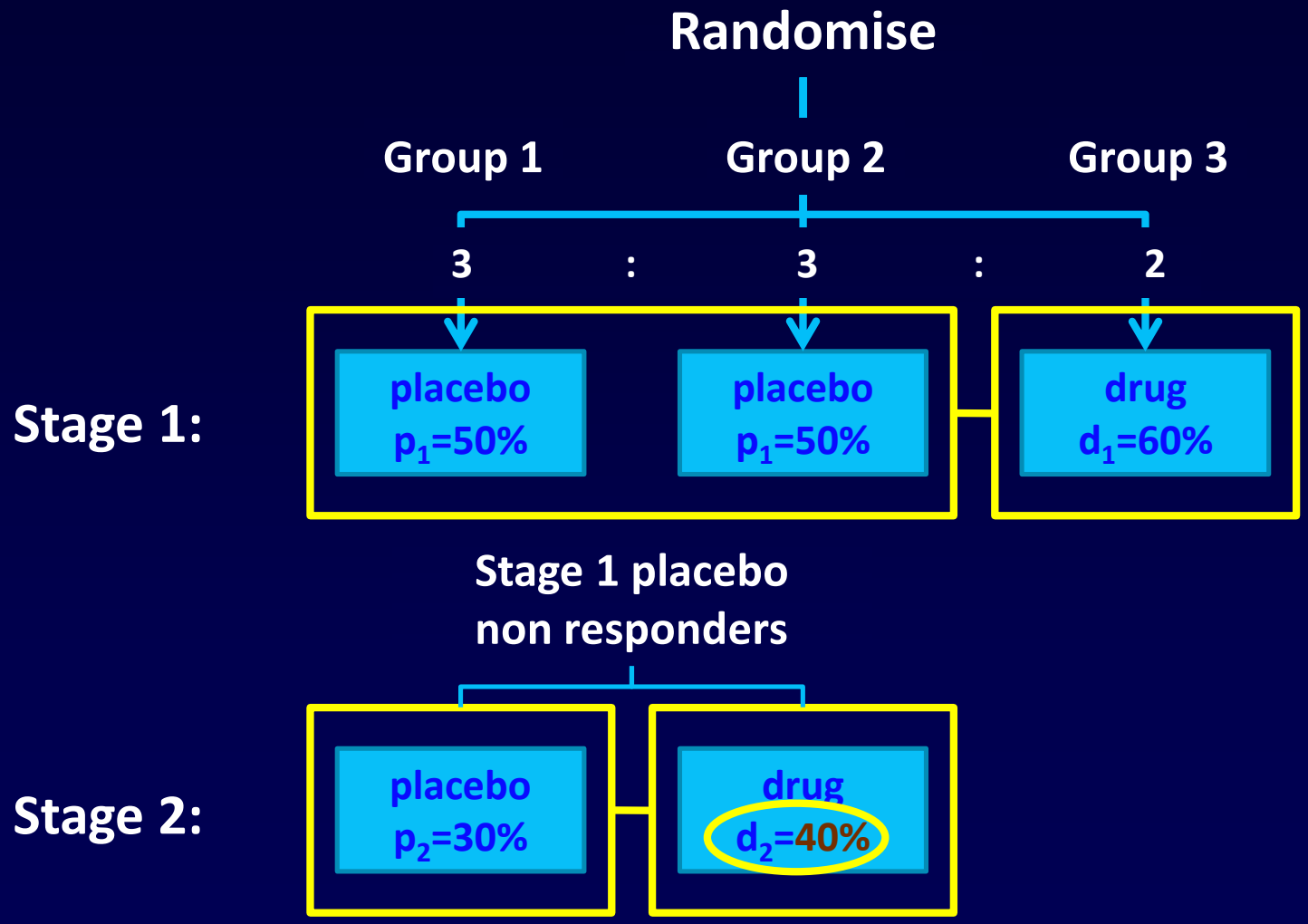
P:P:D	w	N (original)	N' (corrected)
3:3:2	0.70	397	682
	0.95	835	921
	0.50	327	767
	0.30	358	1096
1:1:1	0.70	365	629
	0.95	708	781
	0.50	336	792
	0.30	394	1208
1:1:2	0.70	377	654
	0.95	636	702
	0.50	406	961
	0.30	514	1577
1:1:4	0.70	483	842
	0.95	723	798
	0.50	578	1372
	0.30	762	2340

Regular 1:1 design requires 770 patients

Original SPCD design = 30% vs 50% for Stage 2 placebo non responders

Corrected SPCD design = 40% vs 50% for Stage 2 placebo non responders

Example #1 revisited (again)



When corrected, advantage of the SPCD design is largely lost

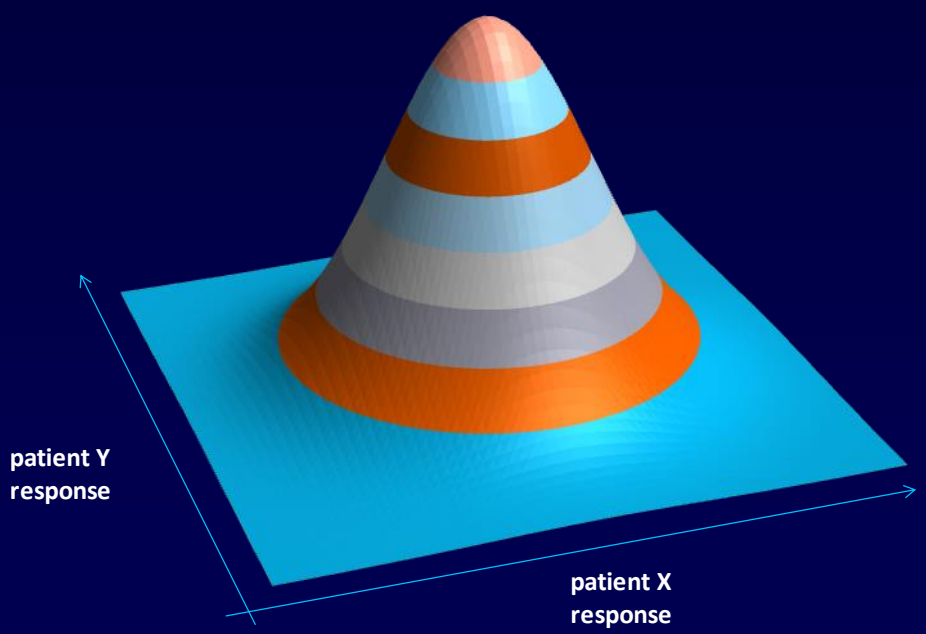
P:P:D	w	N (original)	N' (corrected)
3:3:2	0.70	397	667
	0.95	835	921
	0.50	327	725
	0.30	358	1014
1:1:1	0.70	365	612
	0.95	708	781
	0.50	336	745
	0.30	394	1116
1:1:2	0.70	377	631
	0.95	636	701
	0.50	406	899
	0.30	514	1454
1:1:4	0.70	483	808
	0.95	723	797
	0.50	578	1277
	0.30	762	2155

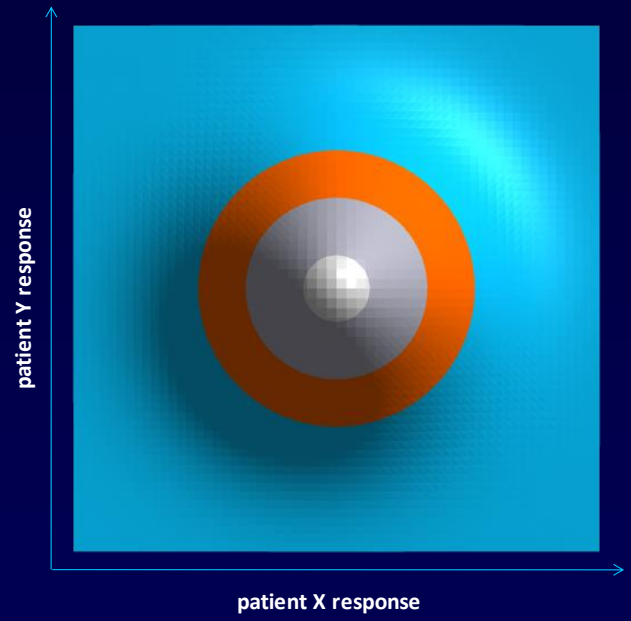
Regular 1:1 design requires 770 patients

Original SPCD design = 30% vs 50% for Stage 2 placebo non responders

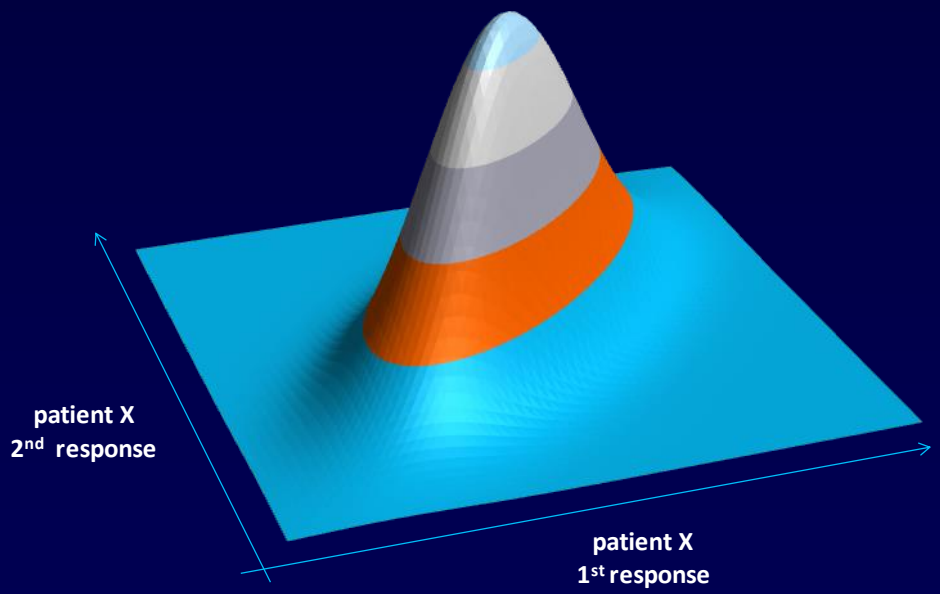
Corrected SPCD design = 30% vs 40% for Stage 2 placebo non responders

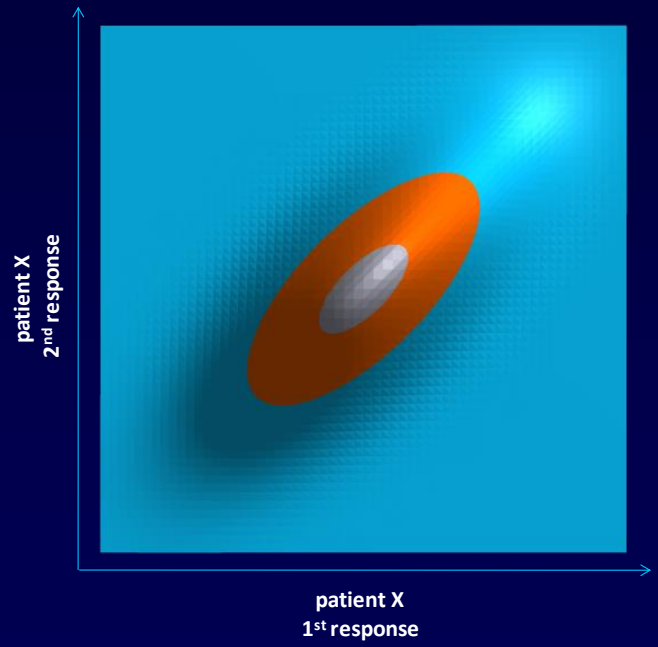
Assessments from different patients are uncorrelated





Repeat assessments within the same patient are correlated





The criticality of correlation

- SPCD design ignores this correlation – many design illustrations are therefore infeasible.

- Response rate in Stage 2 is directly related to response rate in Stage 1 – cannot arbitrarily choose Stage 2 response rates when designing a trial.
  - p_2 = Pr(response to placebo in Stage 2 *given* non-response to placebo in Stage 1 = $\{1-p_1\}$).
  - d_2 = Pr(response to drug in Stage 2 *given* non-response to placebo in Stage 1 = $\{1-p_1\}$).

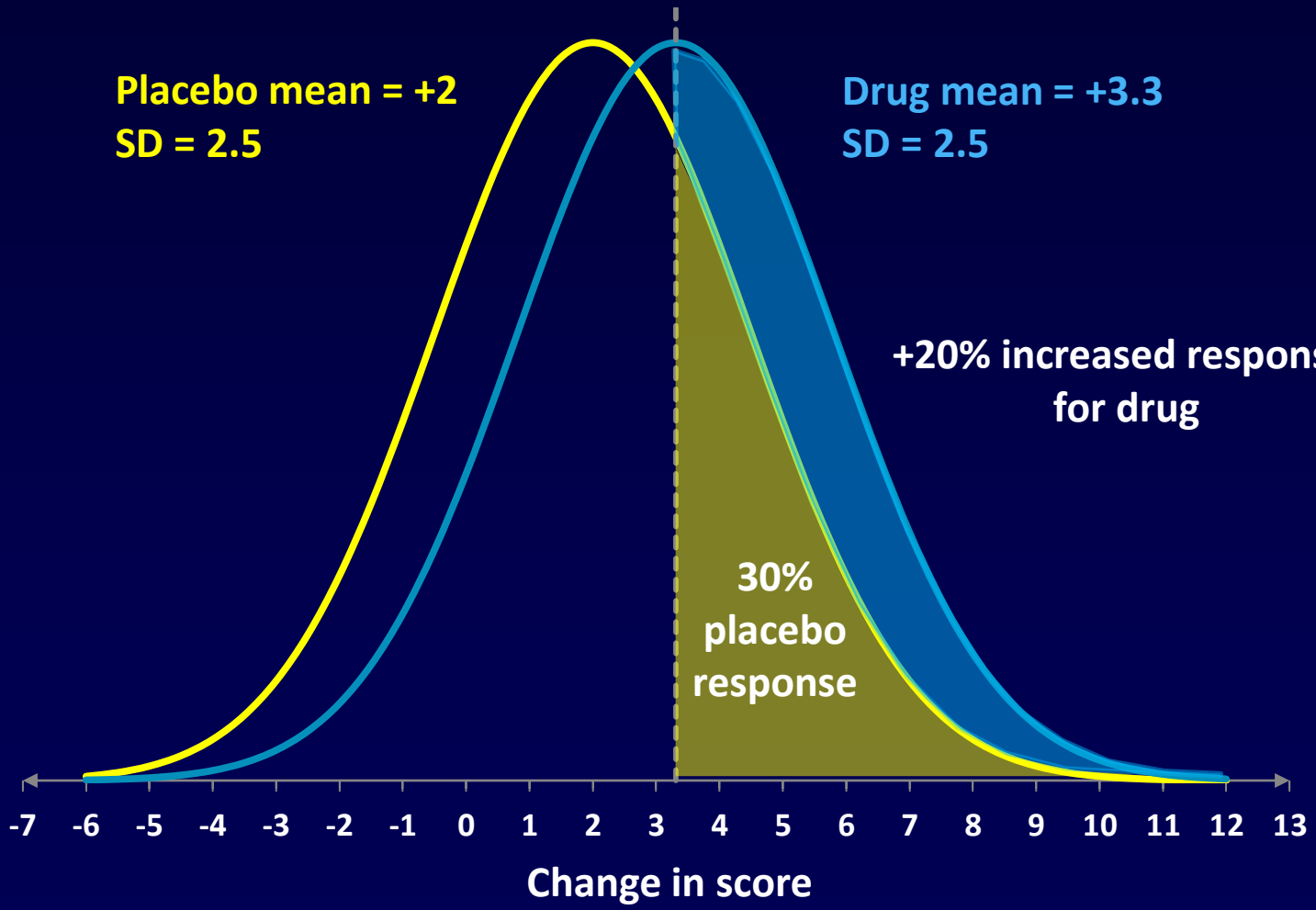
Within patient correlation is important and is not accounted for in the SPCD design

Stage 1 response		Correlation	Pr(response in Stage 1 placebo non-responders)	
p1	d1	ρ	p2	d2
50%	60%	0.00	50.0%	60.0%
		0.25	42.0%	52.2%
		0.50	33.3%	43.9%
		0.75	23.0%	34.1%
		1.00	0%	20.0%
30%	50%	0.00	30.0%	50.0%
		0.25	25.5%	45.0%
		0.50	20.5%	39.8%
		0.75	14.2%	33.9%
		1.00	0%	28.6%

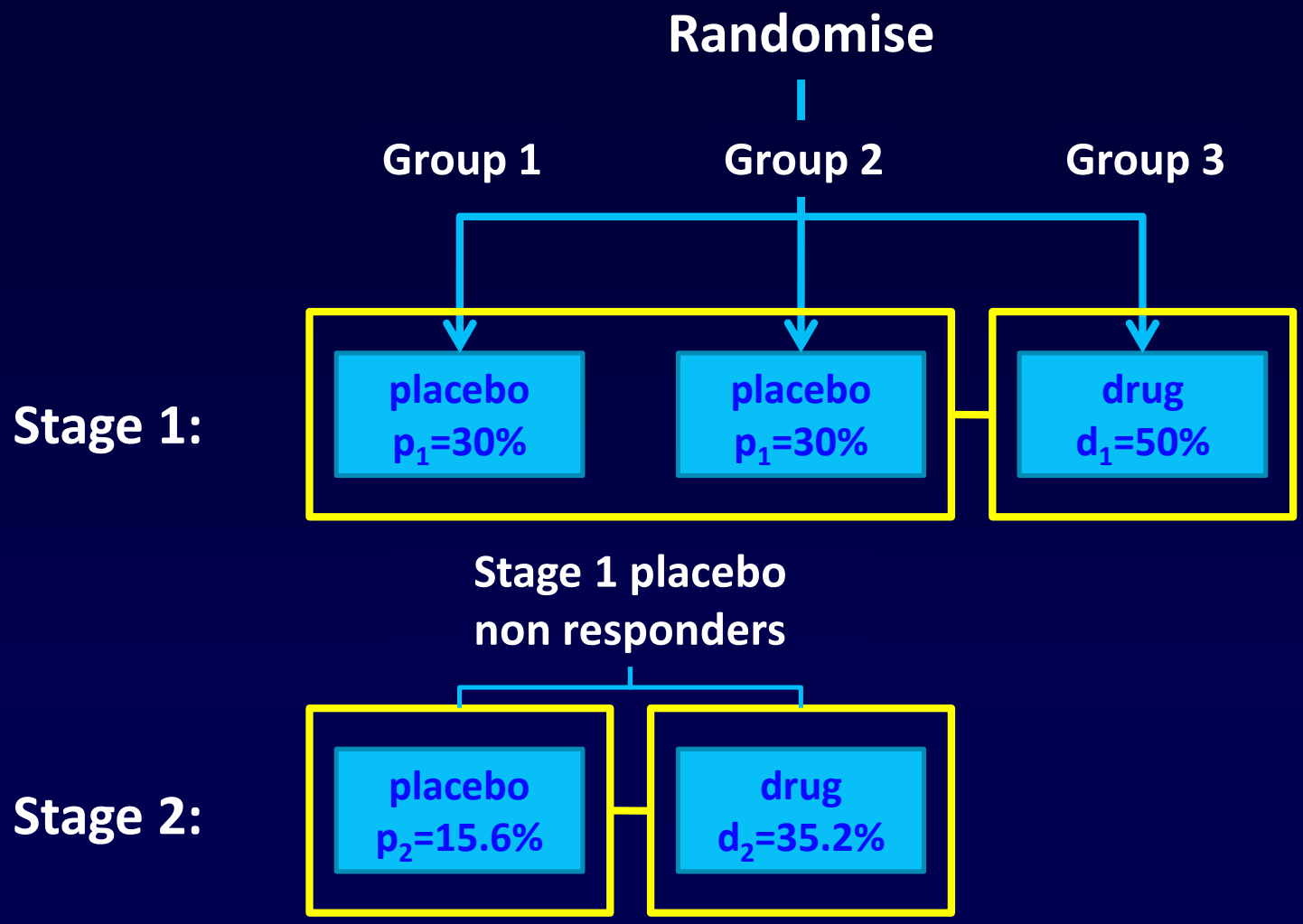
Example #2

- +3.3 unit change or greater required to achieve a 'response'
- Placebo has mean=+2 units, SD 2.5 units
  - 30% responders
- Drug has mean=+3.3 units, SD 2.5 units
  - 50% responders
- Within patient correlation=0.70

Difference in means of +1.3 delivers a +20% increase in response for drug compared to placebo



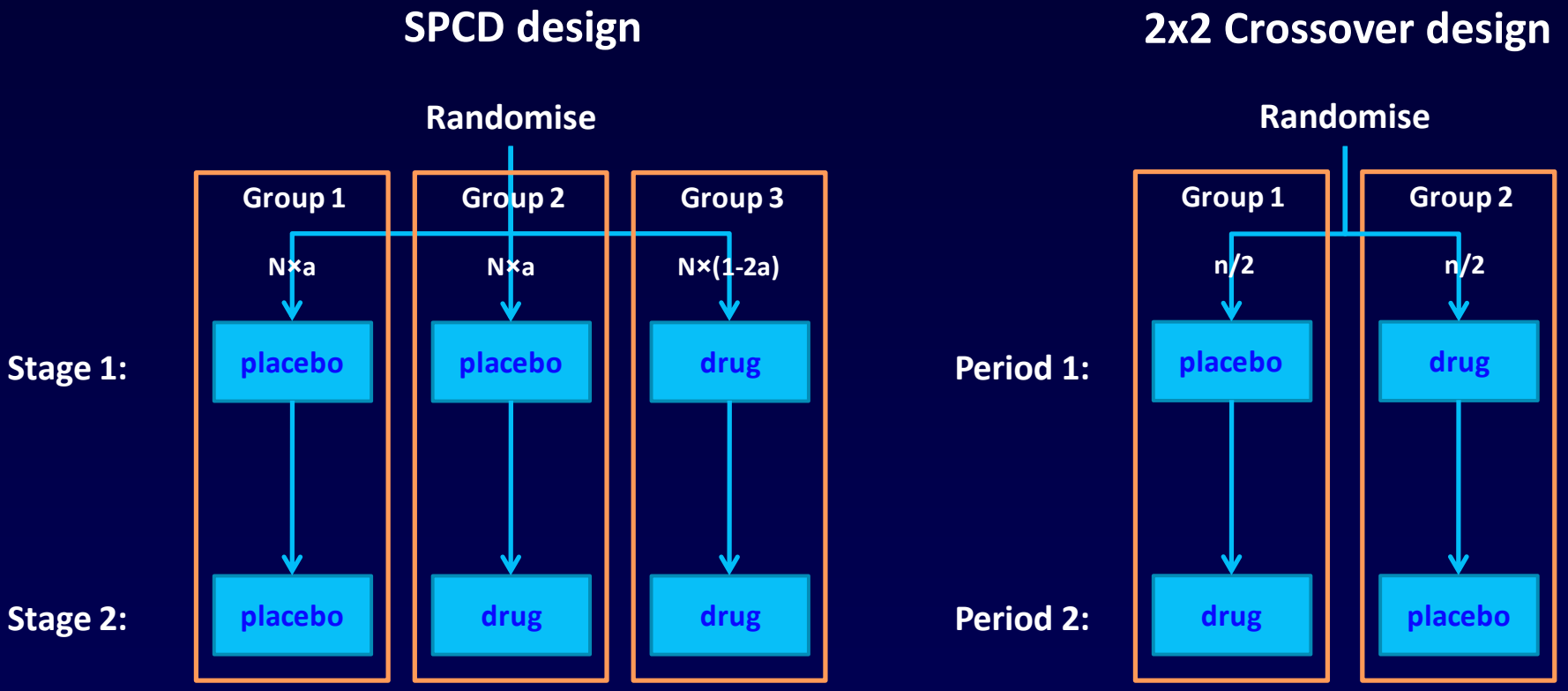
Example #2 Design



Sample size (regular 1:1 design requires 181 patients)

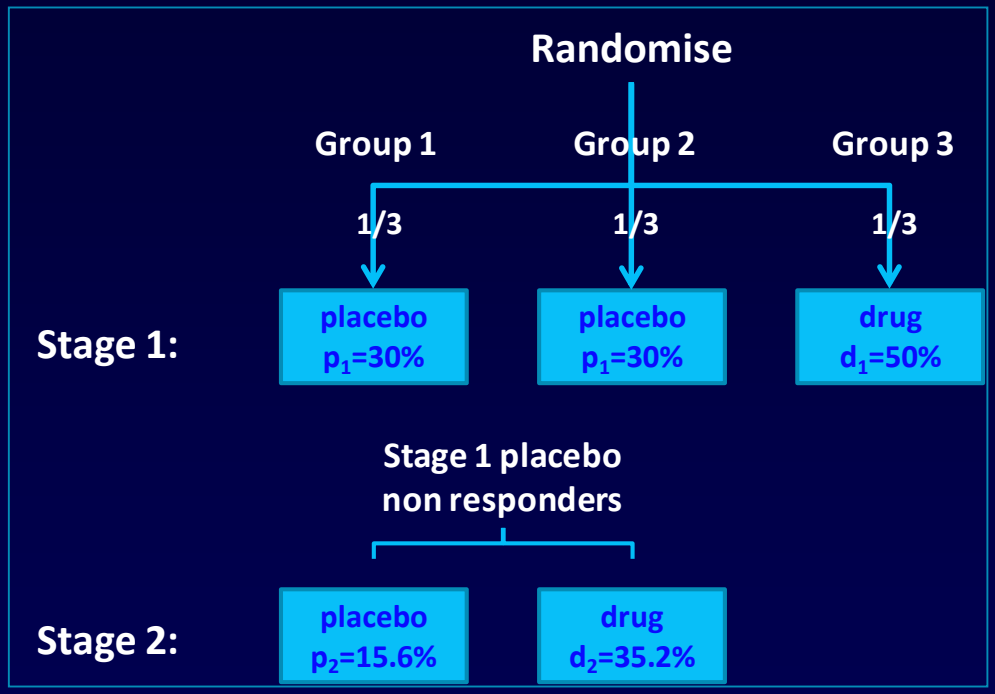
P:P:D	w	N
3:3:2	0.70	149
	0.95	228
	0.50	133
	0.30	251
1:1:1	0.70	131
	0.95	190
	0.50	130
	0.30	172
1:1:2	0.70	126
	0.95	164
	0.50	149
	0.30	220
1:1:4	0.70	153
	0.95	180
	0.50	205
	0.30	210

2x2 Crossover: A Simple Alternative



Example #2 revisited

SPCD design



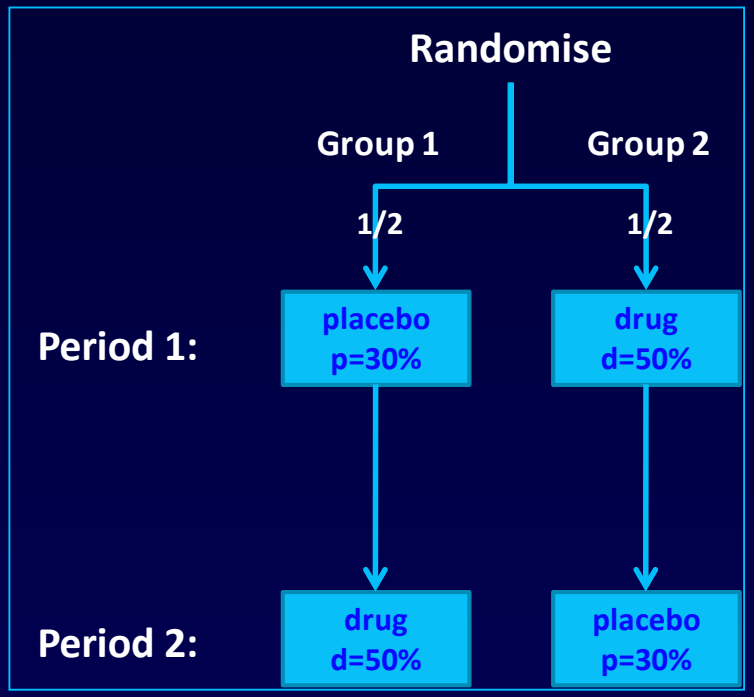
N=126 for 80% power

N=168 for 90% power

w=0.6 weighting to give lowest possible N

1:2 drug vs placebo randomisation

2x2 Crossover design



N=50 for 80% power

N=67 for 90% power

80% power

1:1 drug vs placebo randomisation

2x2 Crossover Design

- Under the same assumptions of treatment effect and within patient correlation, 2x2 crossover is more powerful than the best performing SPCD design
- Example #2
  - Best SPCD design gives N=126 for 80% power compared to N=50 for a 2x2 crossover
  - 2x2 crossover with N=126 would have
    - 99.4% power for a difference of 20%
    - 80% power for differences as low as 12.5%

Summary (1 of 4)

- Two Stage Design
- Stage 1 patients randomised to drug:placebo in a ratio favouring placebo.
  - Authors tend to recommend 1:3 or 1:2
  - Treatment effect = d_1-p_1
- Stage 2 placebo non-responders from Stage 1 receive drug:placebo in a 1:1 ratio.
  - Treatment effect = d_2-p_2
- Overall comparison based on weighted average of treatment effects estimated in Stage 1 and in Stage 2
  - Overall Effect = $w \times (d_1-p_1) + (1-w) \times (d_2-p_2)$

Summary (2 of 4)

- Overall the SPCD will be approx 2x along long as a conventional single stage 1:1 design
- Stage 1 placebo responders do not contribute in Stage 2
  - What happens to these patients and their data?
- Stage 1 patients who continue on drug in Stage 2 also do not contribute
  - What happens to these patients and their data?
- Does it make sense to combine the treatment effect in allcomers in Stage 1 with the treatment effect in non-responders in Stage 2? How is the result to be interpreted?

Summary (3 of 4)

- What value for ‘w’?
  - w = ½ ⇒ equal weight to Stage 1 and Stage 2 effects?
  - w = ¾ ⇒ more weight to Stage 2 than Stage 1?
  - Inherently not a statisitical choice – must be justified and rationalised clinically
- Choice of w has dramatic impact on the performance of the SPCD design
  - N can double and design become less favourable than a conventional single stage 1:1 design
- What choice for randomisation in Stage 1?
  - Design is based upon randomising more patients to placebo than drug in Stage 1, e.g. 1:2 or 1:3. Is this desirable?
  - Choice of randomisation ratio also has a large impact on the performance of the SPCD design

Summary (4 of 4)

- Critically, the SPCD design ignores the correlation present within a patient when given repeated tests
  - Many design illustrations are therefore infeasible.
- Response rate in Stage 2 is directly related to response rate in Stage 1 – cannot arbitrarily choose Stage 2 response rates when designing a SPCD trial.
  - Given drug and placebo response rates in Stage 1 and within patient correlation, Stage 2 response rates are fixed.
- Many of the purported examples of savings in N are therefore likely to be overestimated.
- Under the same assumptions of treatment effect and within patient correlation, a 2x2 crossover is more powerful than the best performing SPCD design

Key points (1)

- Efficiency of SPCD design depends crucially upon:
  - Stage 1 drug:placebo randomization ratio.
  - Relative weighting of Stage 1 vs Stage 2 data.
- Stage 1 randomisation ratios of 1:2 or 1:3 favouring placebo are encouraged and required for best performance of the design.
- Relative weighting of Stage 1 vs Stage 2 data has a dramatic effect on the performance of the SPCD design.
  - Choice of weighting requires clinical rather than statistical justification.

Key points (2)

- Plausibility of combining Stage 1 treatment effect in allcomers with Stage 2 treatment effect in placebo non-responders is debatable.
  - Are these patient populations the same?
  - Can the overall result be interpreted?
- Design ignores within patient correlation therefore examples of savings in N and gains in power are likely to be somehwat overestimated.
- Under the same assumptions of treatment effect and within patient correlation, a 2x2 crossover is more powerful than the best performing SPCD design.