

Adaptive Design Workshop

ISCTM Autumn Meeting 2012

Marina del Rey, California

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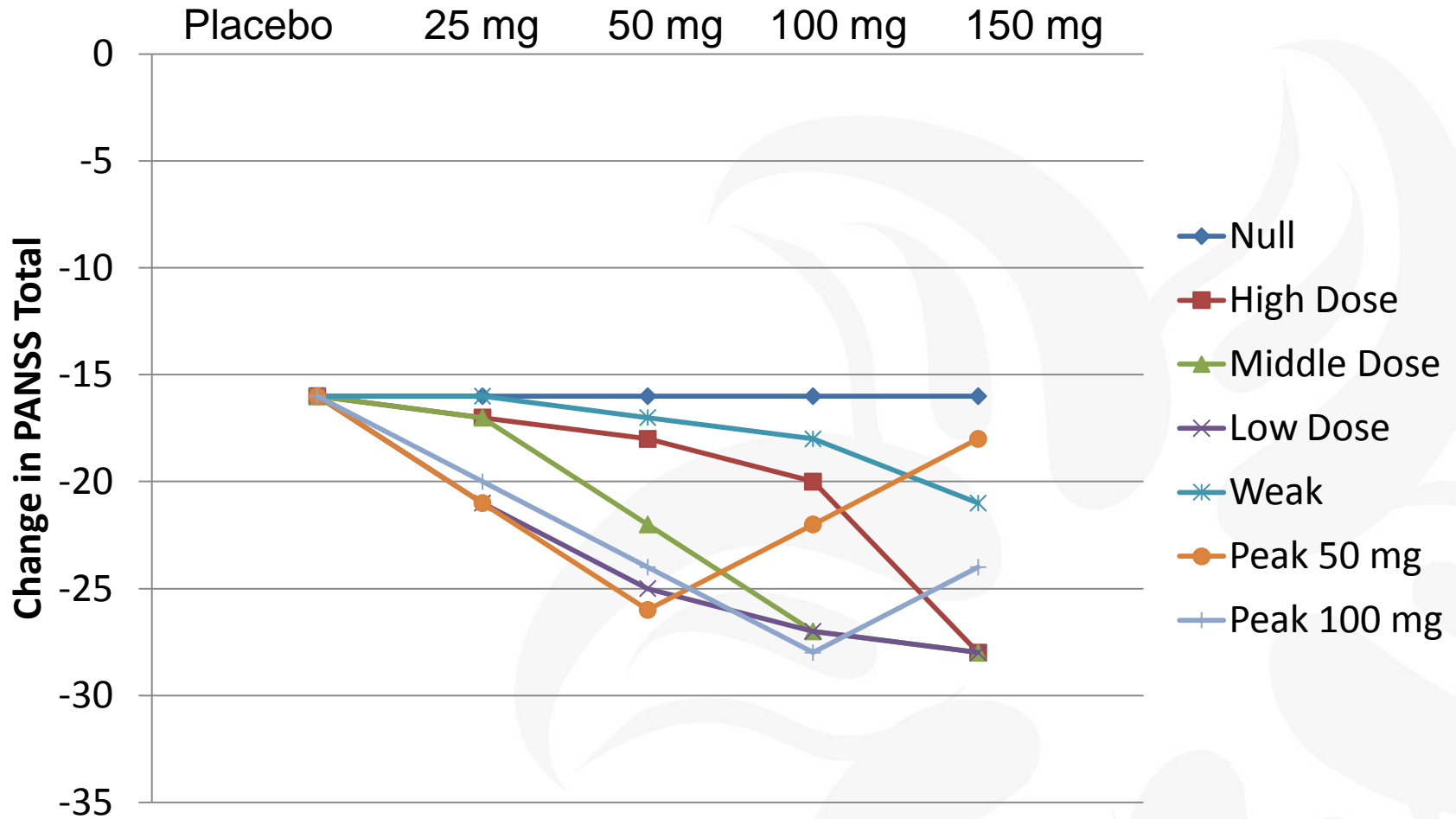
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ADAPTIVE VS. TRADITIONAL DESIGN



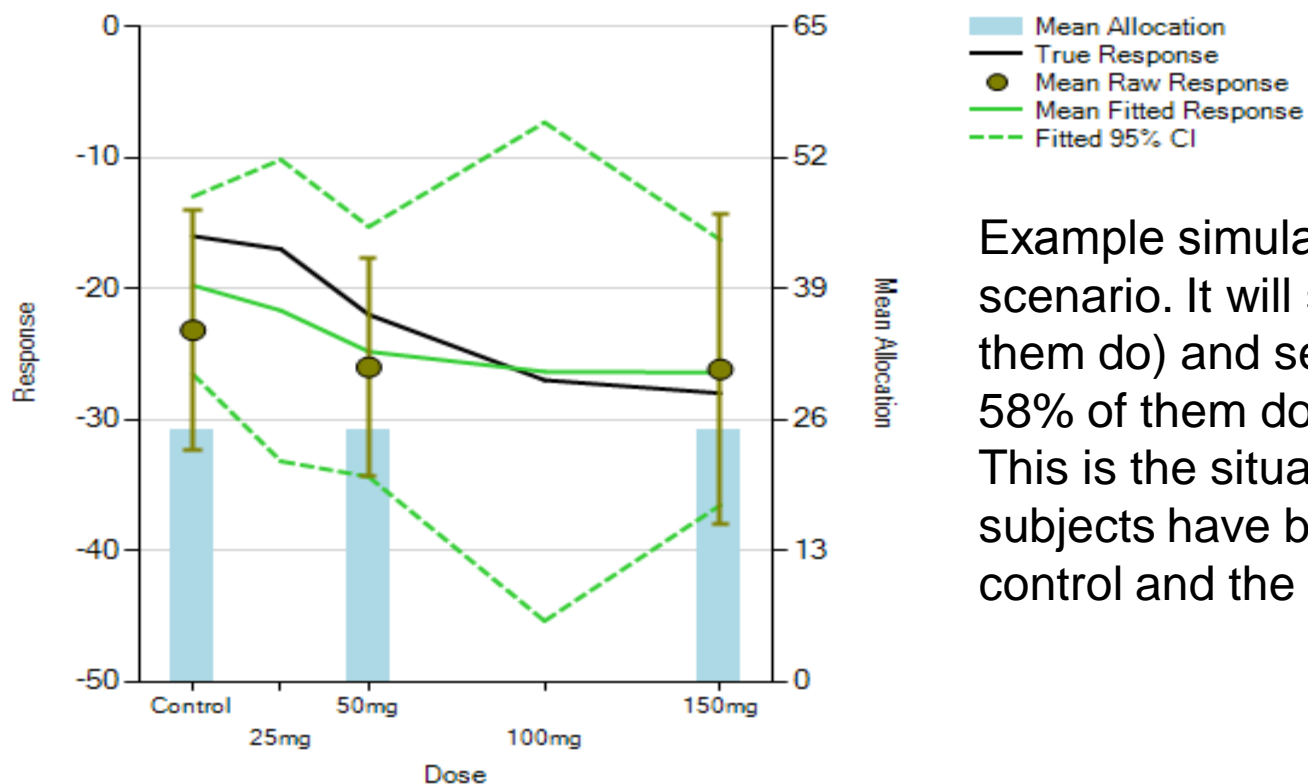
Dose Curve Scenarios



Illustration

Response and Subject Allocation (Week: 16)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middle dose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0

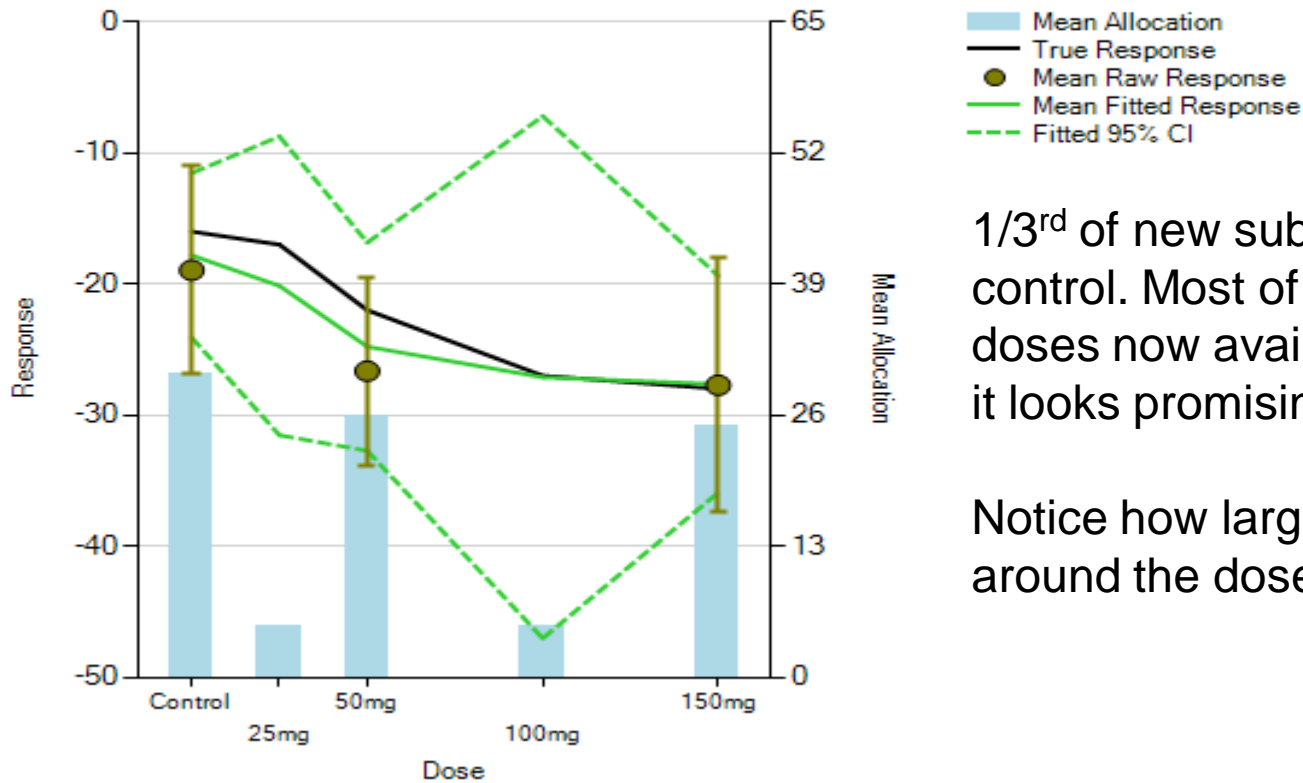


Example simulation from 'middle dose' scenario. It will stop early (as 67% of them do) and select the correct dose (as 58% of them do).

This is the situation at the first interim, 25 subjects have been allocated to each of control and the 50mg and 150mg doses.

Response and Subject Allocation (Week: 18)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middle dose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0

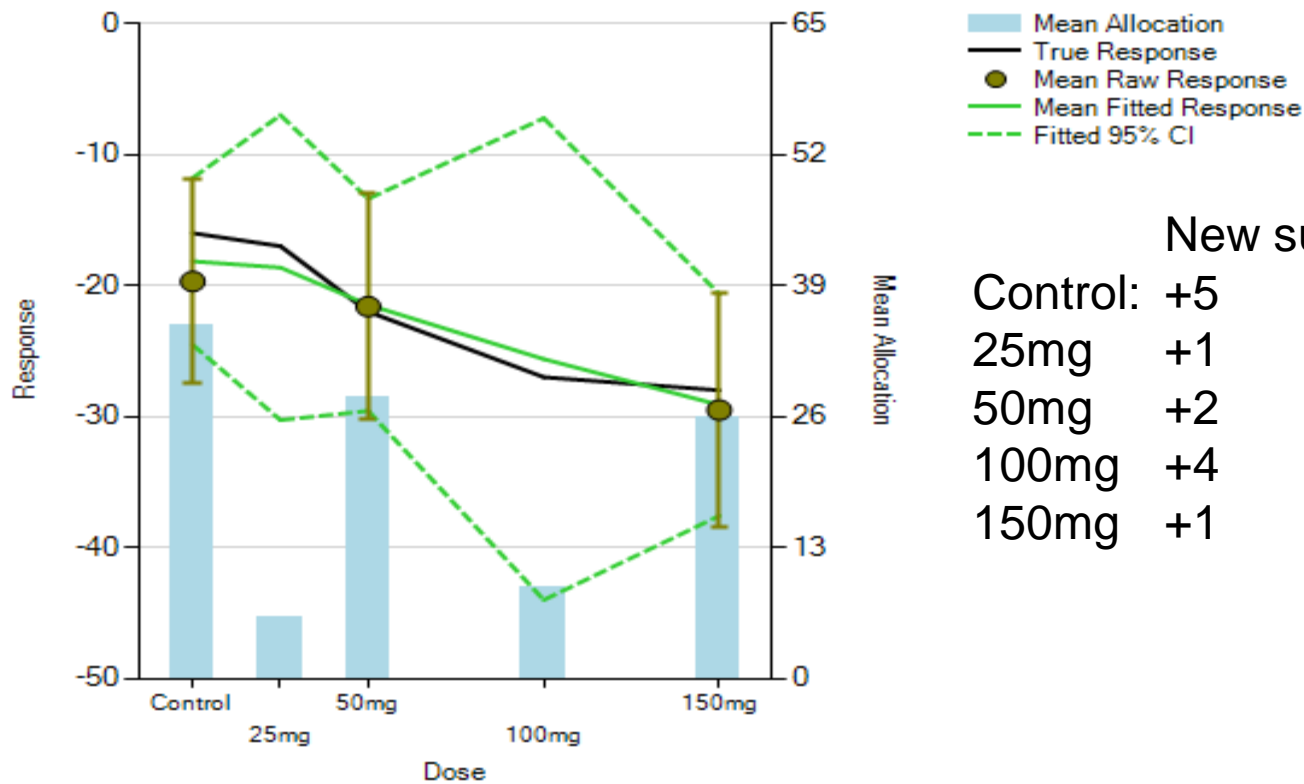


1/3rd of new subjects are allocated to control. Most of the rest to the new doses now available and one to 50mg as it looks promising.

Notice how large the error estimates are around the doses with no data yet.

Response and Subject Allocation (Week: 20)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middledose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0

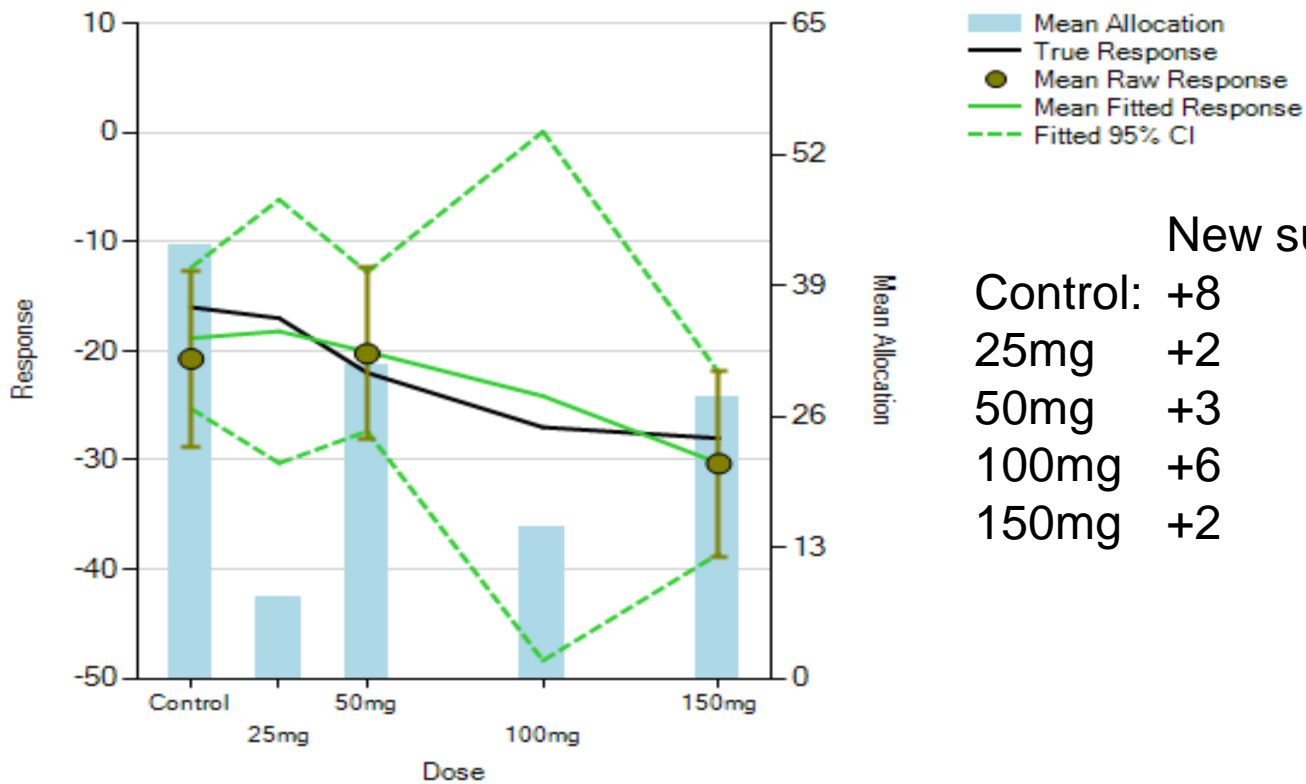


New subjects P(MED)

Control:	+5	-
25mg	+1	0.10
50mg	+2	0.19
100mg	+4	0.30
150mg	+1	0.25

Response and Subject Allocation (Week: 22)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middle dose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0

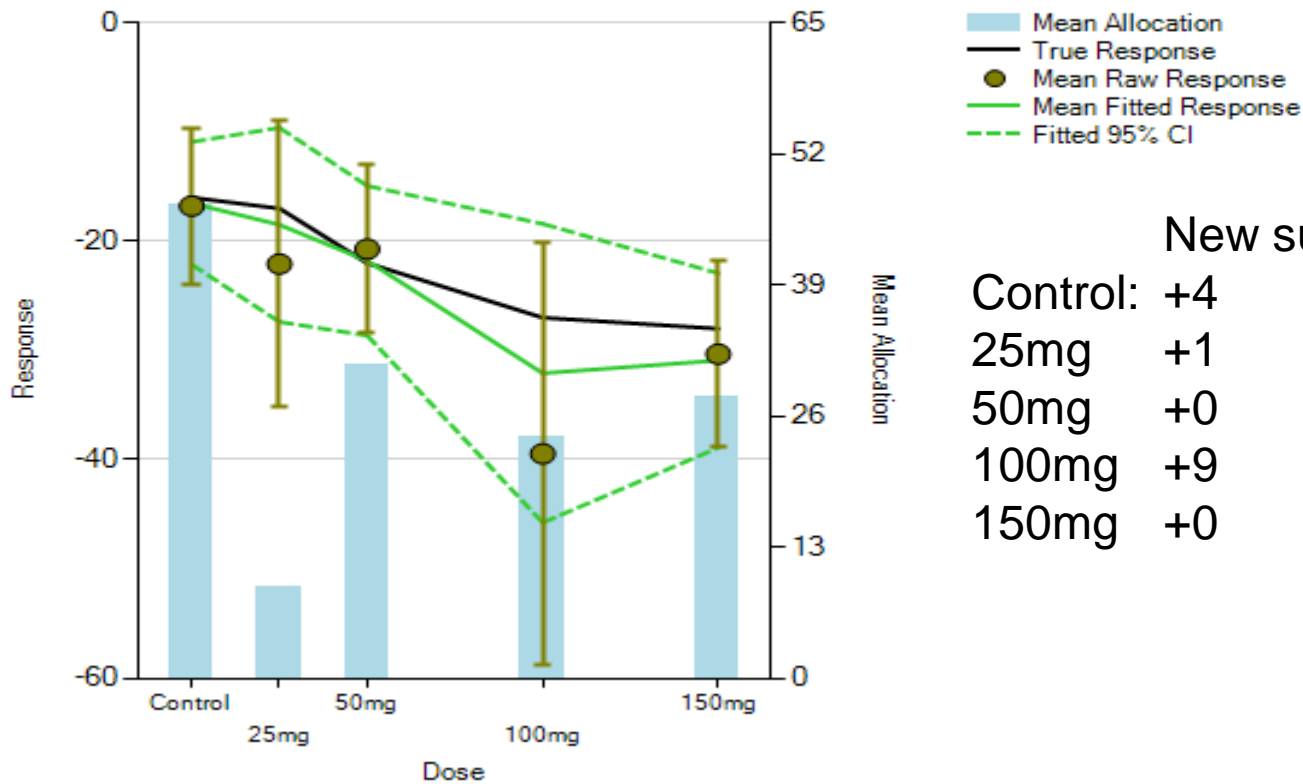


New subjects P(MED)

Control:	+8	-
25mg	+2	0.08
50mg	+3	0.08
100mg	+6	0.37
150mg	+2	0.33

Response and Subject Allocation (Week: 24)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middledose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0

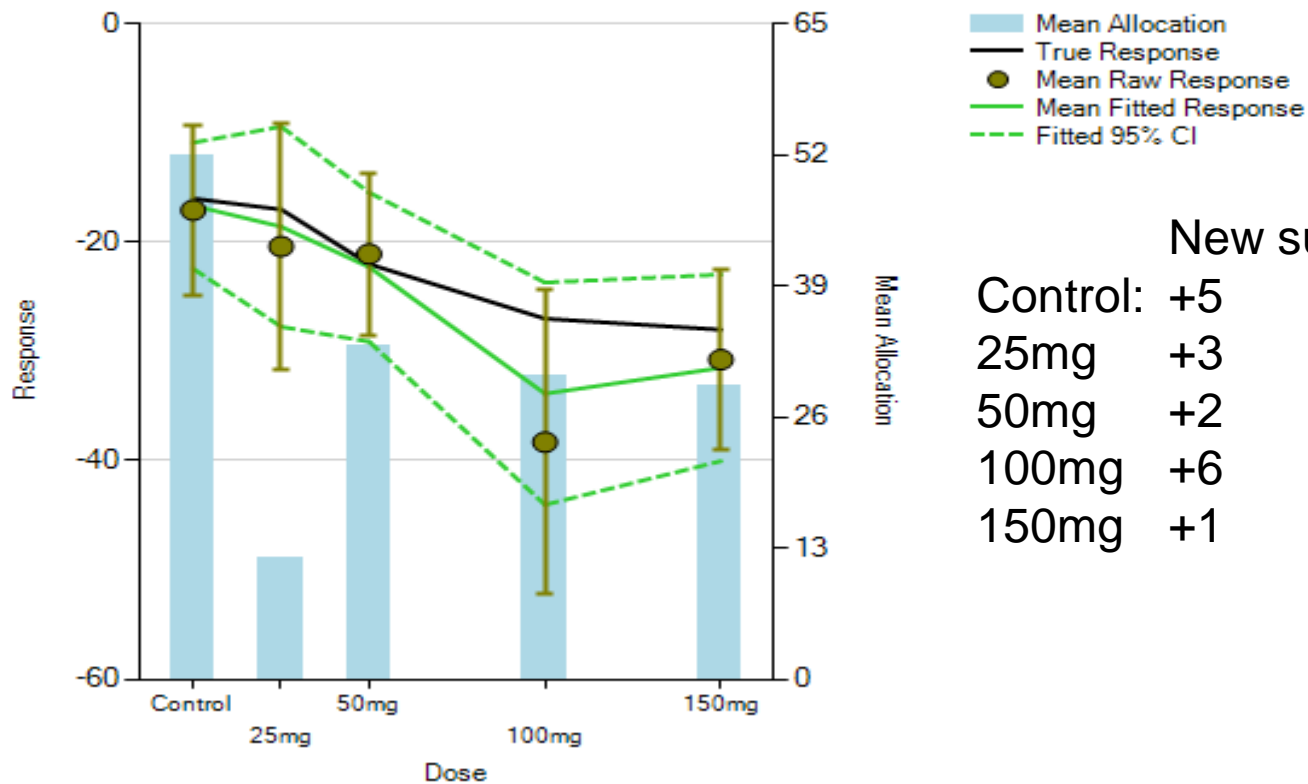


New subjects P(MED)

Control:	+4	-
25mg	+1	0.14
50mg	+0	0.24
100mg	+9	0.53
150mg	+0	0.07

Response and Subject Allocation (Week: 26)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middle dose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0

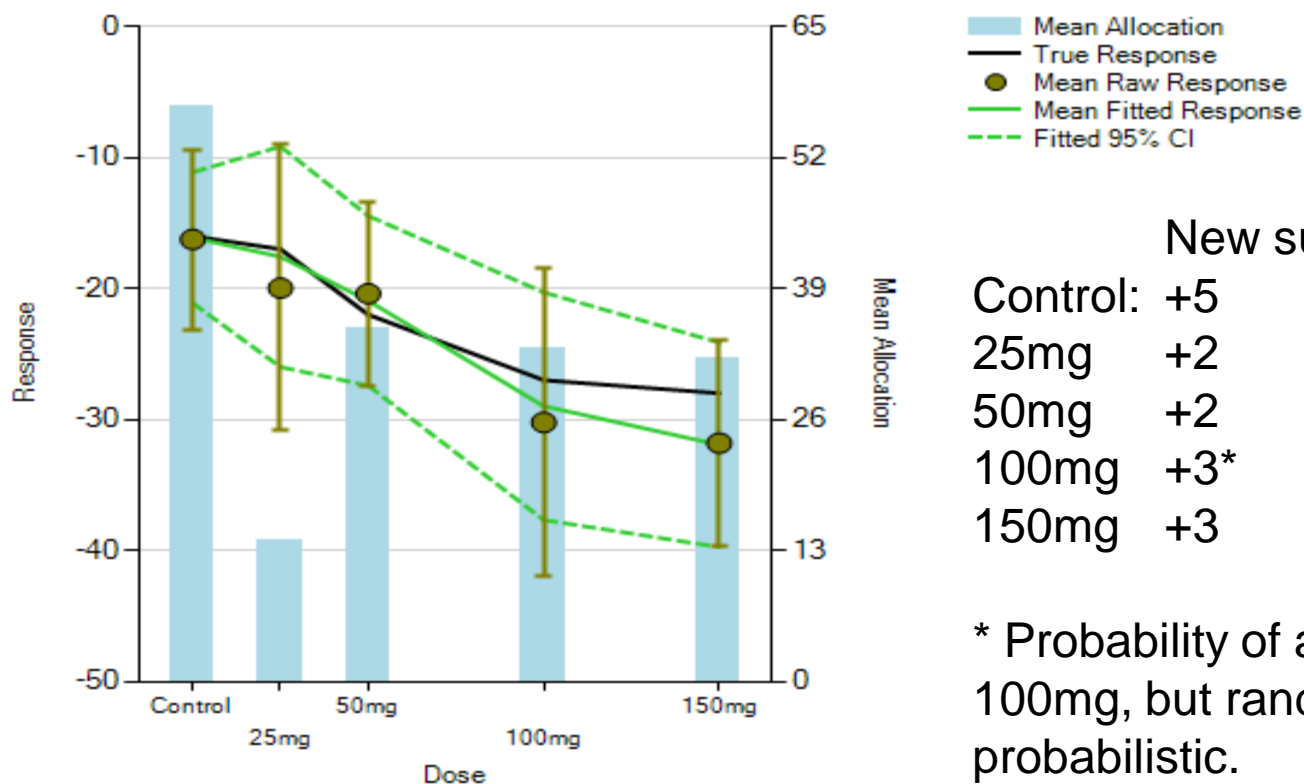


New subjects P(MED)

Control:	+5	-
25mg	+3	0.14
50mg	+2	0.27
100mg	+6	0.56
150mg	+1	0.02

Response and Subject Allocation (Week: 28)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middledose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0



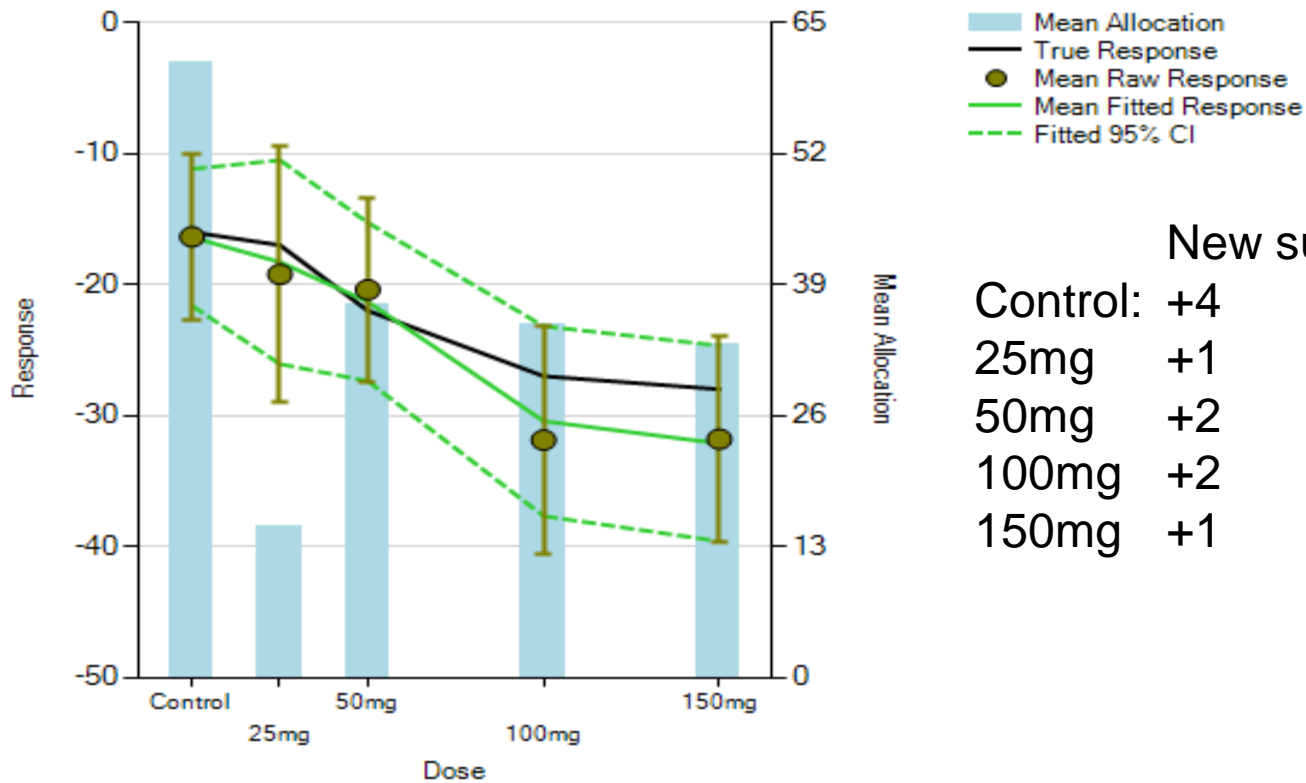
New subjects P(MED)

Control:	+5	-
25mg	+2	0.11
50mg	+2	0.25
100mg	+3*	0.53
150mg	+3	0.10

* Probability of allocation still favours 100mg, but randomisation is probabilistic.

Response and Subject Allocation (Week: 30)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middle dose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0



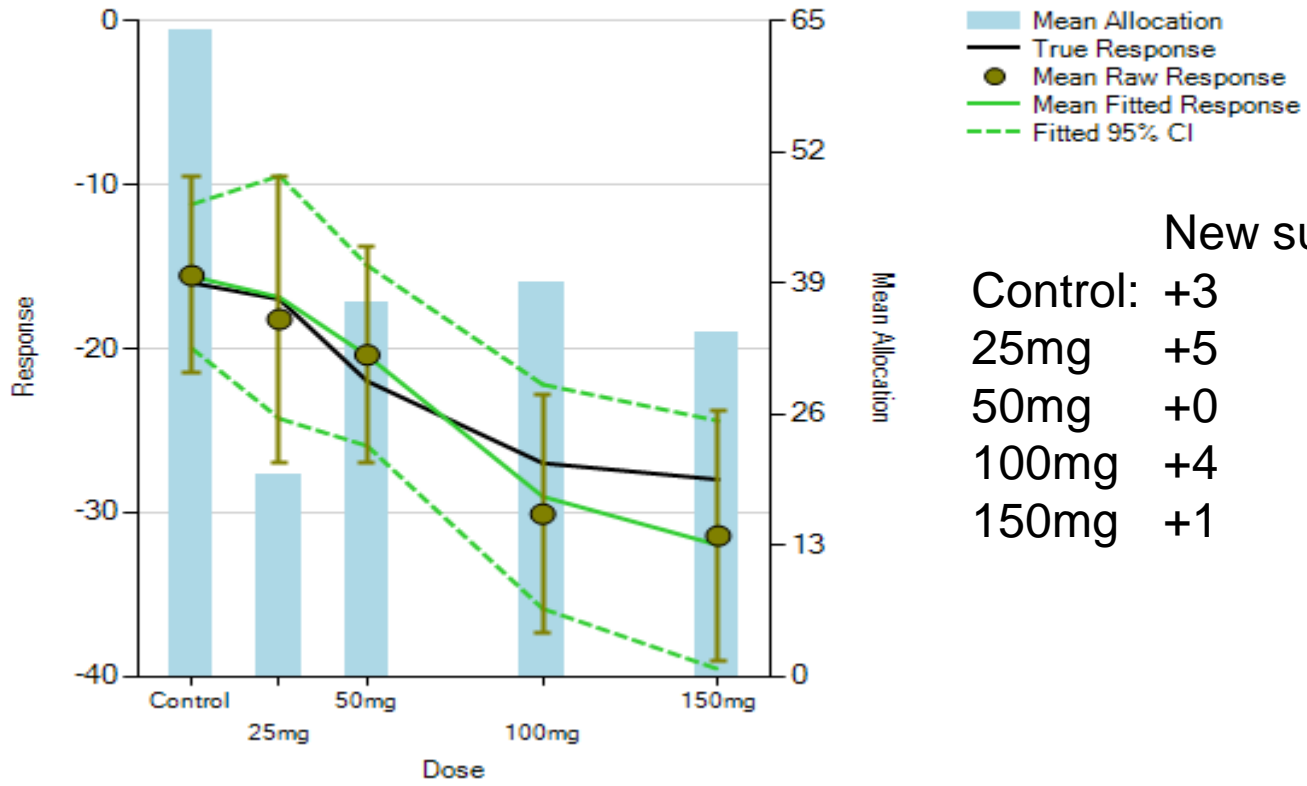
New subjects P(MED)

Control:	+4	-
25mg	+1	0.12
50mg	+2	0.22
100mg	+2	0.60
150mg	+1	0.05

9th Interim – trial stops

Response and Subject Allocation (Week: 32)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middledose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0



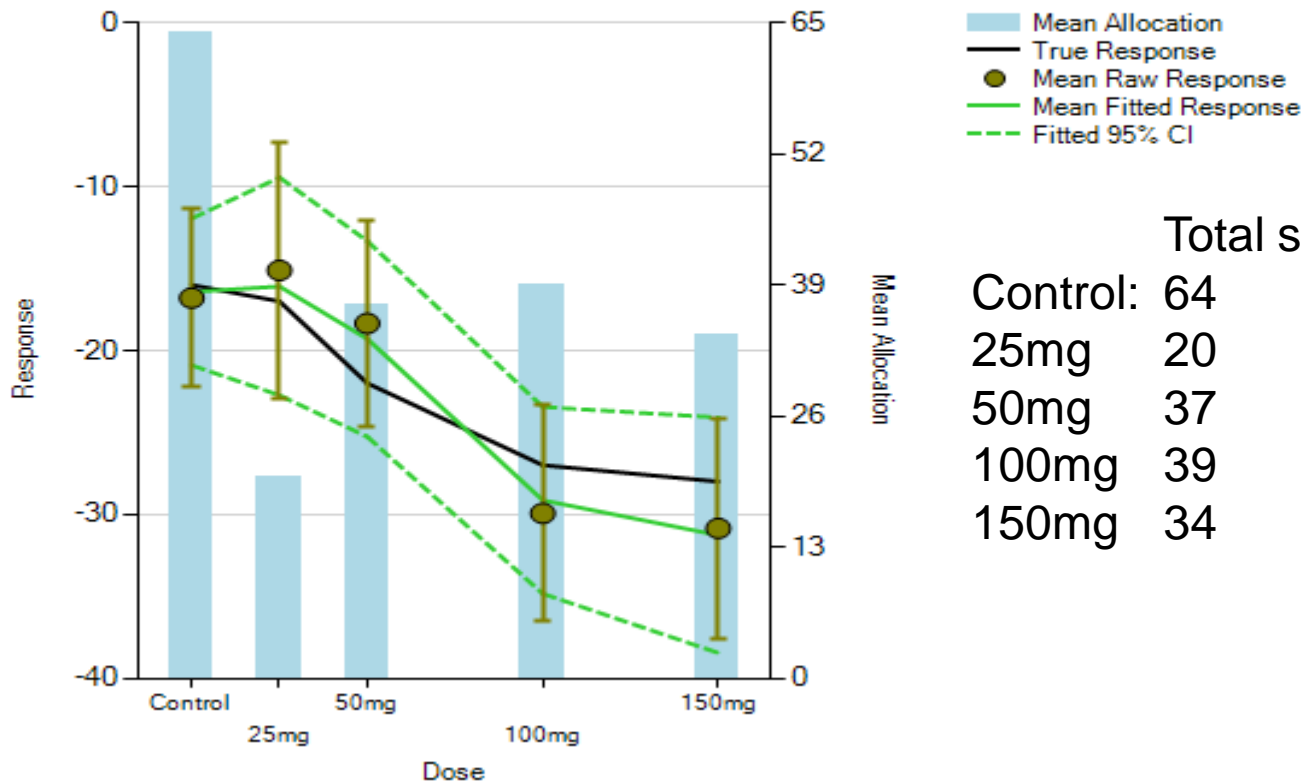
New subjects P(MED)

Control:	+3	-
25mg	+5	0.07
50mg	+0	0.23
100mg	+4	0.65
150mg	+1	0.05

Final analysis 6 weeks later

Response and Subject Allocation (Week: 38)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middledose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0



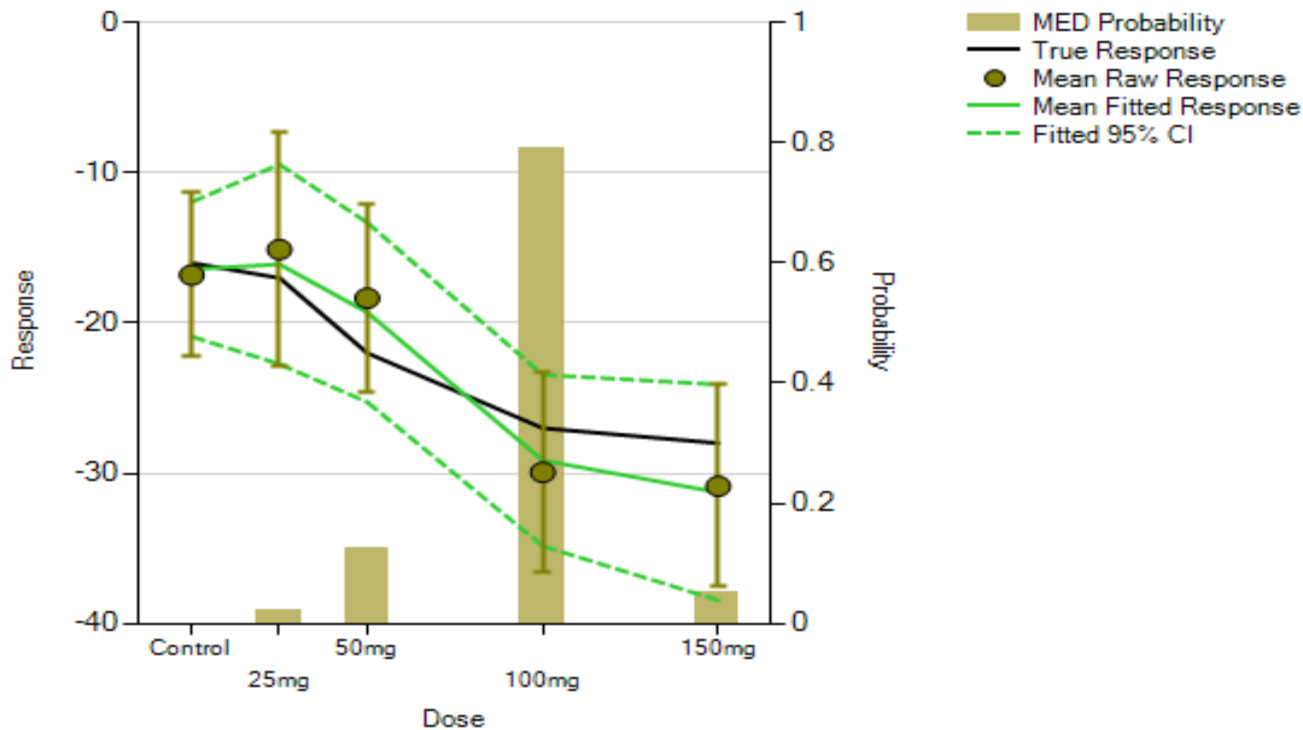
Total subjects P(MED)

Control:	64	-	
25mg	20		0.02
50mg	37		0.12
100mg	39		0.79
150mg	34		0.02

Final estimate of MED

Response and MED Selection (Week: 38)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Middledose" Design: "Dose Finding Continuous"
Simulations: 1000 Version: 2.4.0



MED = minimum dose with response less than control by -7

Scenario	Fail PoC	Fail before Cap	Fail at Cap	Success	Mean Sample Size
Null - fixed	0.814	0.0	0.168	0.018	118 / 325
<i>adaptive</i>	<i>0.379</i>	<i>0.563</i>	<i>0.028</i>	<i>0.007</i>	<i>125 / 273</i>
Weak	0.586	0.0	0.214	0.200	142 / 325
<i>adaptive</i>	<i>0.143</i>	<i>0.448</i>	<i>0.069</i>	<i>0.197</i>	<i>169 / 288</i>
High Dose	0.183	0.0	0.194	0.623	204 / 325
<i>adaptive</i>	<i>0.017</i>	<i>0.046</i>	<i>0.002</i>	<i>0.898</i>	<i>155 / 248</i>
Middle Dose	0.148	0.0	0.151	0.701	201 / 325
<i>adaptive</i>	<i>0.006</i>	<i>0.012</i>	<i>0.001</i>	<i>0.968</i>	<i>111 / 241</i>
Low Dose	0.117	0.0	0.196	0.687	232 / 325
<i>adaptive</i>	<i>0.006</i>	<i>0.009</i>	<i>0</i>	<i>0.974</i>	<i>124 / 247</i>
Peak 50 mg	0.259	0.0	0.187	0.554	180 / 325
<i>adaptive</i>	<i>0.057</i>	<i>0.13</i>	<i>0.02</i>	<i>0.698</i>	<i>152 / 252</i>
Peak 100mg	0.245	0.0	0.215	0.540	192 / 325
<i>adaptive</i>	<i>0.025</i>	<i>0.03</i>	<i>0</i>	<i>0.911</i>	<i>114 / 253</i>

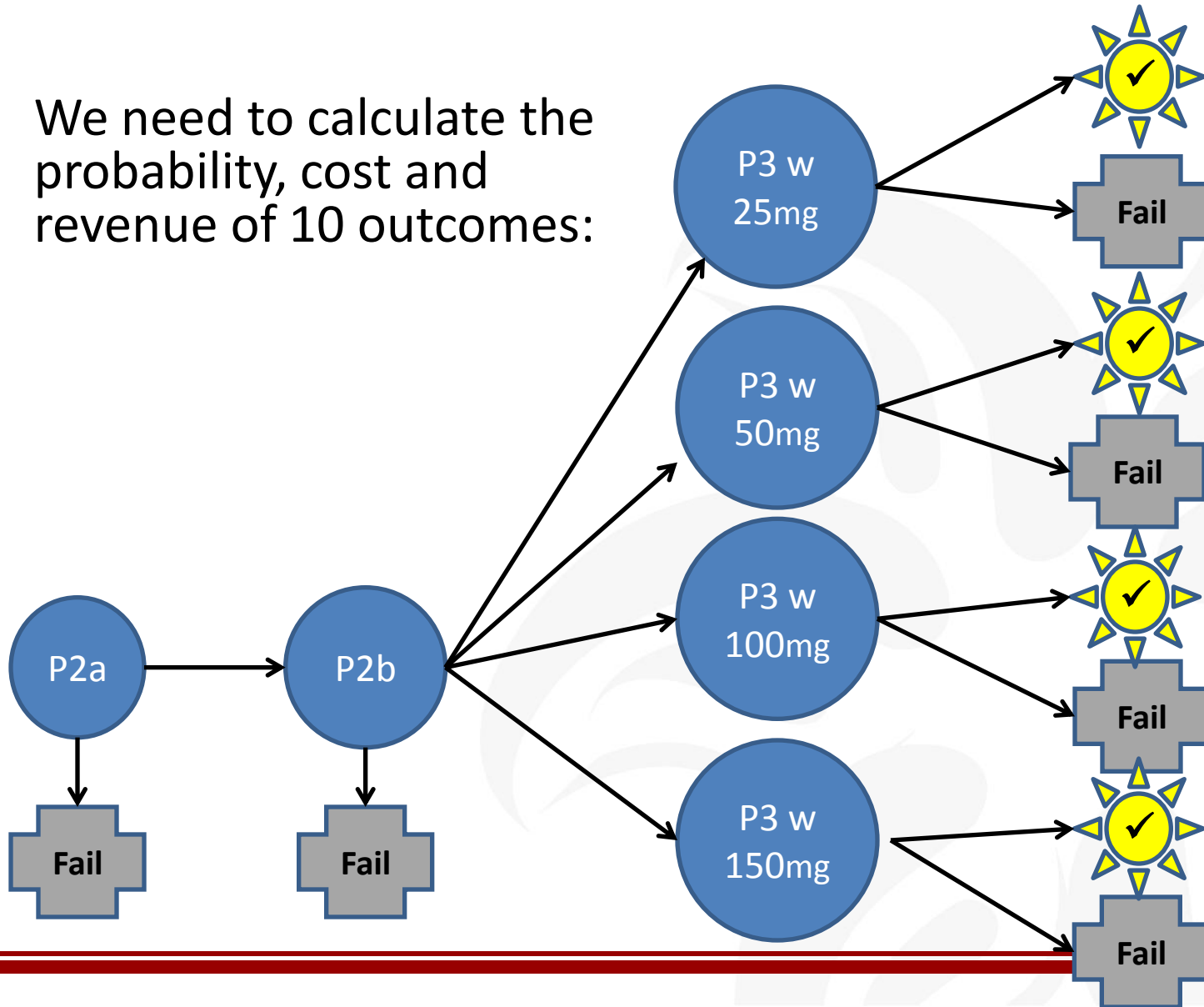
Scenario	Control	25mg	50mg	100mg	150mg
High Dose	-16	-17	-18	-20	-28
<i>fix'd P(MED)</i>	0.000	0.005	0.005	0.071	0.542
<i>adpt P(MED)</i>	0.000	0.017	0.024	0.151	0.701
Middle Dose	-16	-17	-22	-27	-28
<i>fix'd P(MED)</i>	0.000	0.020	0.114	0.368	0.119
<i>adpt P(MED)</i>	0.000	0.038	0.293	0.577	0.058
Low Dose	-16	-21	-25	-27	-28
<i>fix'd P(MED)</i>	0.000	0.204	0.196	0.207	0.080
<i>adpt P(MED)</i>	0.000	0.206	0.525	0.201	0.039
Peak 50 mg	-16	-21	-26	-22	-18
<i>fix'd P(MED)</i>	0.000	0.037	0.502	0.004	0.012
<i>adpt P(MED)</i>	0.000	0.203	0.478	0.007	0.000
Peak 100mg	-16	-20	-24	-28	-24
<i>fix'd P(MED)</i>	0.000	0.054	0.143	0.154	0.190
<i>adpt P(MED)</i>	0.000	0.136	0.471	0.296	0.003

ASSESSING VALUE OF EACH DESIGN



Thus in each success scenario

- We need to calculate the probability, cost and revenue of 10 outcomes:



NPV per scenario (\$M)

Scenario	Fixed Design	Adaptive seamless P2a/b
Null	-10.32	-11.68
Weak	-20.17	-22.06
High Dose	650.05	1024.96
Middle Dose	477.05	756.06
Low Dose	282.23	431.13
Peak at 50mg	314.47	363.04
Peak at 100mg	201.90	484.58

Summary

- Best depends on relative expected likelihood of different scenarios.
- Say we think
 - 40% Null
 - 40% Weak
 - 20% Positive (4% each of 5 scenarios)
- Probability weighted eNPV
 - Fixed: \$65M
 - Adaptive: \$109M