Ph 2/3 Trial for Selepressin in the Treatment of Vasopressor-Dependent Septic Shock

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Trial Basics

- Selepressin:
  - selective vasopressin V1a agonist for treatment of vasopressor-dependent septic shock
- Arms created by level of concentration – allowing multiple "doses" to be blinded and infusion rates can vary:

Treatment Arm	Starting Dose (ng/kg/min)	Maximum Dose (ng/kg/min)
0	0	0
1	1.7	2.5
2	2.5	3.75
3	3.5	5.25
4	5.0	7.5

Berry Consultants
Statistical Innovation

FERRING
PHARMACEUTICALS

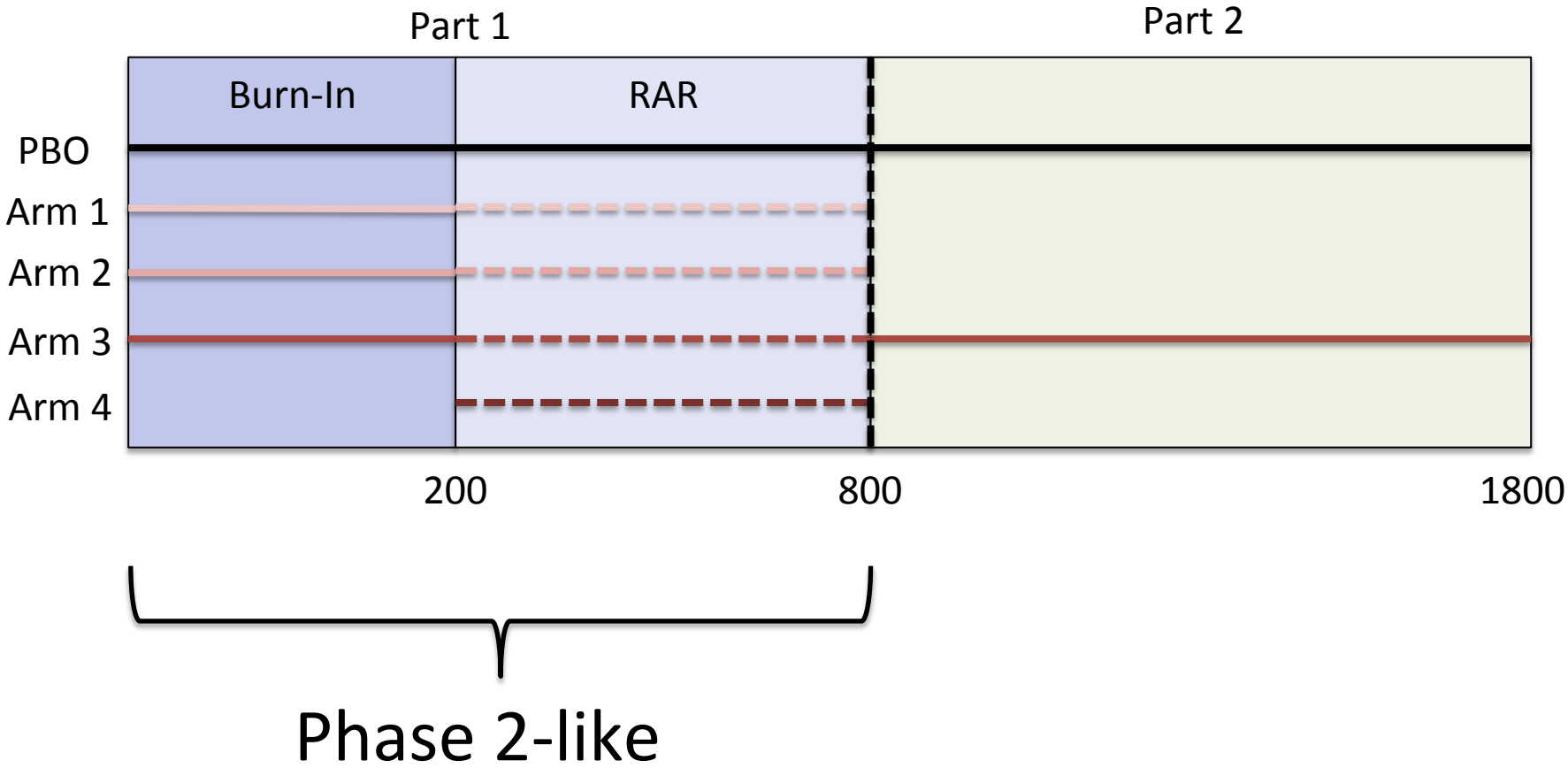
Trial Basics

- Double-blind, placebo-controlled
- "Pivotal Trial" Endpoint
  - Composite mortality/morbidity endpoint

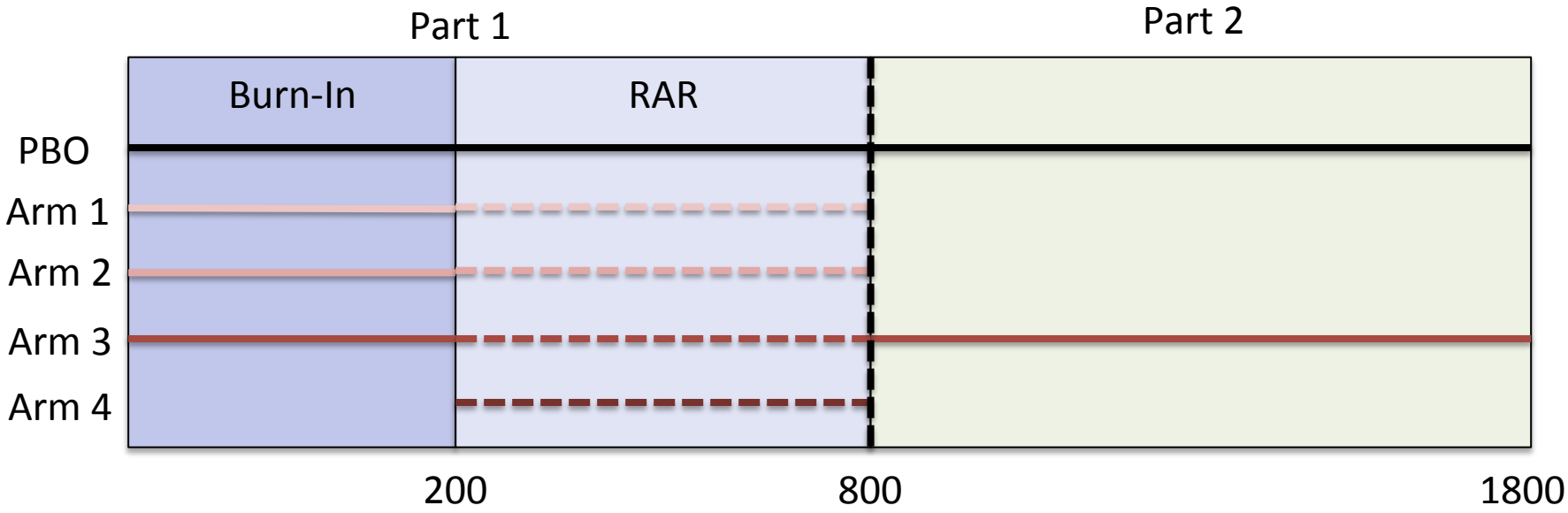
Possible Phase 2?

- 200 patient study of a "biomarker" for dose selection (2 arms given fixed nature?)
  - Then phase III
- 400 patient trial of doses on primary endpoint to select dose and make phase 3 go/no-go
  - Then phase III
- 800 patient trial of doses on primary endpoint to select dose and make phase 3 go/no-go
  - Then phase III

Adaptive Phase 2

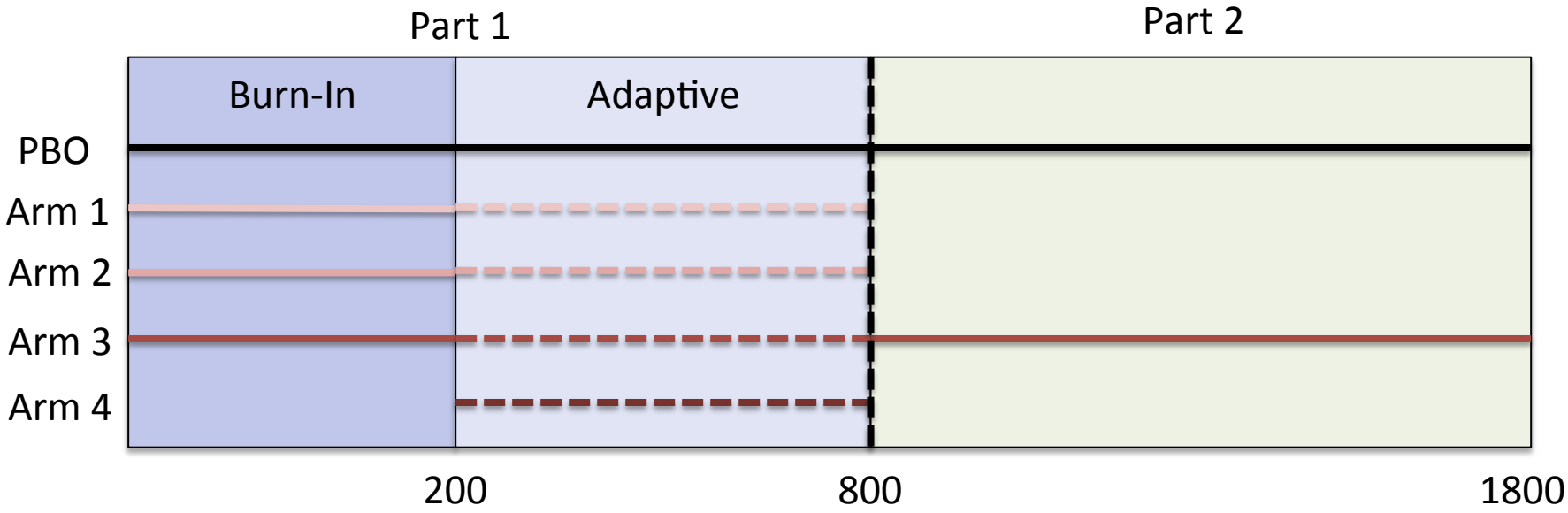


Part 1: Burn-In



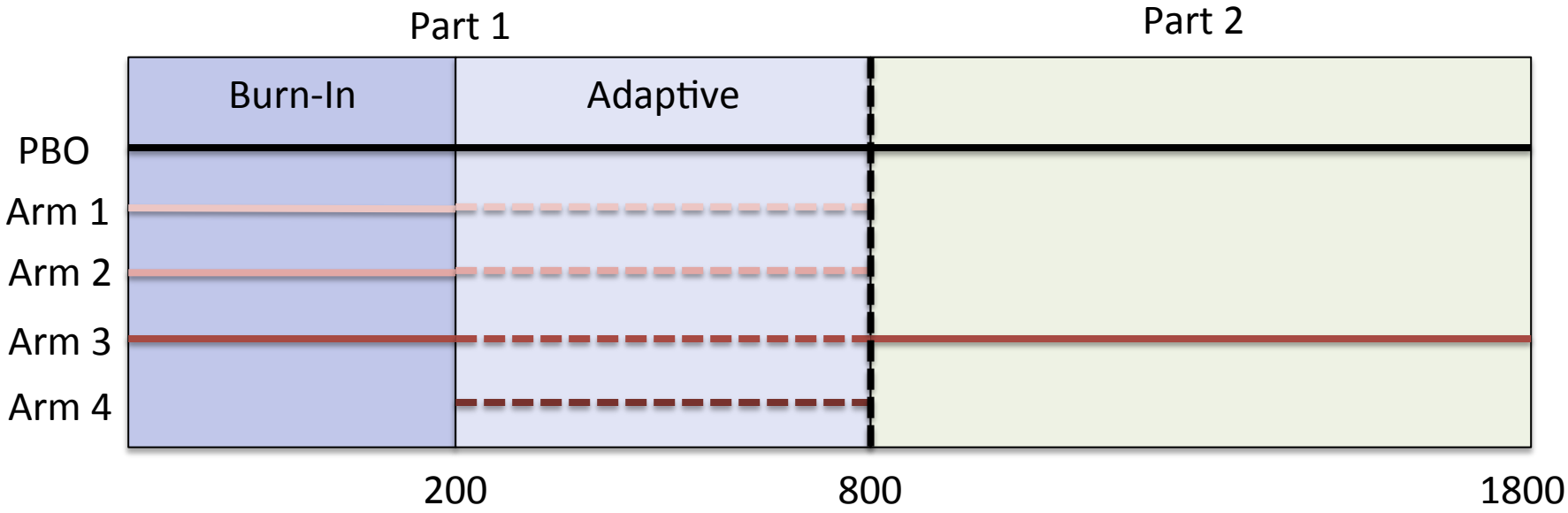
- Start with 3 doses + PBO during 200 patient burn-in
  - 3:2:2:2:0 (Arms 0:1:2:3:4)

Part 1: Adaptive



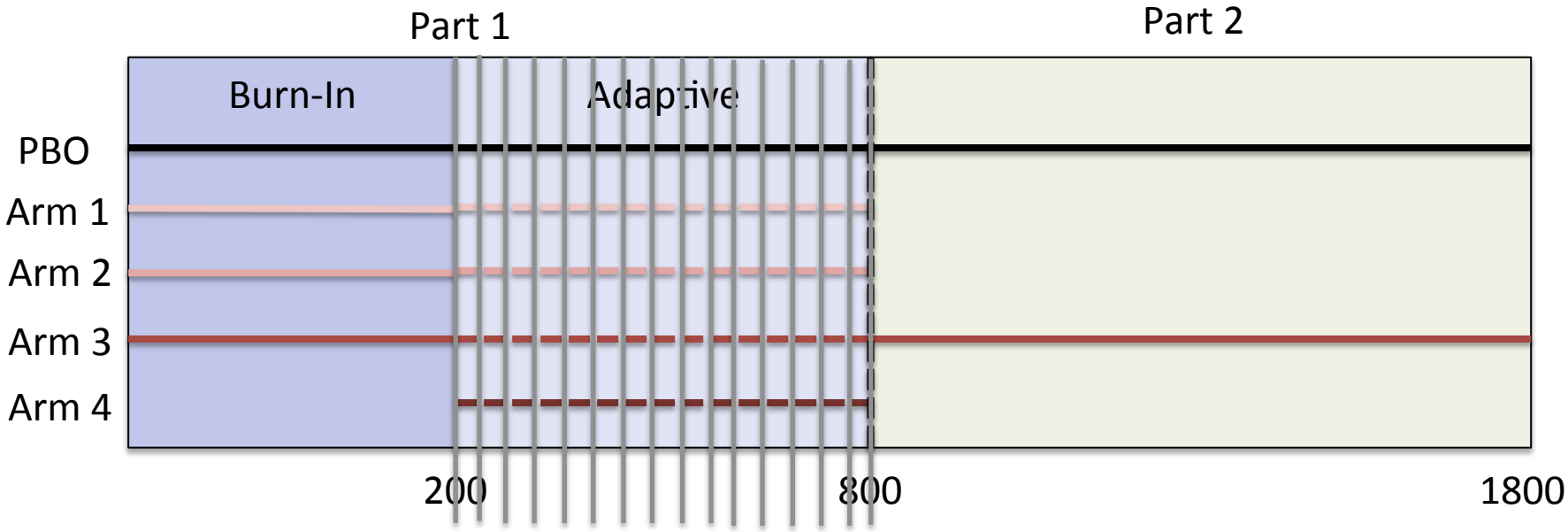
- Interims occur from 200-800 continue monthly for Part 1
  - Create response adaptive randomization over active arms (1/3 : ? : ? : ? : ?) for next month
  - Futility / Go to Part 2 decisions

Part 2: Confirm



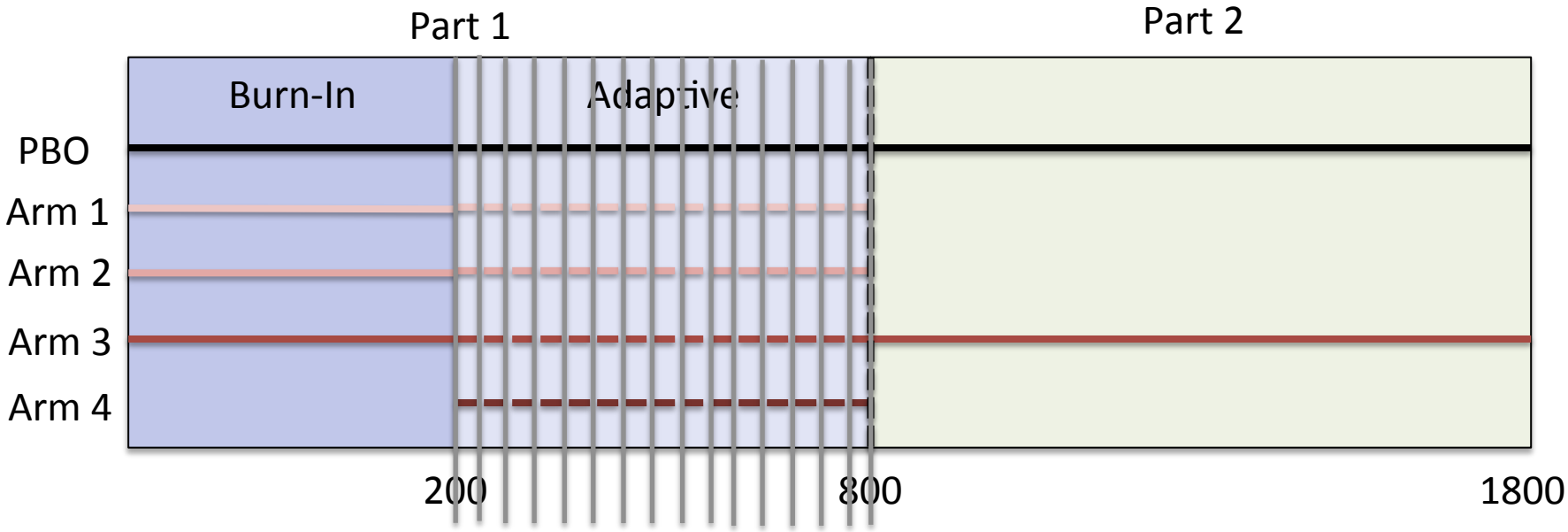
- Enroll 1:1 to PBO and selected 'target' dose to make the final sample size 1800
  - Part 2 minimum is 1000 patients
  - Futility analyses every month

Part 1: RAR



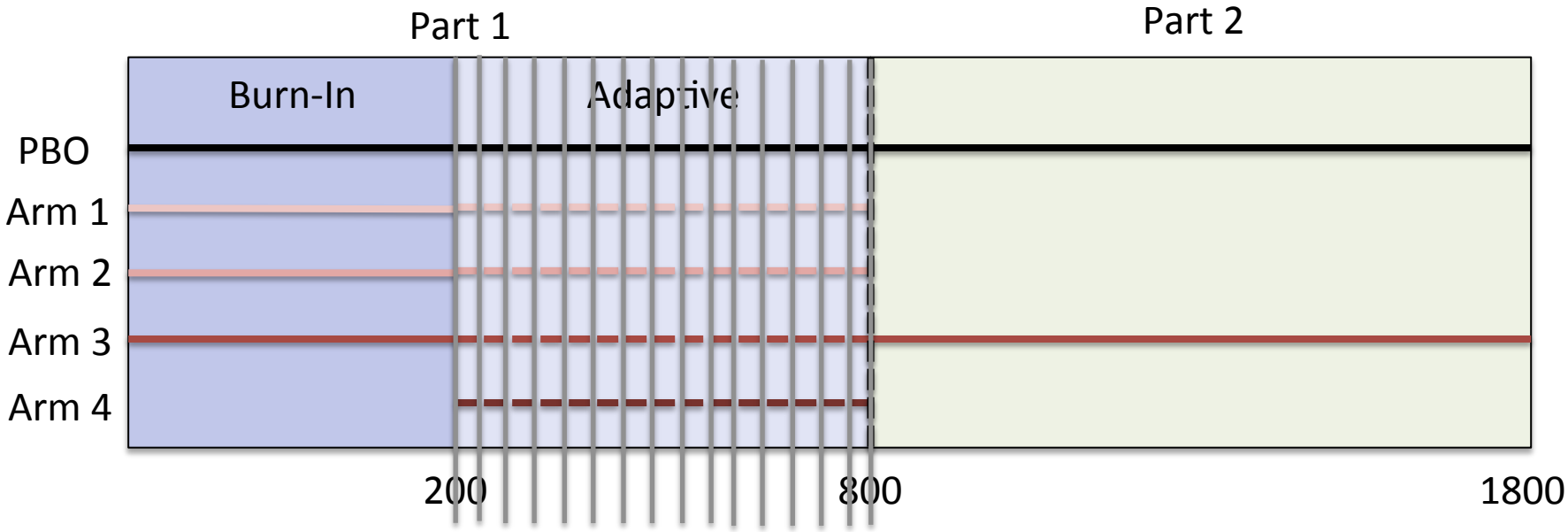
- Randomization probability proportional to the probability the arm maximizes the effect on the primary endpoint
  - Open "Arm 4" if ≥ 50% probability Arm 3 has better effect on the primary endpoint than Arm 2.

Part 1: Decisions



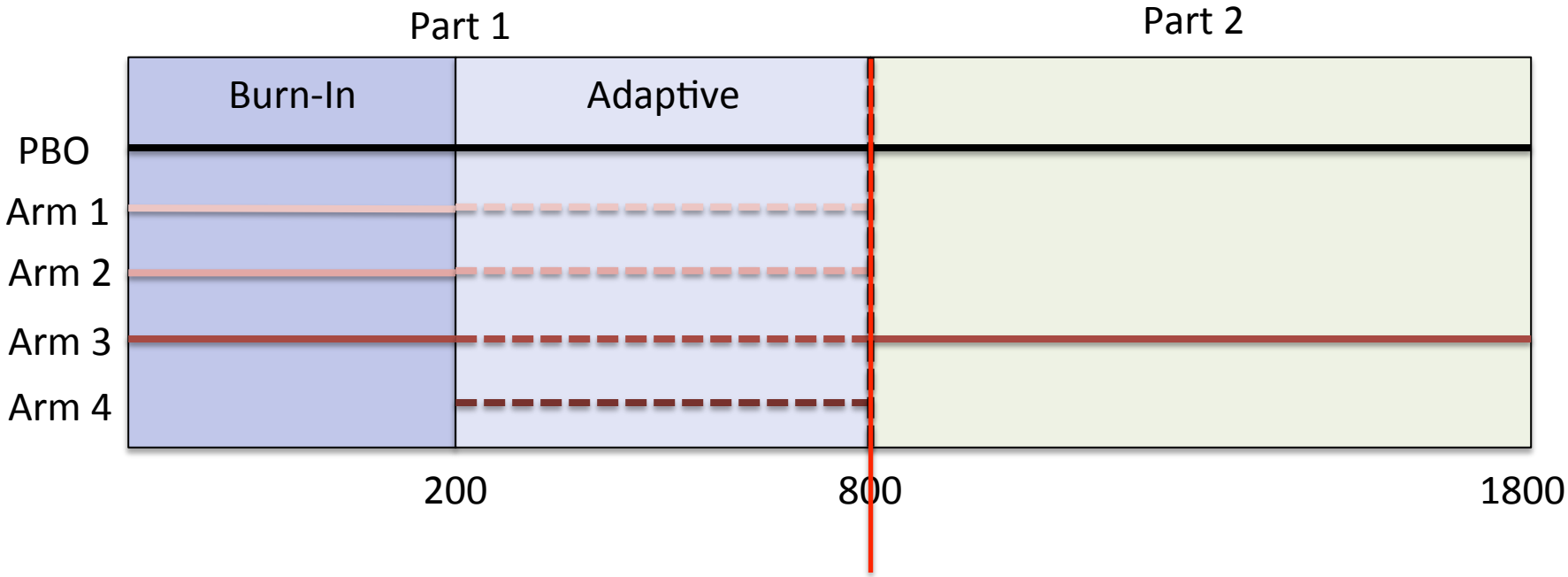
- Go to Part 2 if (n≥300)
  - Predictive probability of superiority @ 1800 with most likely maximum dose ≥ 90%

Part 1: Decisions



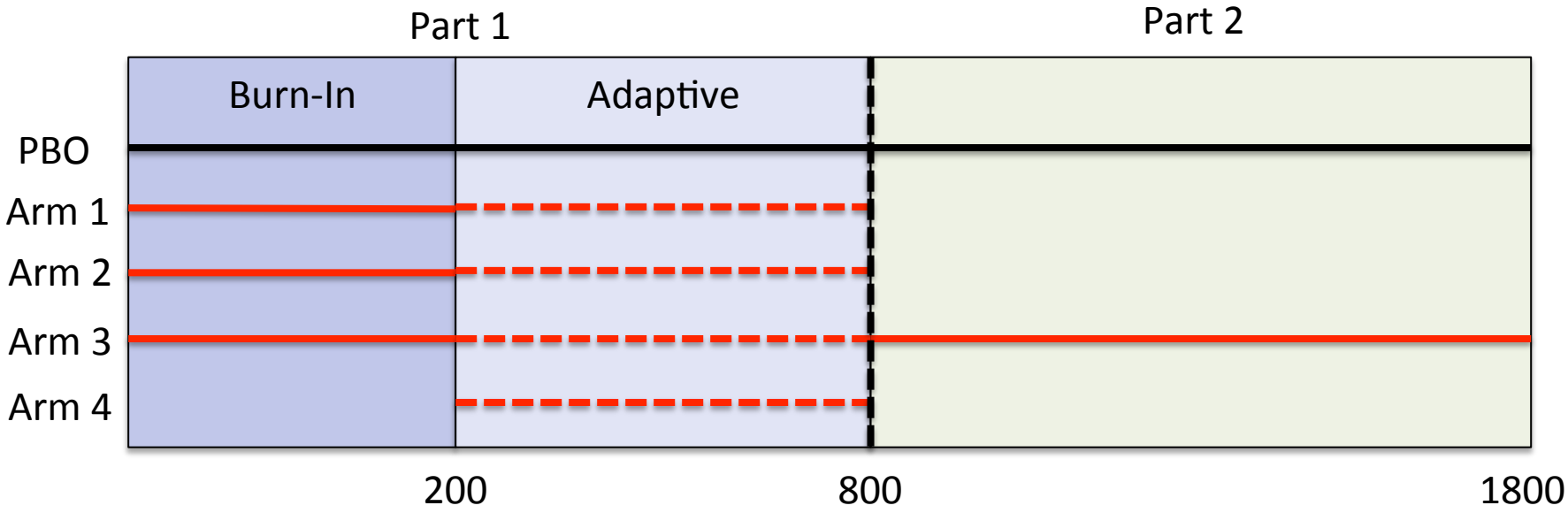
- Stop for futility if
  - Predictive probability of superiority @ 1800 with most likely maximum dose < 5%

Part 1: n=800 Decision



- Go to Part 2 if (n=800)
  - Predictive probability of superiority @ 1800 with most likely maximum dose ≥ 25%
  - If not stop the trial

Final Analysis



- Pool all selepressin arms (Part 1 & Part 2) in final analysis vs. PBO with Wilcoxon Test (Van Elteren's) at the 0.025 level
- Type I error controlled analysis of superiority

Bayesian Statistical Model

- Statistical model to drive all adaptations
- Model mixture of death and morbidity outcome for survivors
  - Proportional effect for selepressin treatment arms (α_1,…, α_4)
- Model for morbidity for survivors
  - Proportional effect for selepressin treatment arms (θ_1,…, θ_4)
- Inverted U-Dose-Response models

Operating Characteristics

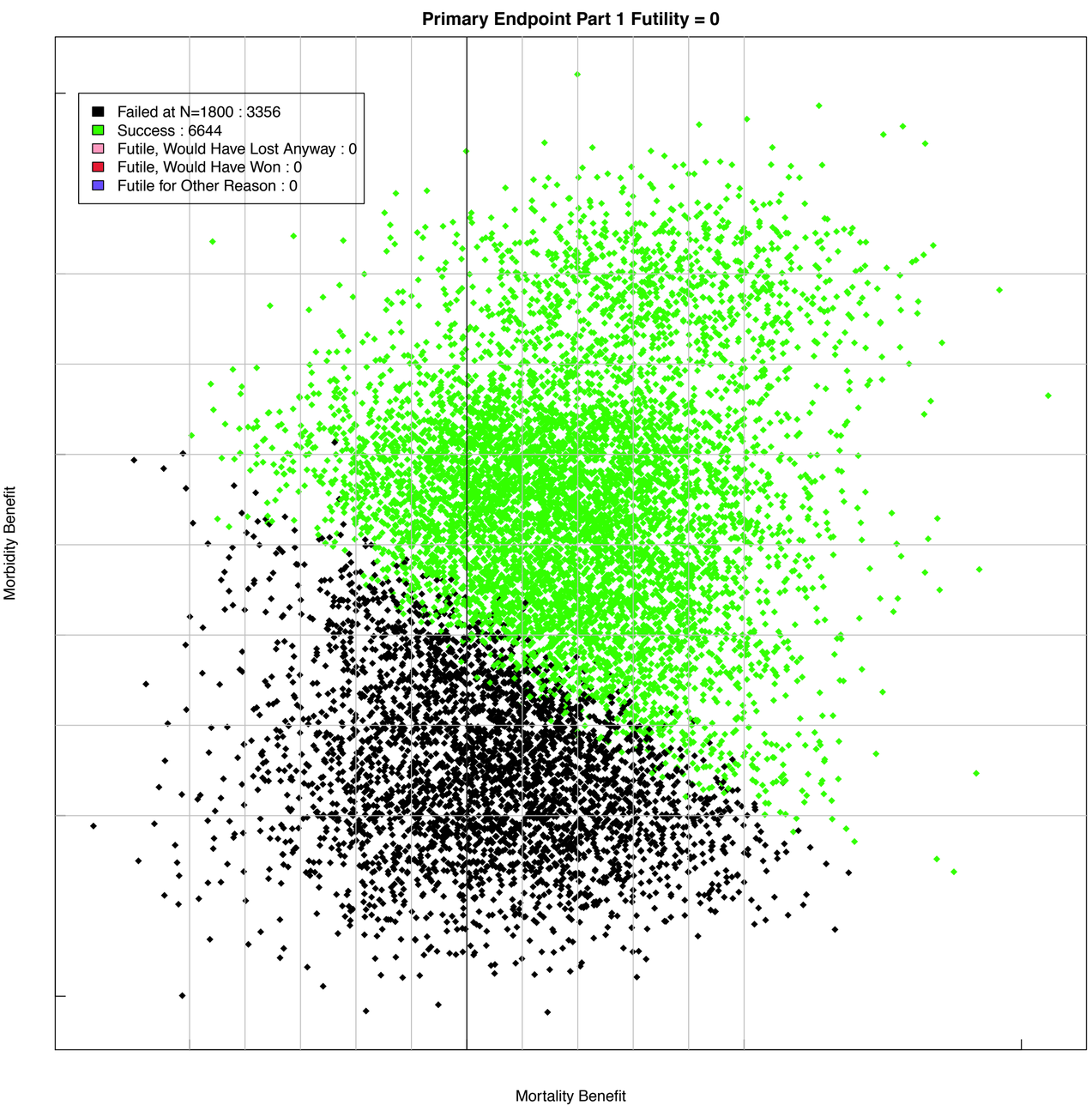
Scenario (Effect)	Prop. Of Trials			Mean Sample Size			
	Success	Part 2	1800	Total	Part 1	Part 2	Target Dose
0	.016	.148	.043	770.5	638.6	131.9	709.5
A	.127	.370	.187	1069.4	694.6	374.8	712.2
B	.497	.680	.569	1442.2	665.6	776.6	741
C	.854	.895	.875	1690.3	582.4	1107.9	756.5
D	.983	.986	.985	1785.2	501.6	1283.6	776.5
E	1	1	1	1800	441	1359	796.1
F	1	1	1	1800	438.3	1361.7	806.1

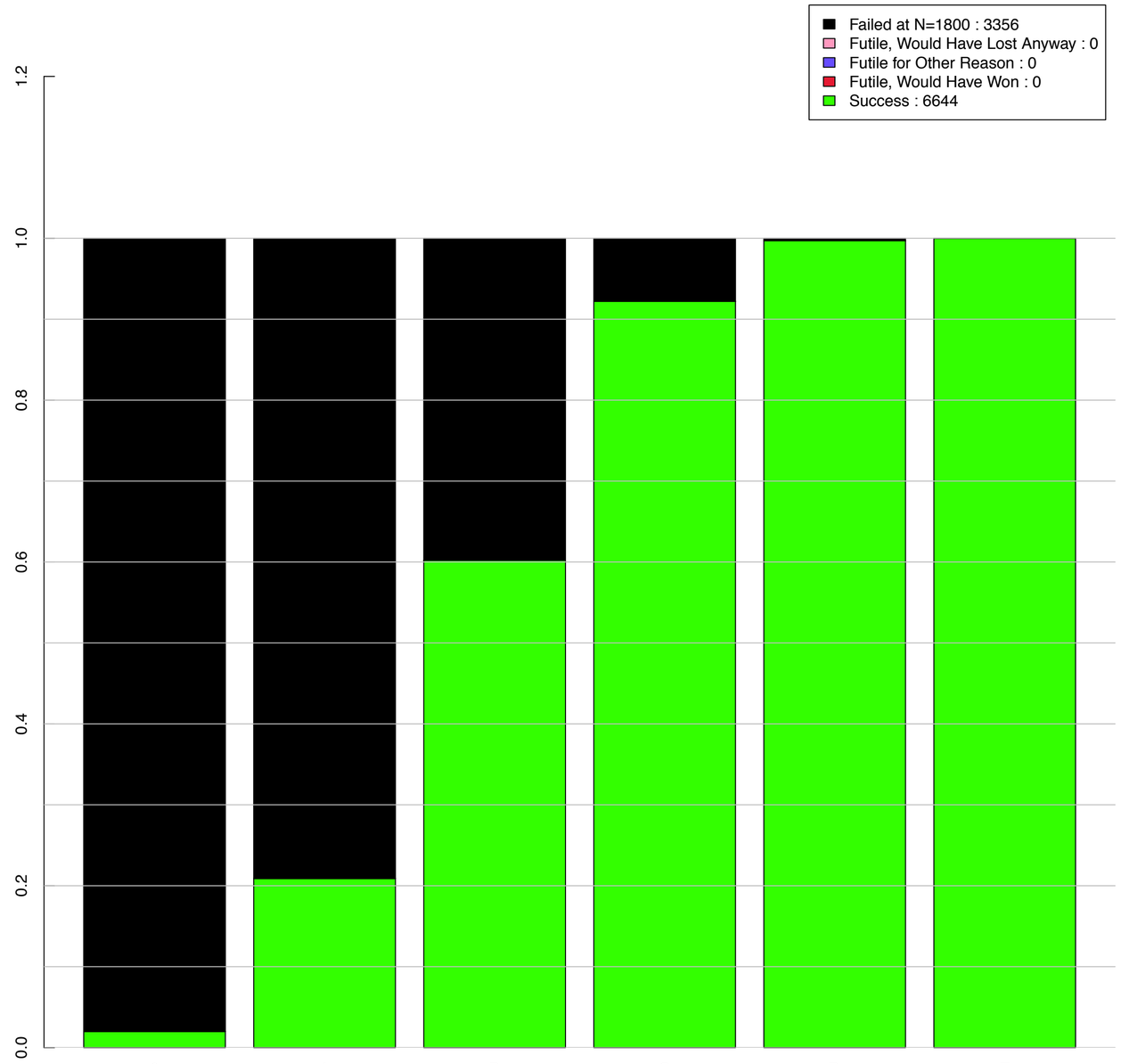
Individual Scenarios

Arm	True Effect	Prop of Trials		Mean Sample Size		
		Target	Target & Win	Total	Part 1	Part 2
PBO	**0**	**0**	**0**	**638.6**	**131.9**	**709.5**
Dose 1	C	.194	.181	694.6	374.8	712.2
Dose 2	C	.456	.440	665.6	776.6	741
Dose 3	C	.234	.225	582.4	1107.9	756.5
Dose 4	C	.011	.008	501.6	1283.6	776.5
PBO	**0**	**0**	**0**	**618.8**	**178.9**	**439.9**
Dose 1	A	.021	.011	185.2	173.2	12.0
Dose 2	B	.206	.155	266.9	142.6	124.3
Dose 3	C	.432	.390	362.0	109.7	252.3
Dose 4	C	.093	.085	96.8	45.8	51.0
PBO	**0**	**0**	**0**	**701.8**	**164.3**	**537.5**
Dose 1	C	.317	.292	402.6	215.2	187.4
Dose 2	C	.489	.468	427.2	123.6	303.6
Dose 3	B	.077	.053	124.6	78.1	46.5
Dose 4	A	0	0	13.4	13.4	0

Simulation

- Trial conducted through extensive simulations
  - Example trials, cut-offs, modeling, sample sizes, power, dose selection, etc… *type I error*
- Example of value of simulations for futility thresholds prospectively…


Primary Endpoint Part 1 Futility = 0
Failed at N=1800 : 3356
Success : 6644
Futile, Would Have Lost Anyway : 0
Futile, Would Have Won : 0
Futile for Other Reason : 0
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 3356
Futile, Would Have Lost Anyway : 0
Futile for Other Reason : 0
Futile, Would Have Won : 0
Success : 6644
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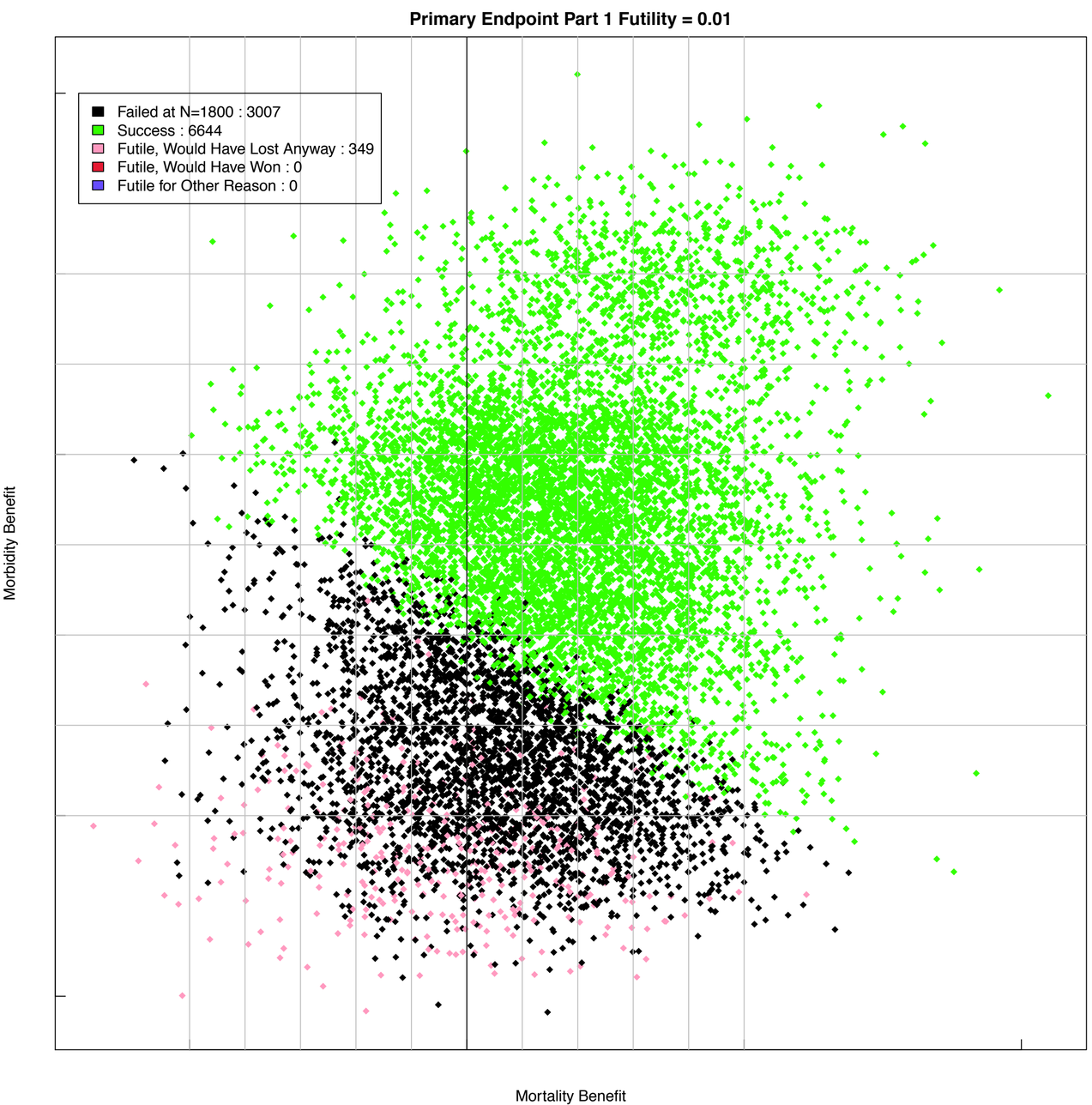
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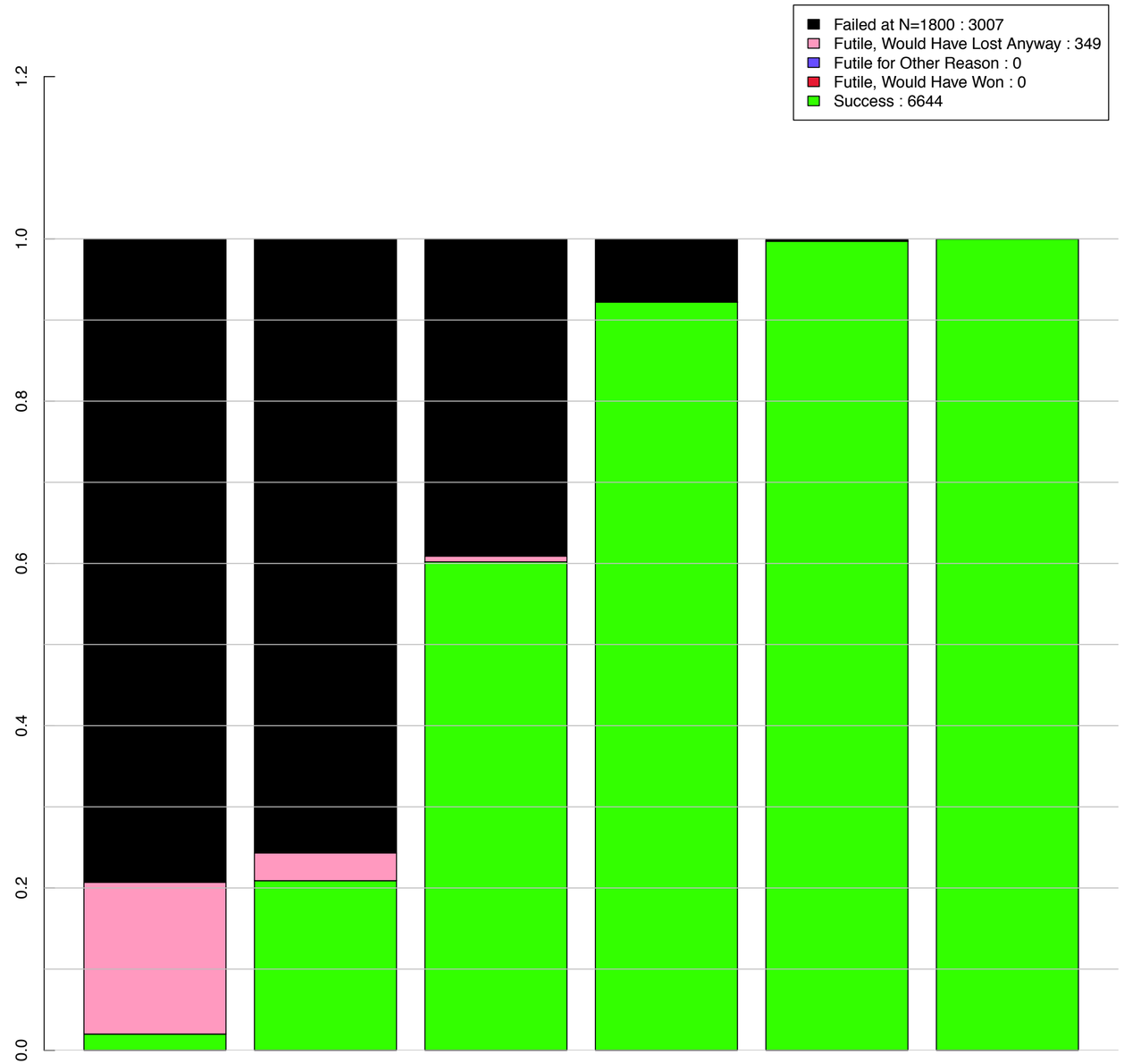
Futile, Would Have Lost Anyway : 349
Futile, Would Have Won : 0
Futile for Other Reason : 0
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 3007
Futile, Would Have Lost Anyway : 349
Futile for Other Reason : 0
Futile, Would Have Won : 0
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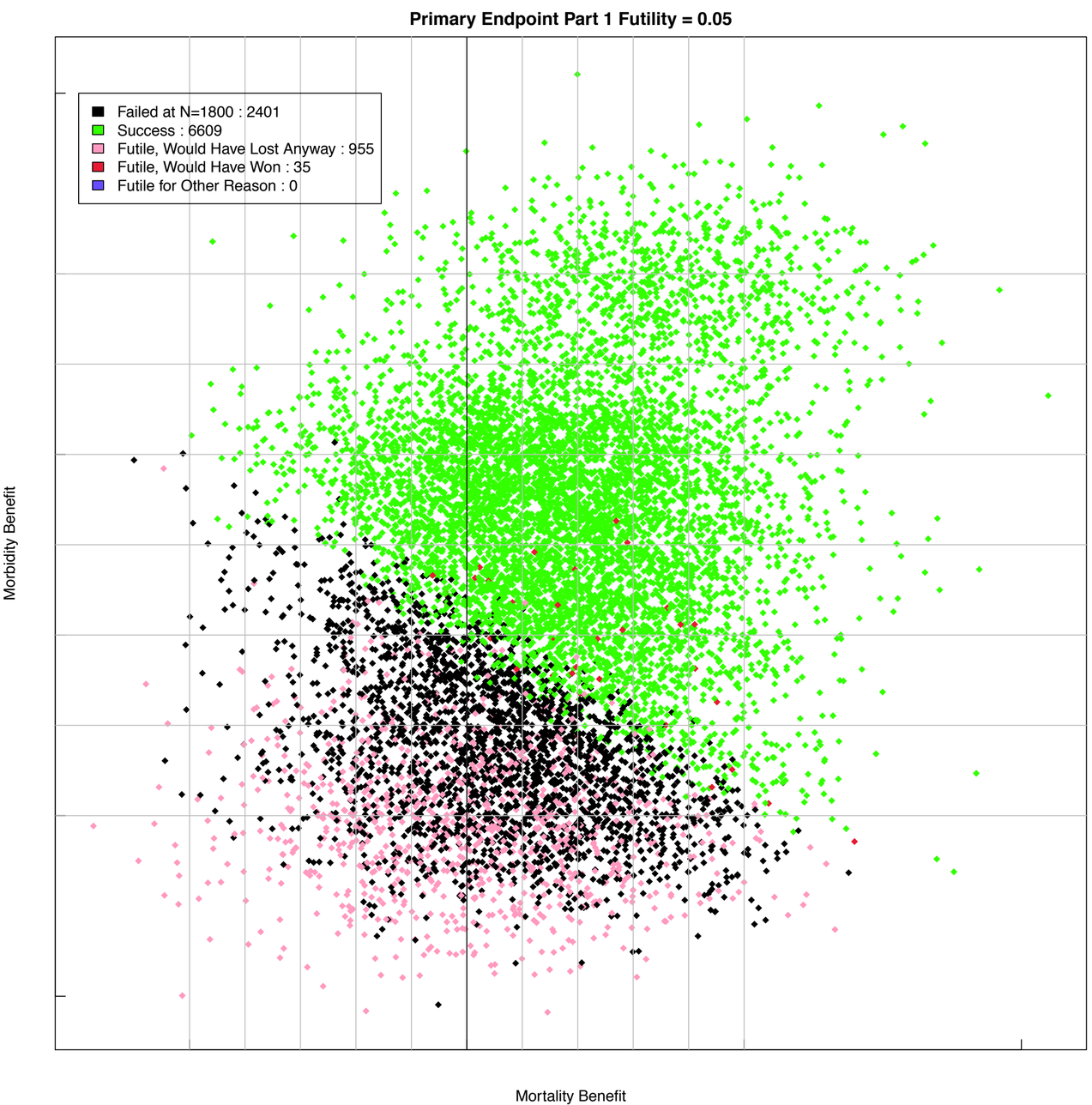
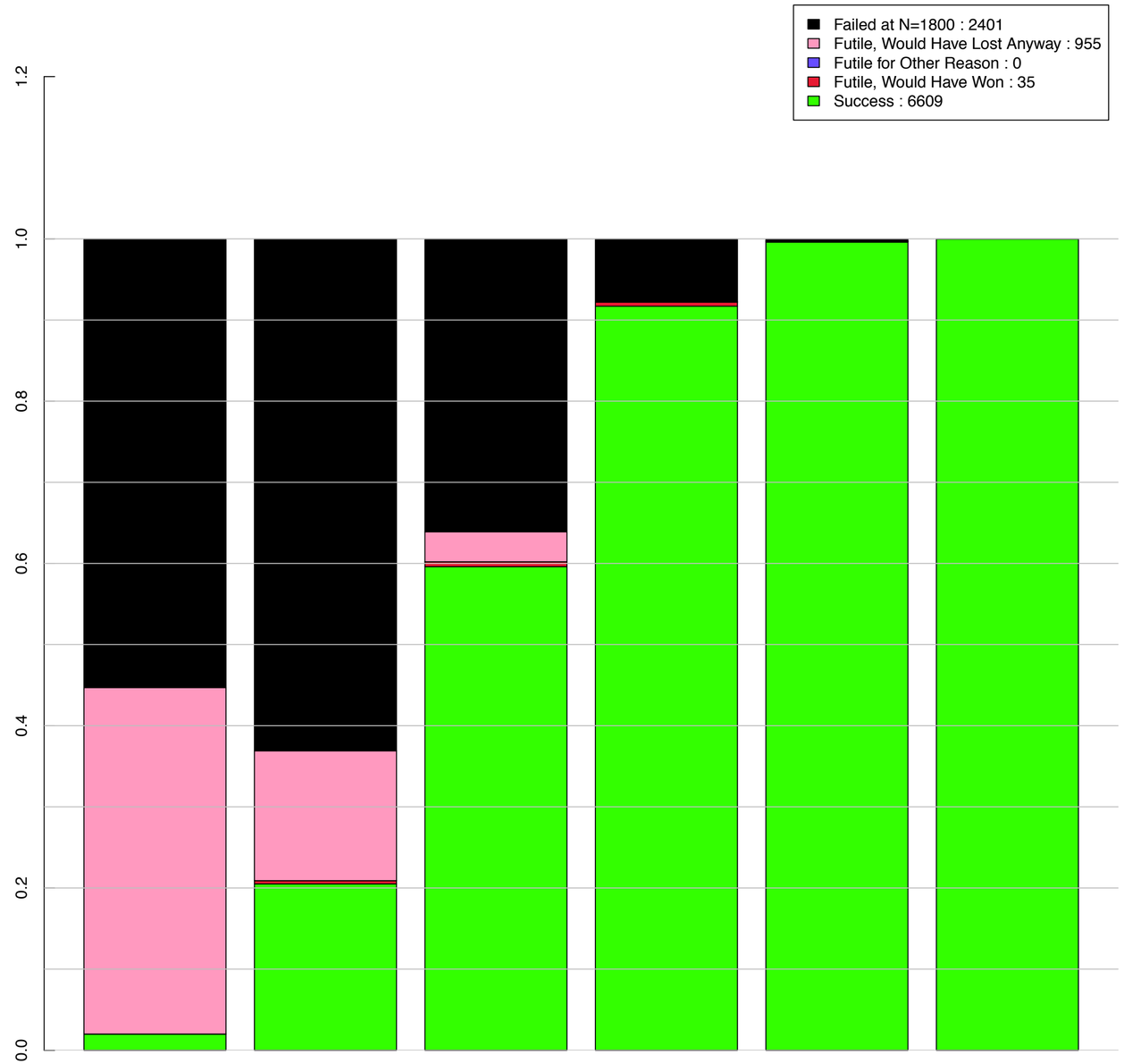

Primary Endpoint Part 1 Futility = 0.05
Failed at N=1800 : 2401
Success : 6609
Futile, Would Have Lost Anyway : 955
Futile, Would Have Won : 35
Futile for Other Reason : 0
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 2401
Futile, Would Have Lost Anyway : 955
Futile for Other Reason : 0
Futile, Would Have Won : 35
Success : 6609
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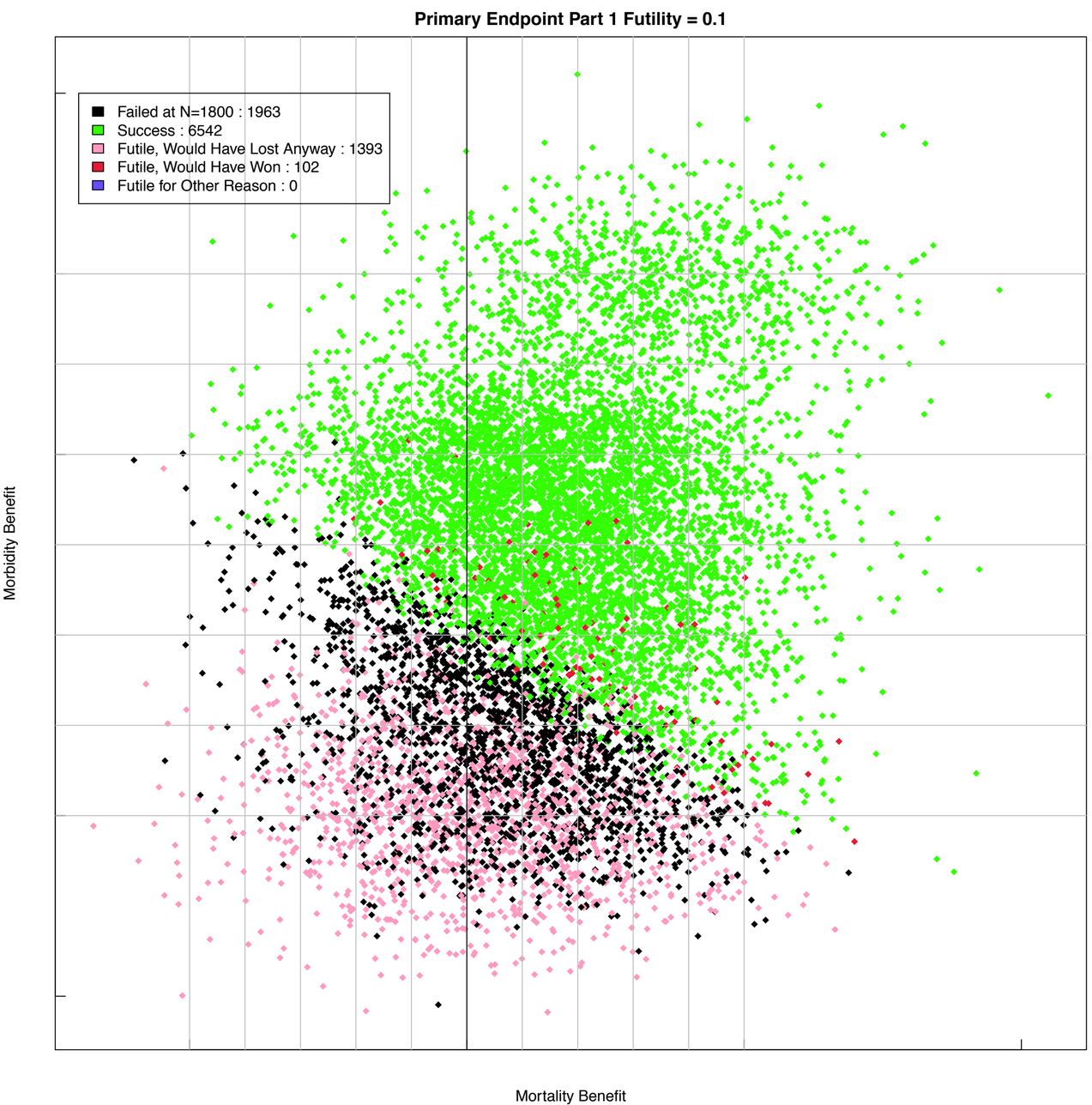
Primary Endpoint Part 1 Futility = 0.1
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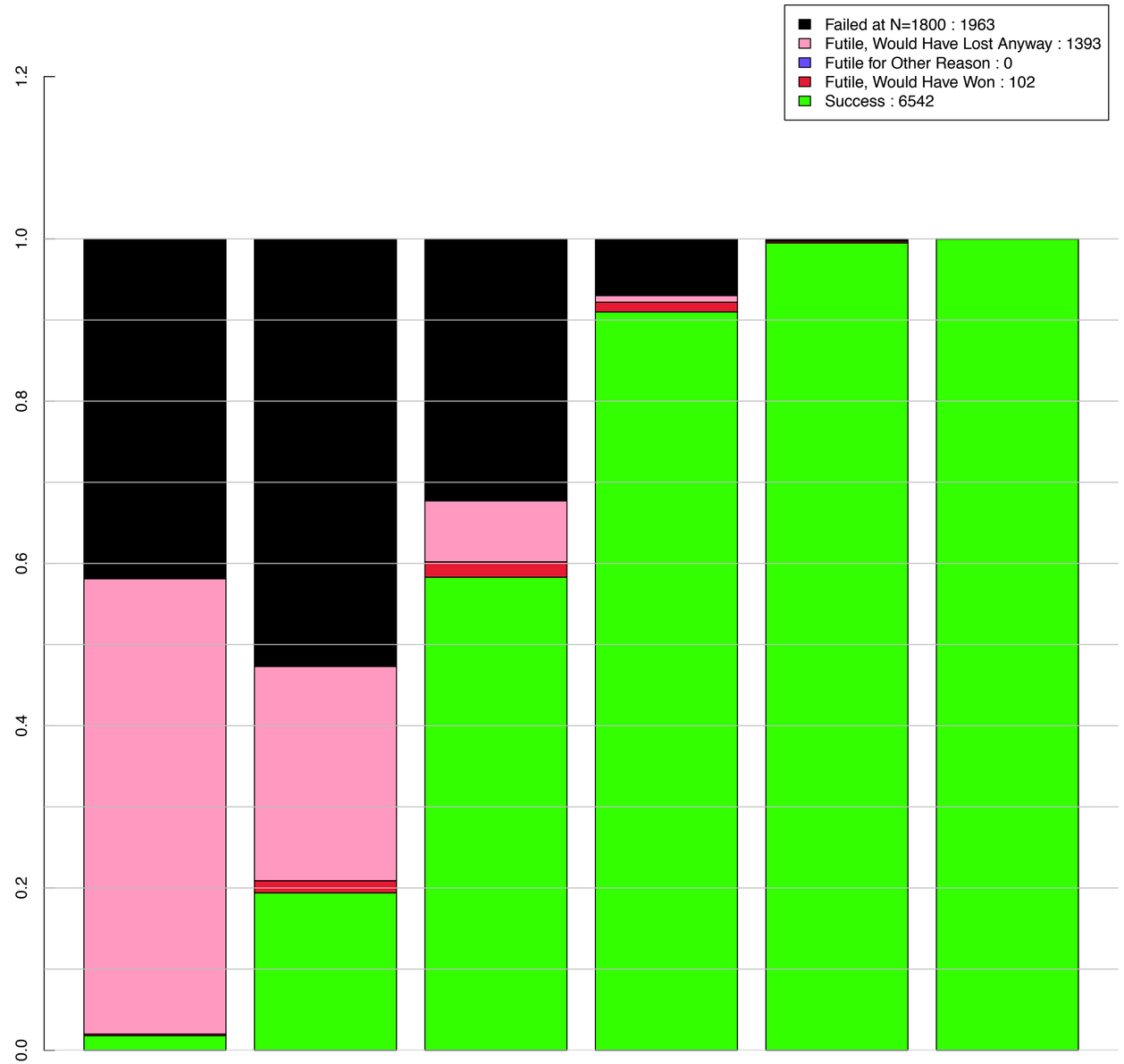
Success : 6542
Futile, Would Have Lost Anyway : 1393
Futile, Would Have Won : 102
Futile for Other Reason : 0
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 1963
Futile, Would Have Lost Anyway : 1393
Futile for Other Reason : 0
Futile, Would Have Won : 102
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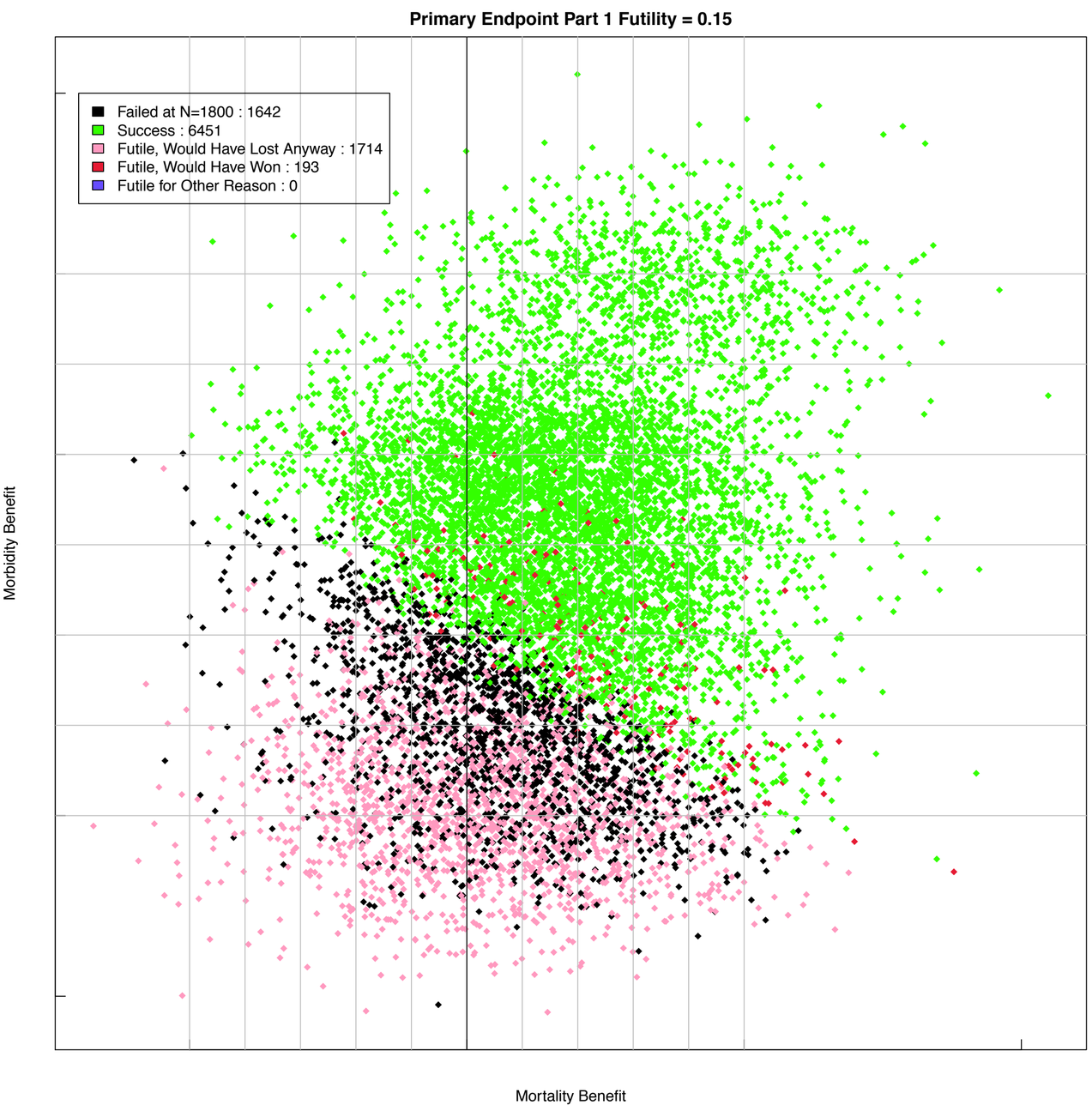
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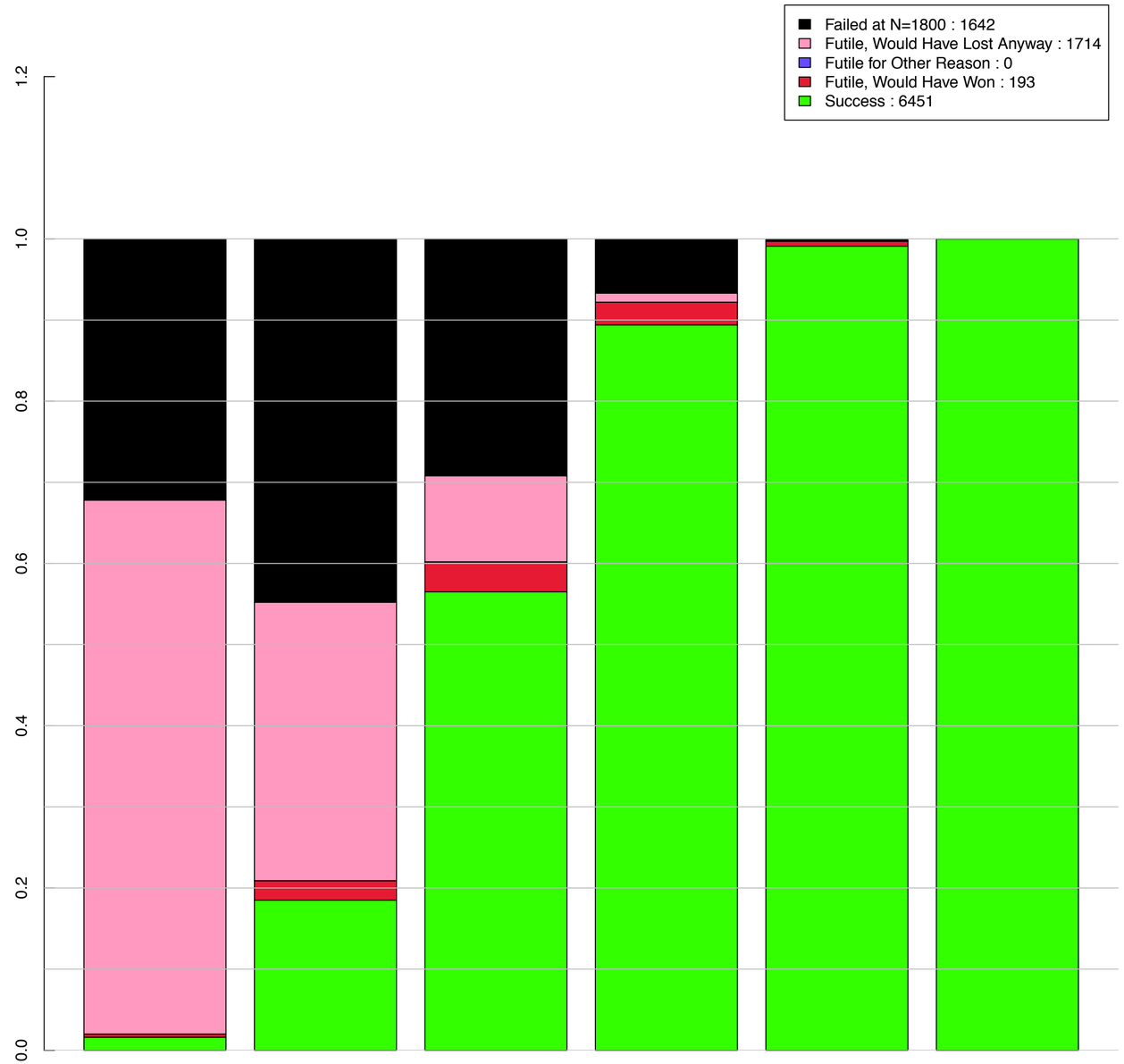
Futile, Would Have Won : 193
Futile for Other Reason : 0
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 1642
Futile, Would Have Lost Anyway : 1714
Futile for Other Reason : 0
Futile, Would Have Won : 193
Success : 6451
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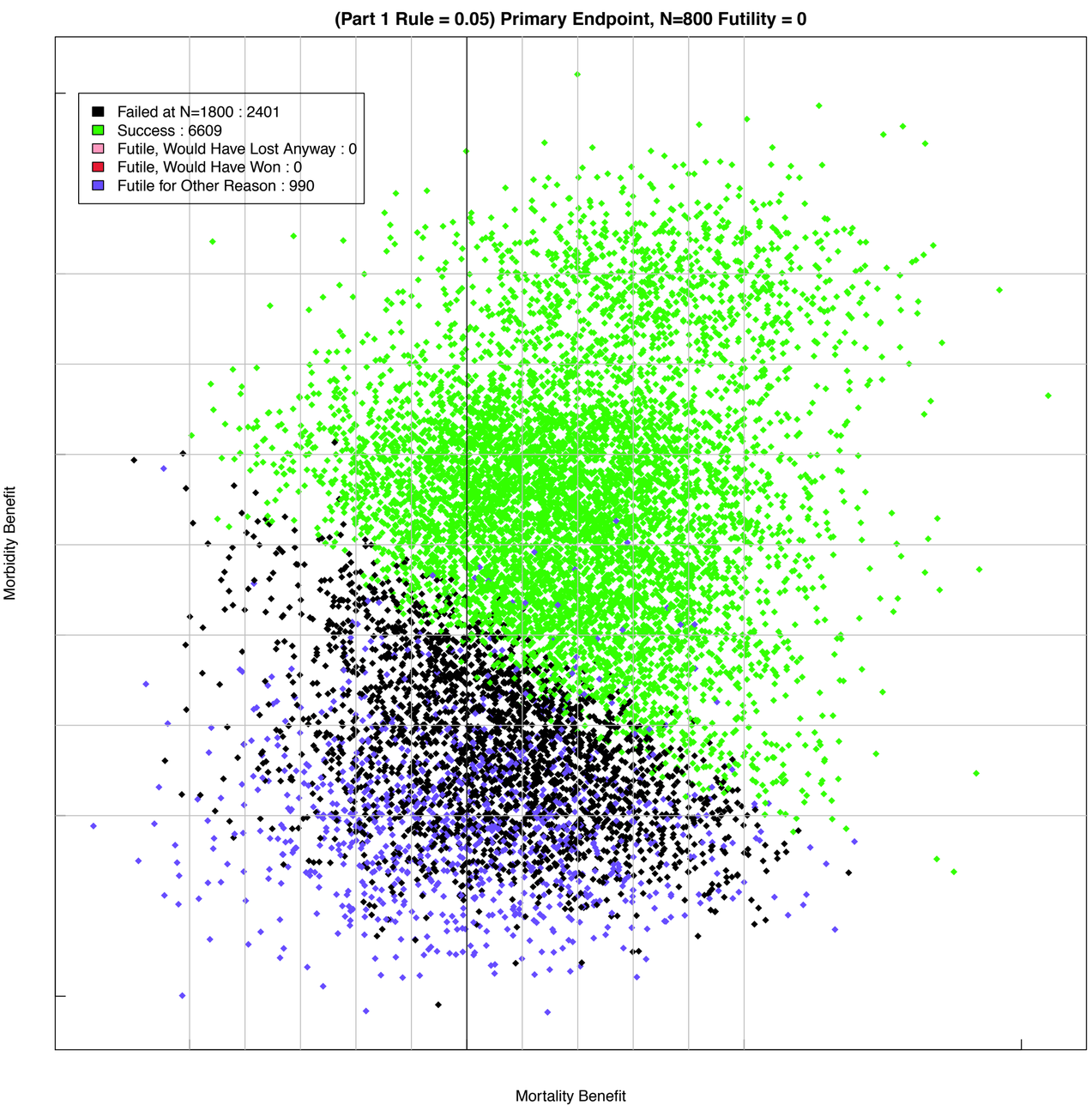
(Part 1 Rule = 0.05) Primary Endpoint, N=800 Futility = 0
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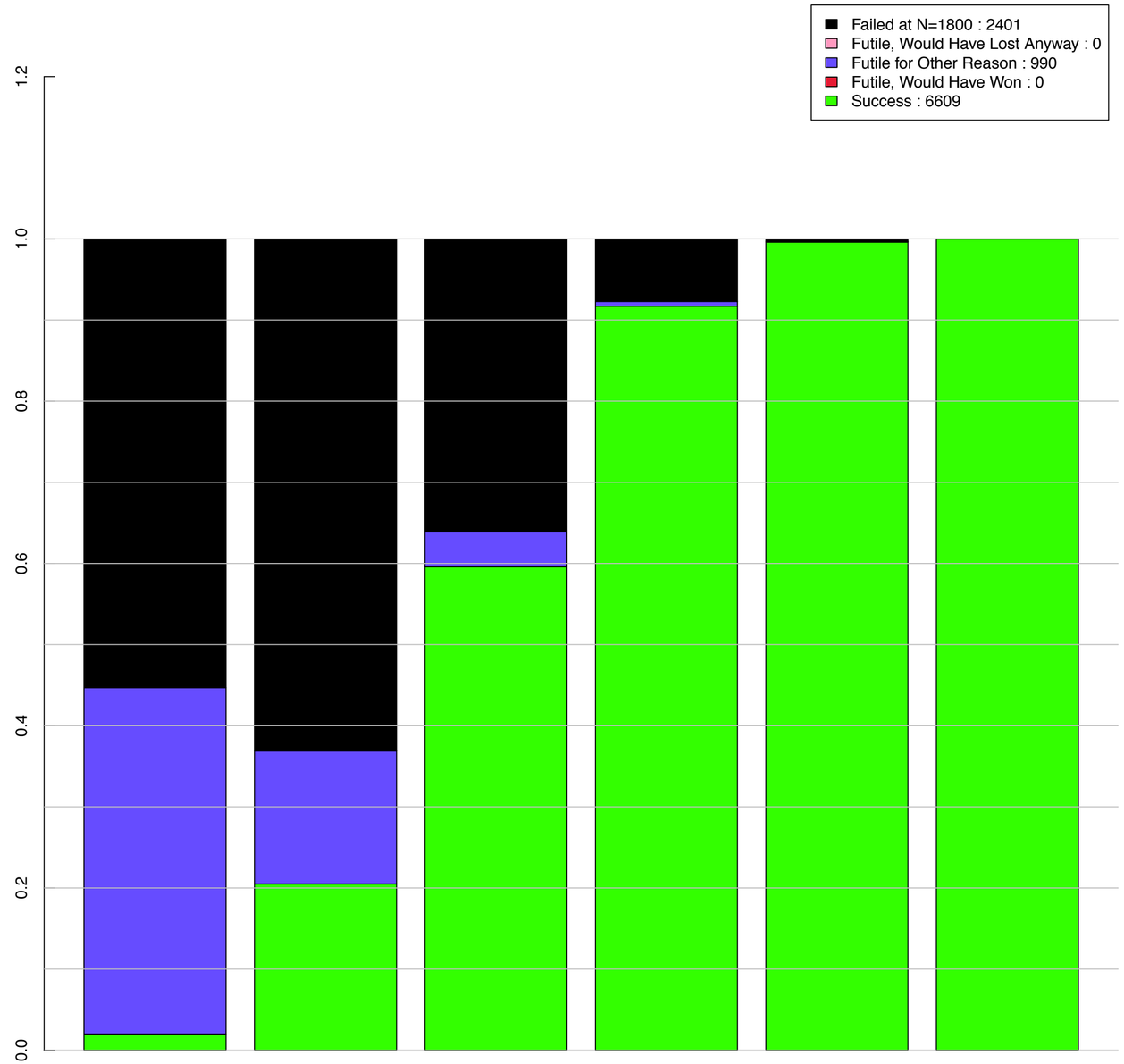
Futile, Would Have Lost Anyway : 0
Futile, Would Have Won : 0
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 2401
Futile, Would Have Lost Anyway : 0
Futile for Other Reason : 990
Futile, Would Have Won : 0
Success : 6609
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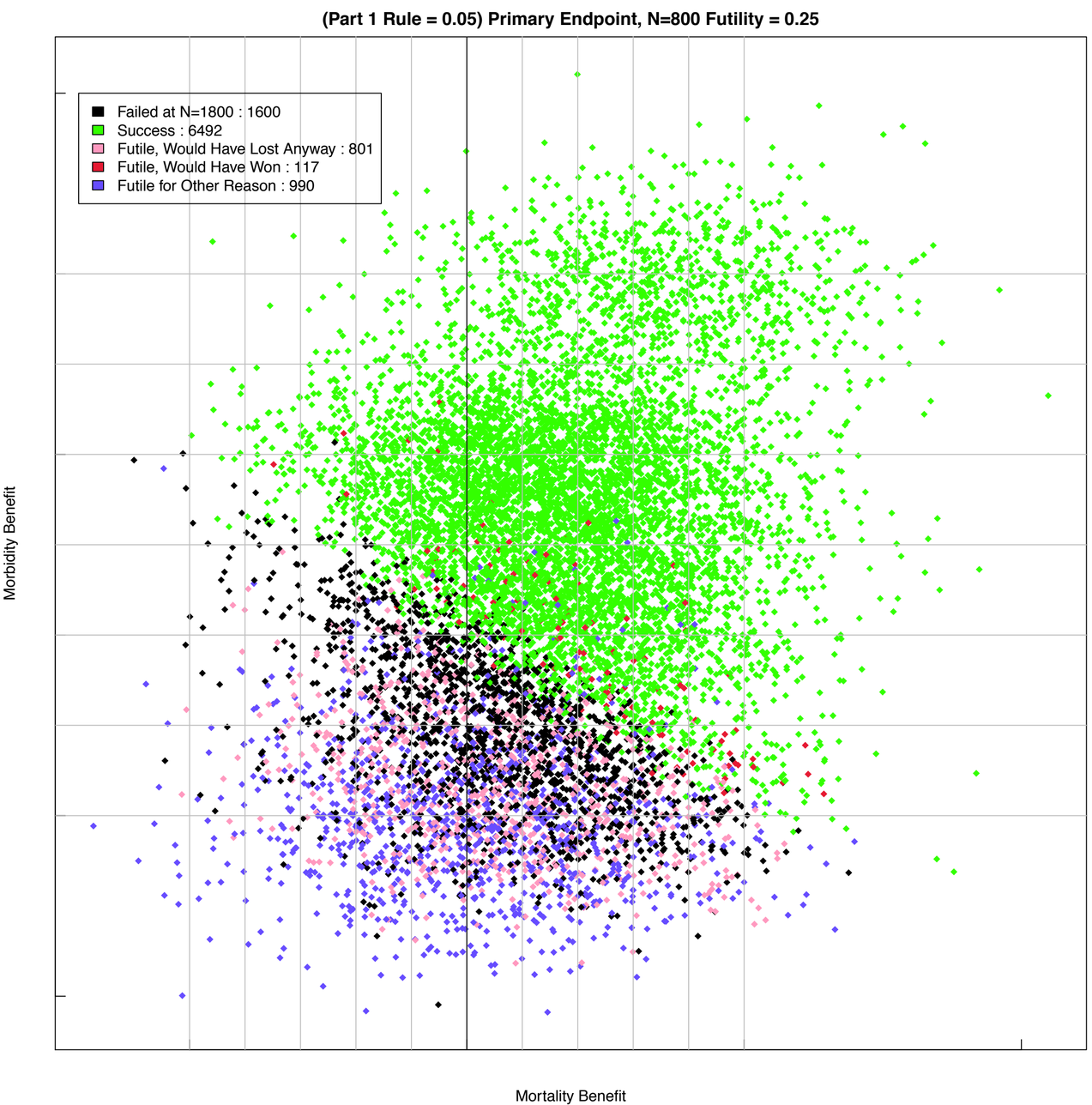
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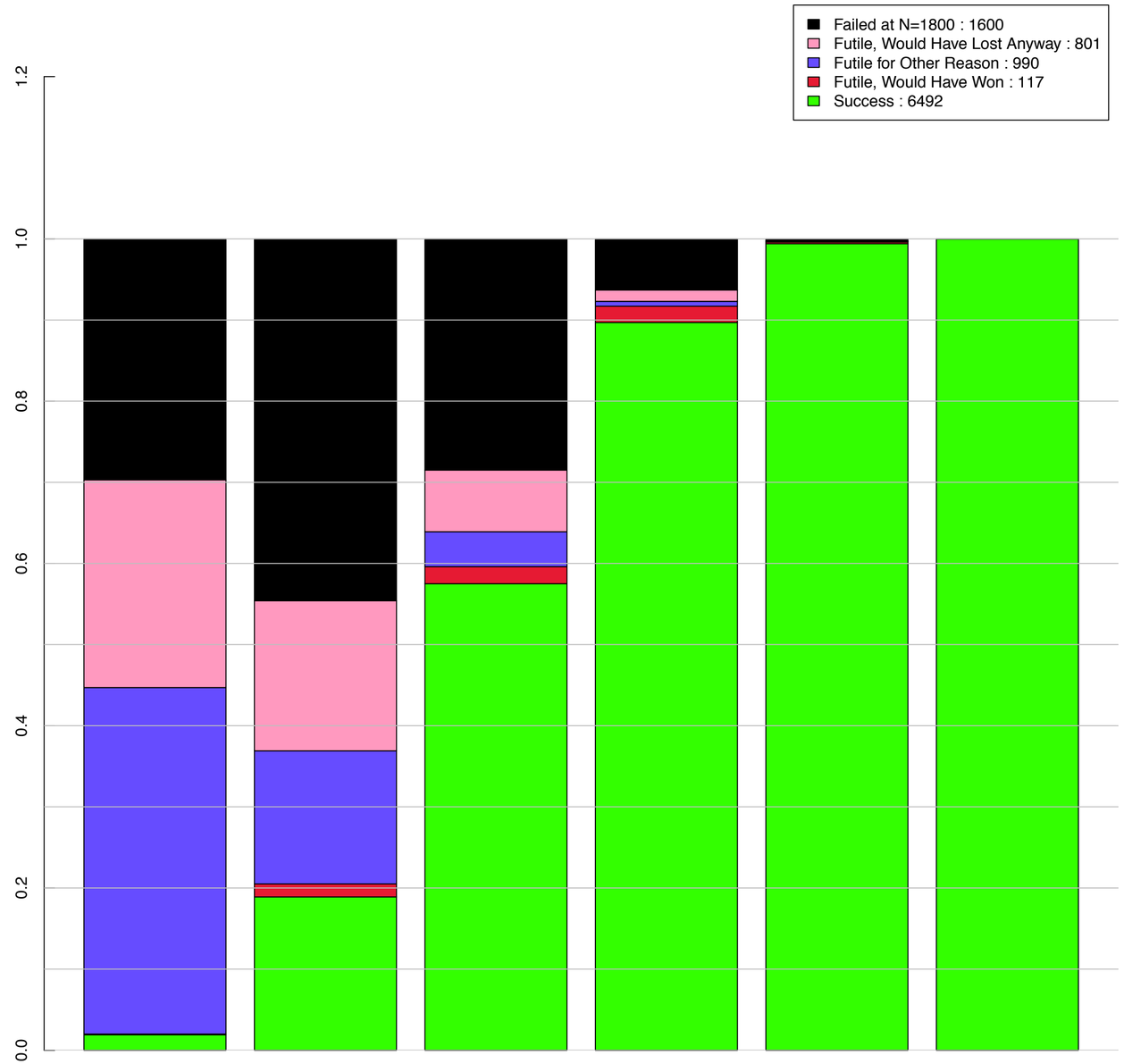
Futile, Would Have Lost Anyway : 801
Futile, Would Have Won : 117
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 1600
Futile, Would Have Lost Anyway : 801
Futile for Other Reason : 990
Futile, Would Have Won : 117
Success : 6492
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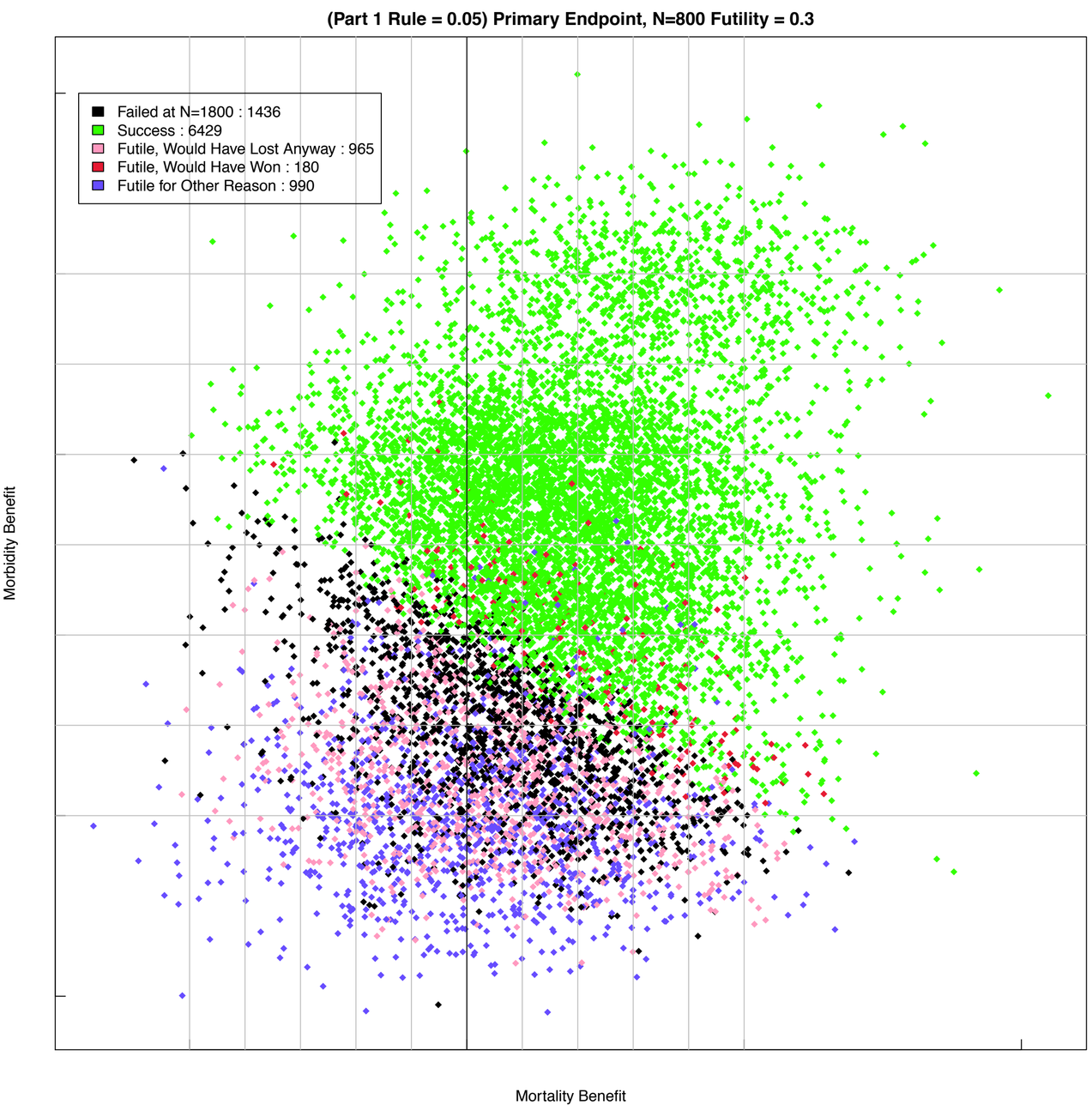
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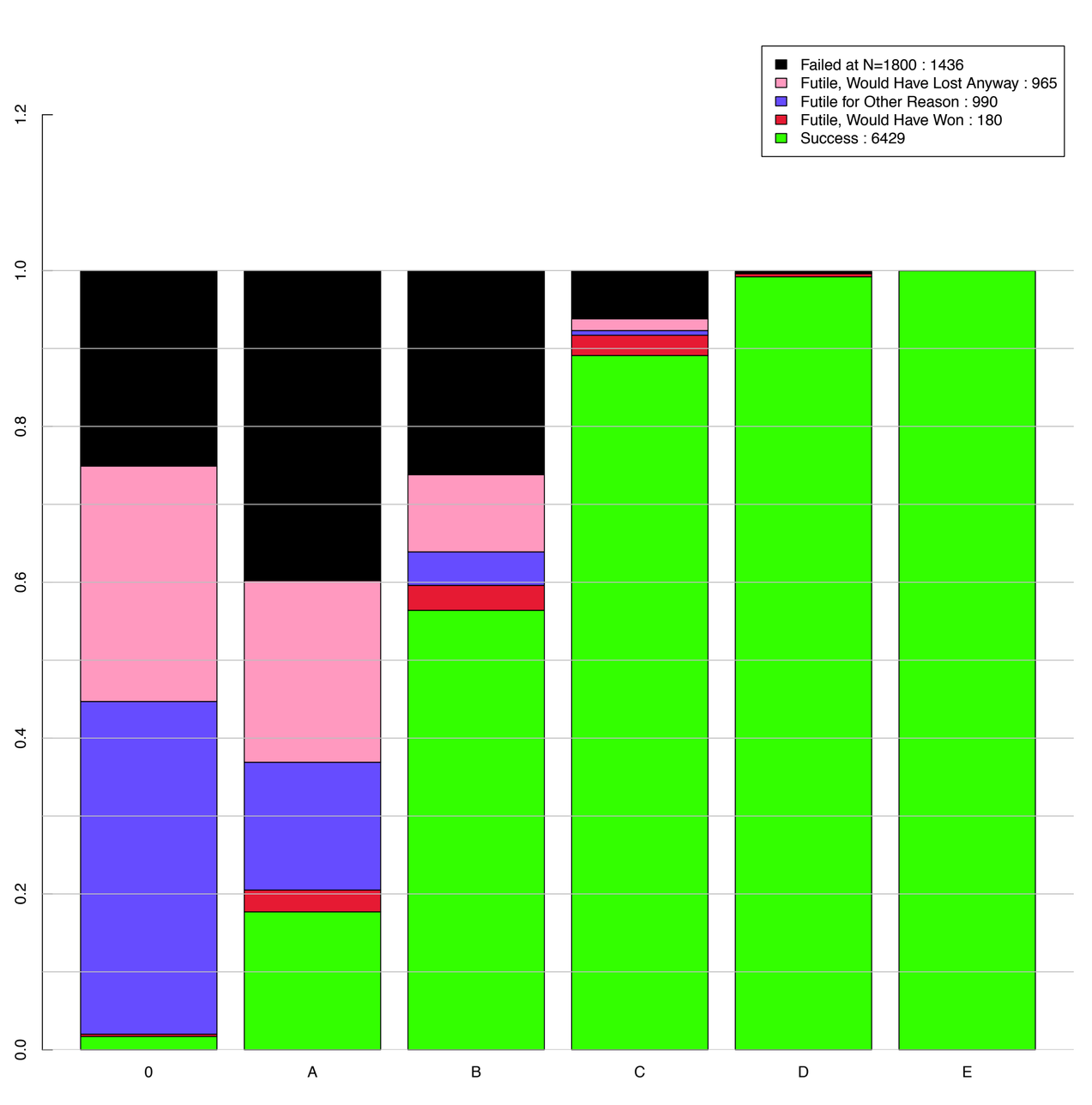
Success : 6429
Futile, Would Have Lost Anyway : 965
Futile, Would Have Won : 180
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 1436
Futile, Would Have Lost Anyway : 965
Futile for Other Reason : 990
Futile, Would Have Won : 180
Success : 6429
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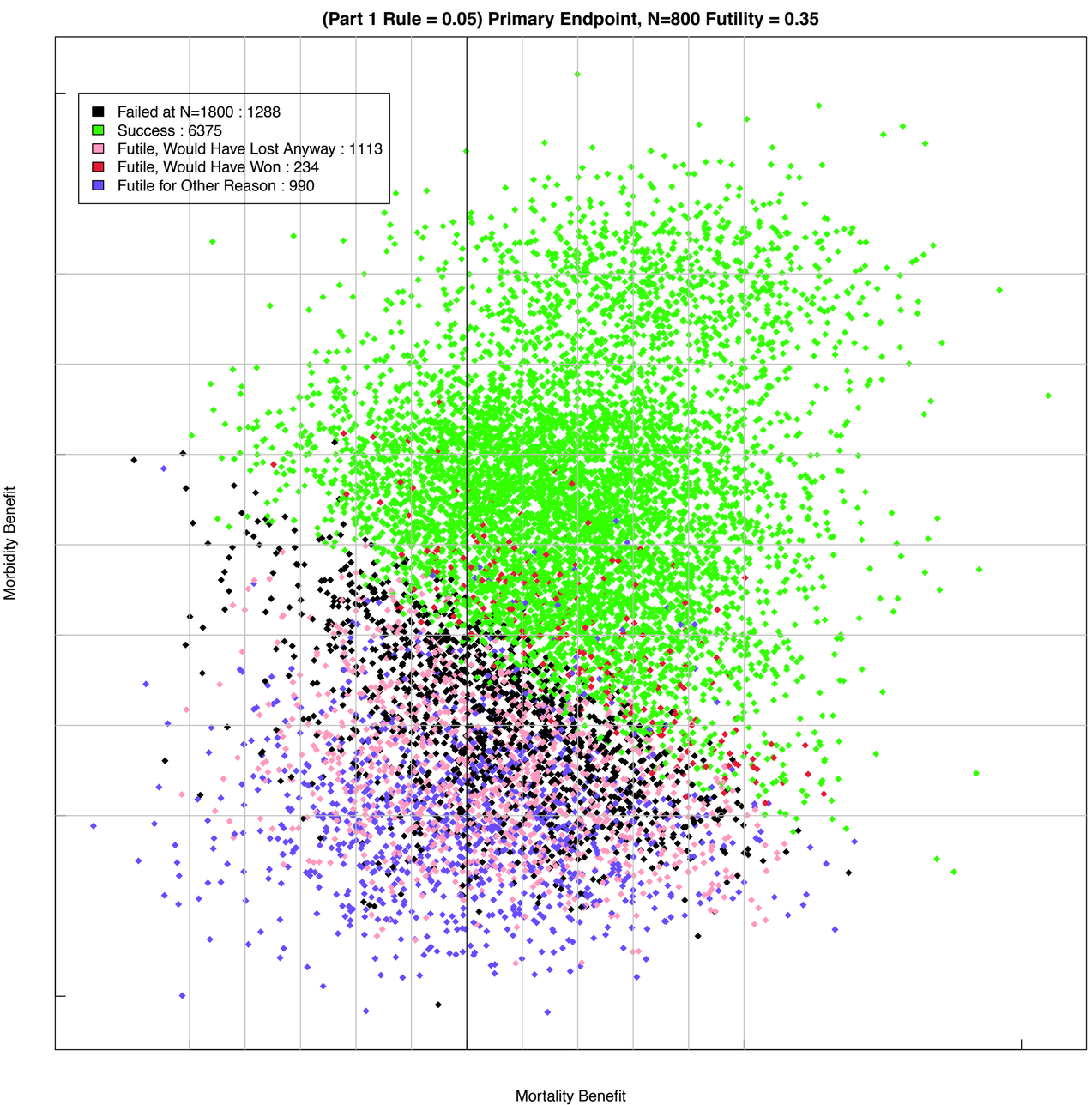
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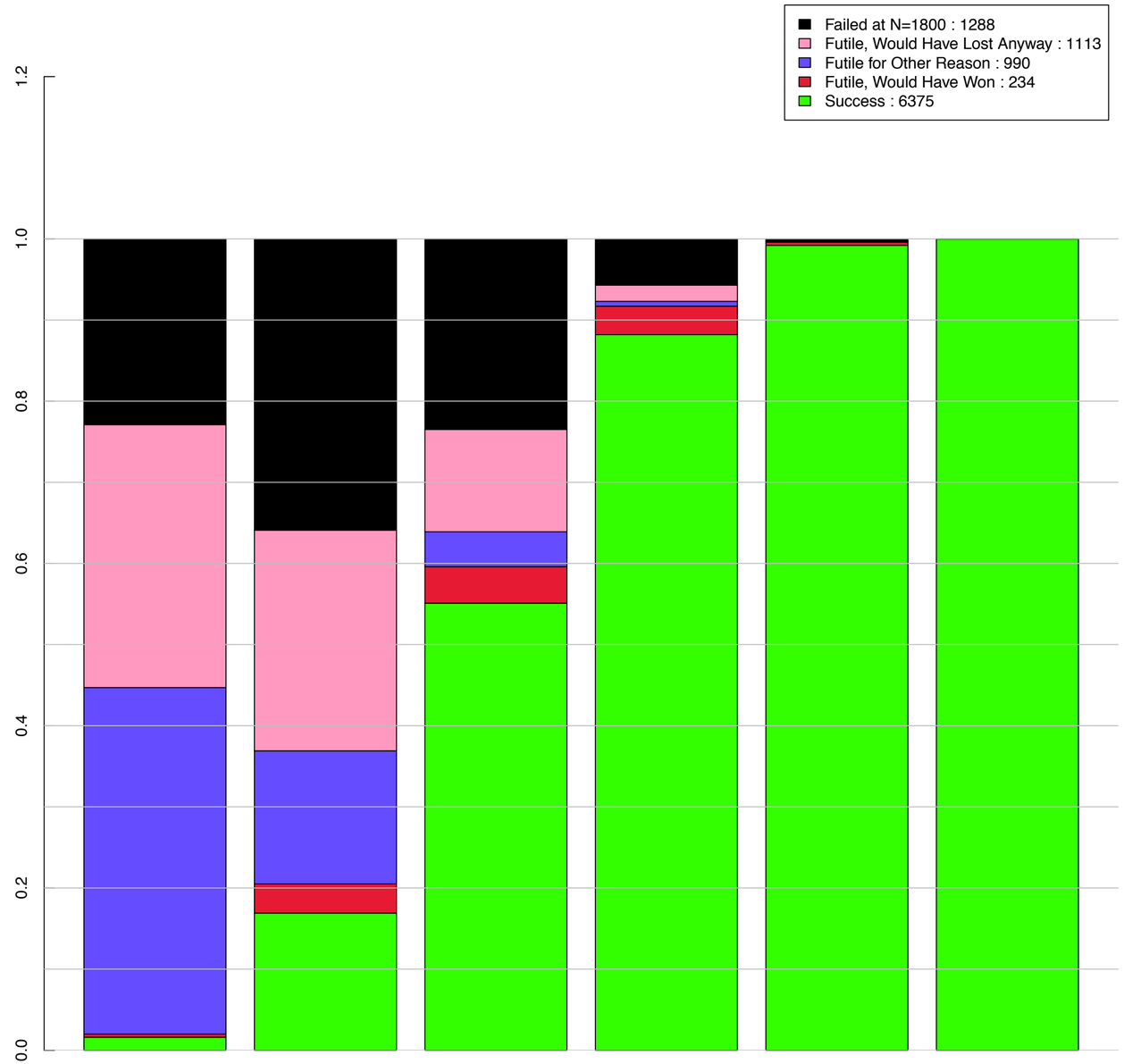
Failed at N=1800 : 1288
Success : 6375
Futile, Would Have Lost Anyway : 1113
Futile, Would Have Won : 234
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 1288
Futile, Would Have Lost Anyway : 1113
Futile for Other Reason : 990
Futile, Would Have Won : 234
Success : 6375
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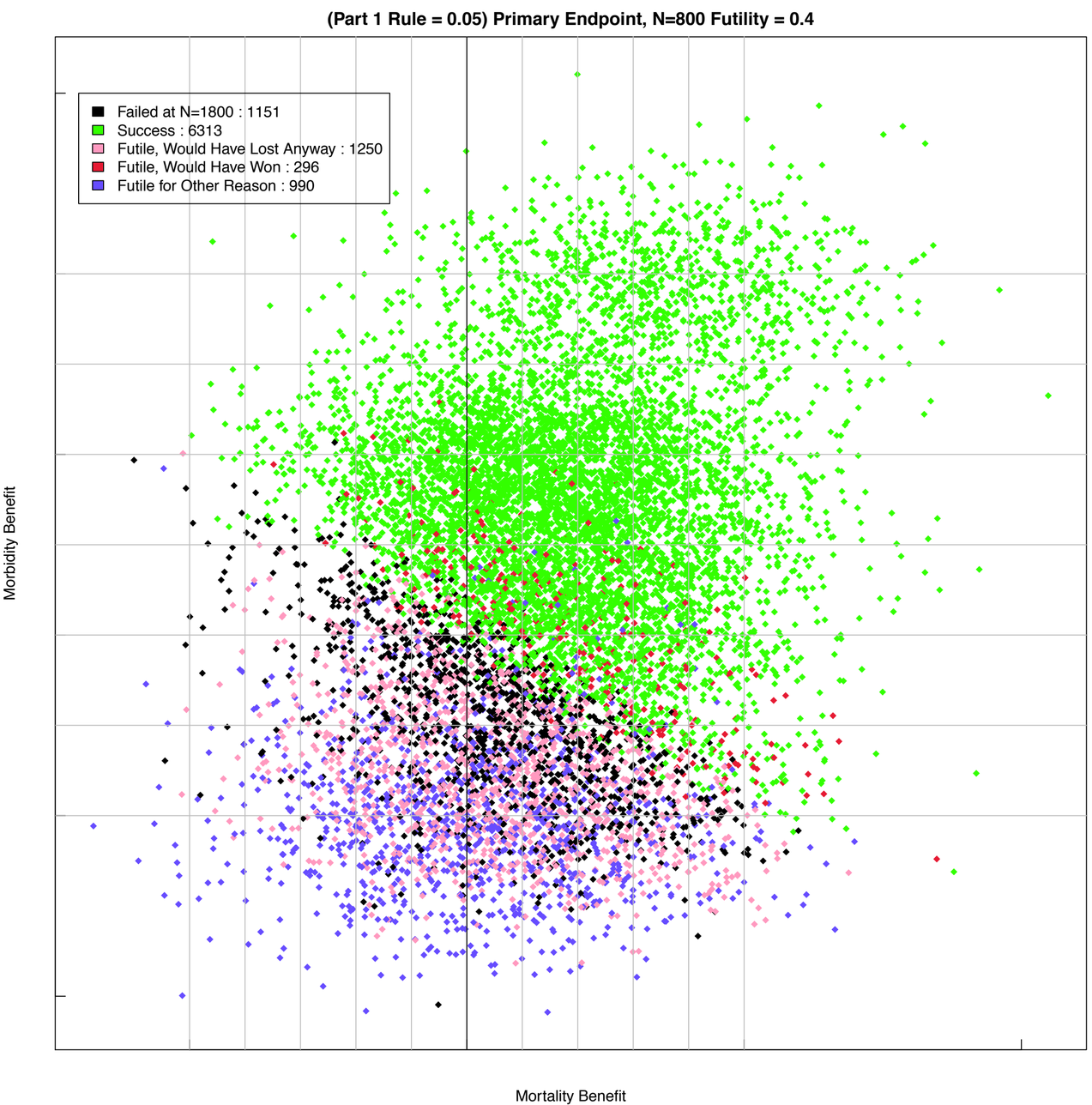
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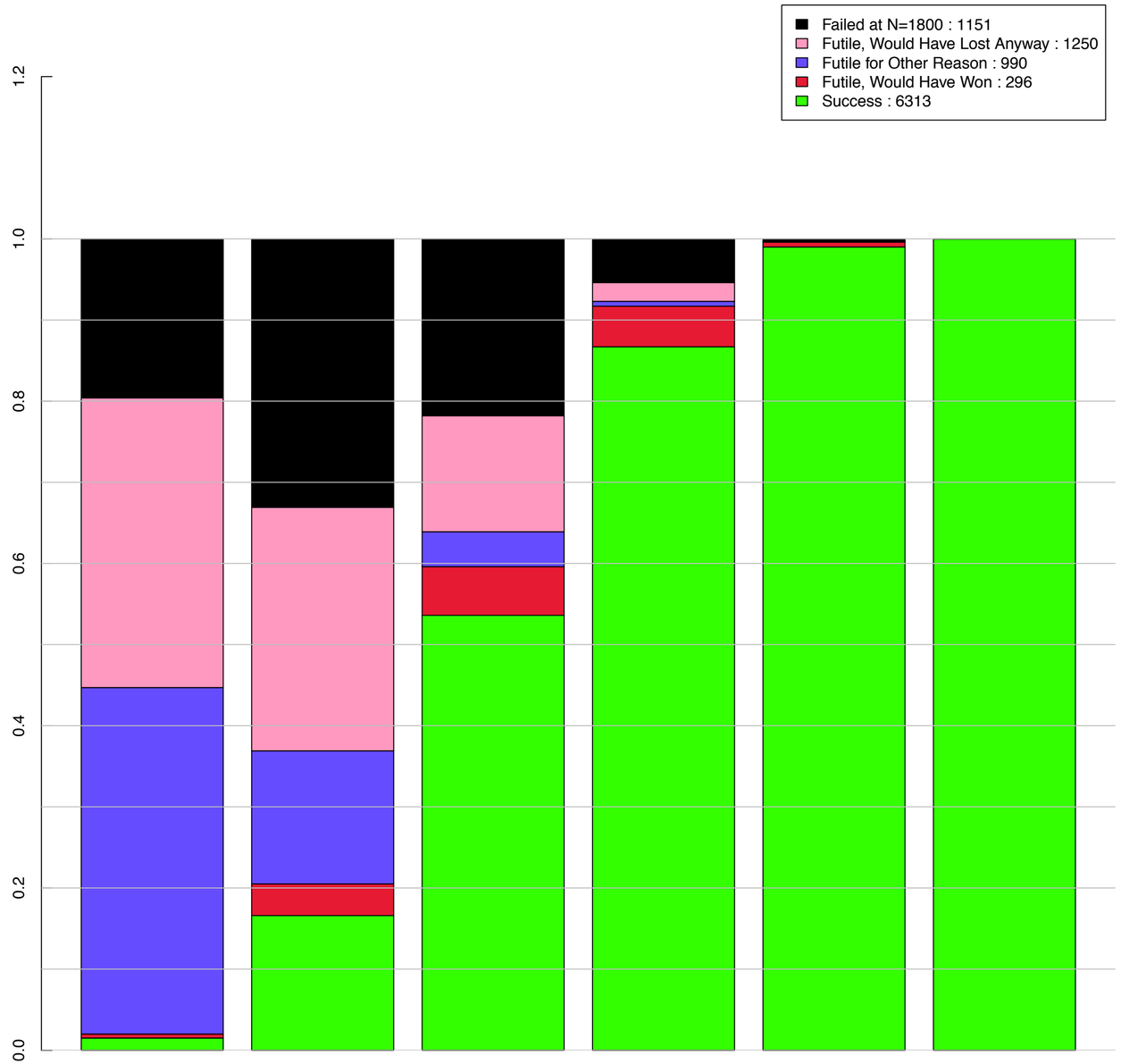
Futile, Would Have Lost Anyway : 1250
Futile, Would Have Won : 296
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 1151
Futile, Would Have Lost Anyway : 1250
Futile for Other Reason : 990
Futile, Would Have Won : 296
Success : 6313
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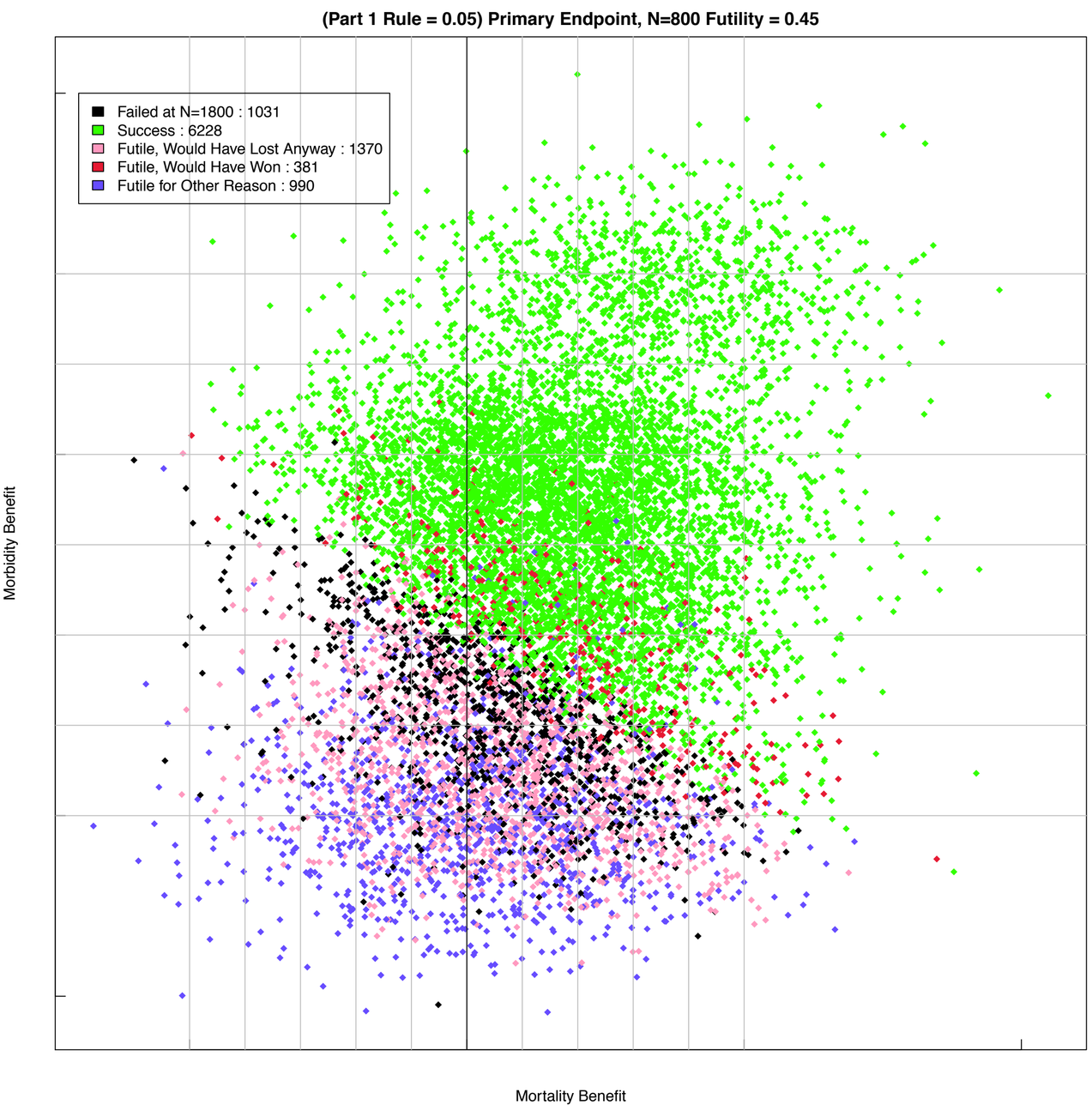
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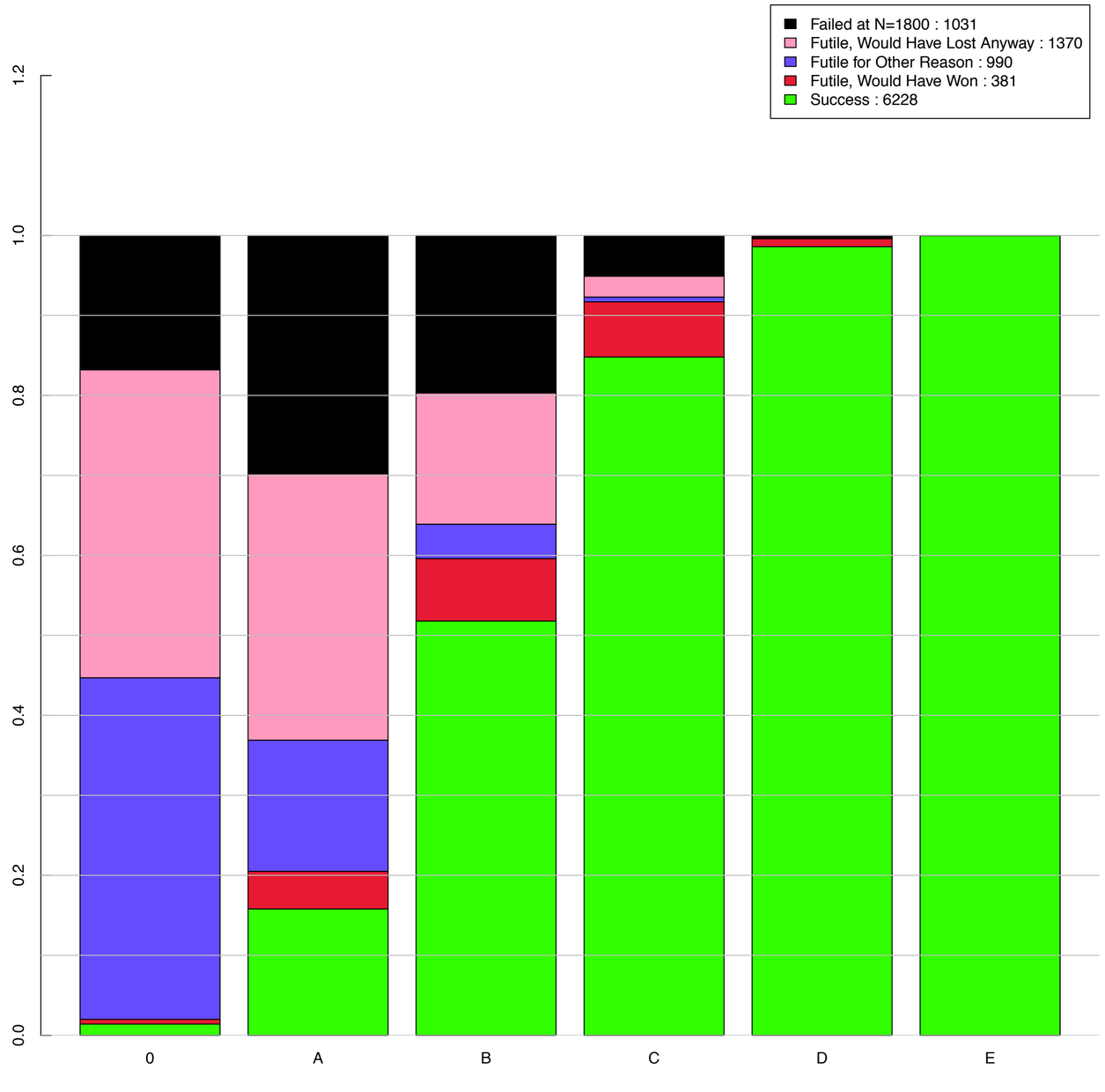
Futile, Would Have Lost Anyway : 1370
Futile, Would Have Won : 381
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 1031
Futile, Would Have Lost Anyway : 1370
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Futile, Would Have Won : 381
Success : 6228
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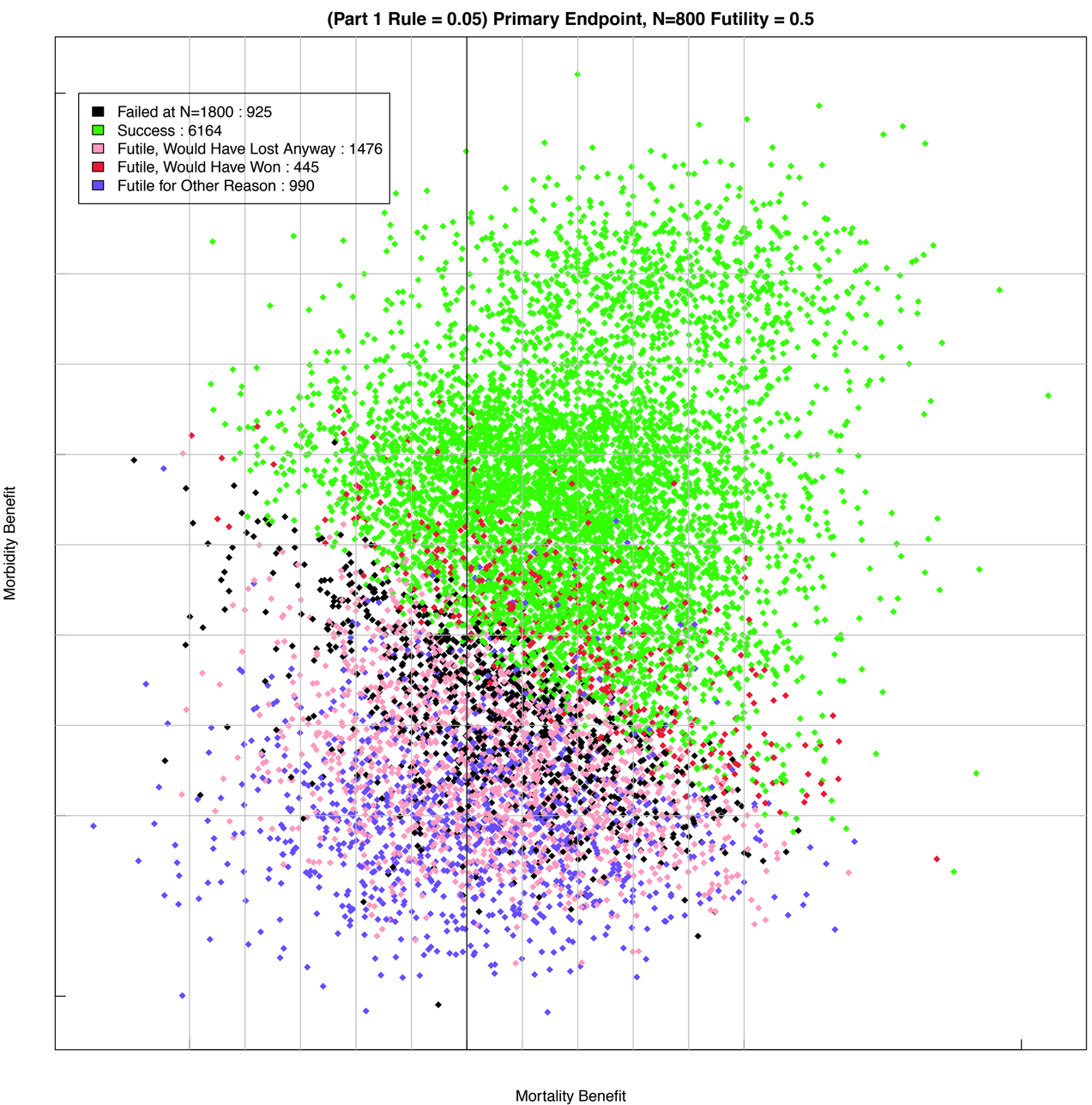
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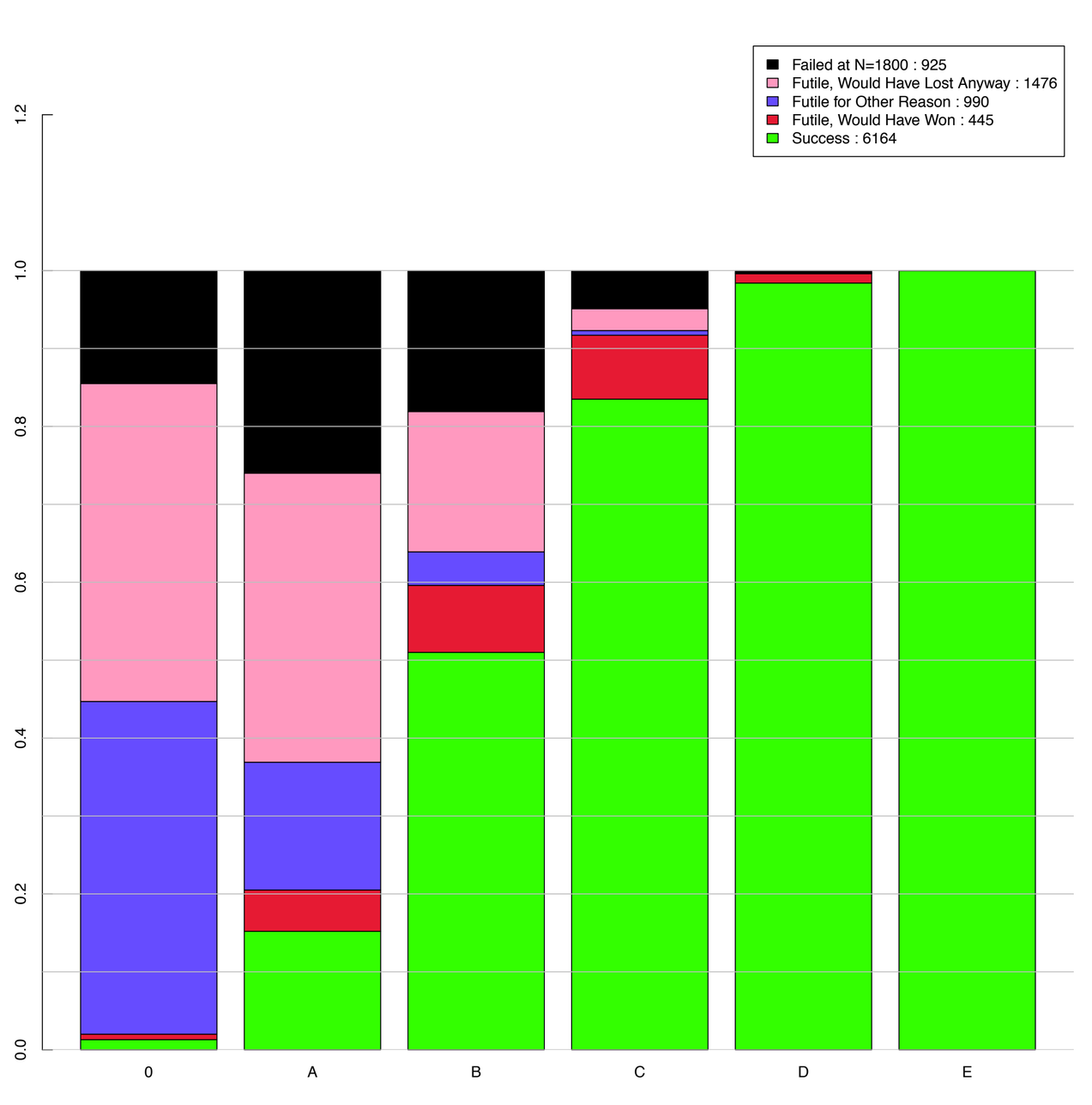
Futile, Would Have Won : 445
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 925
Futile, Would Have Lost Anyway : 1476
Futile for Other Reason : 990
Futile, Would Have Won : 445
Success : 6164
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A
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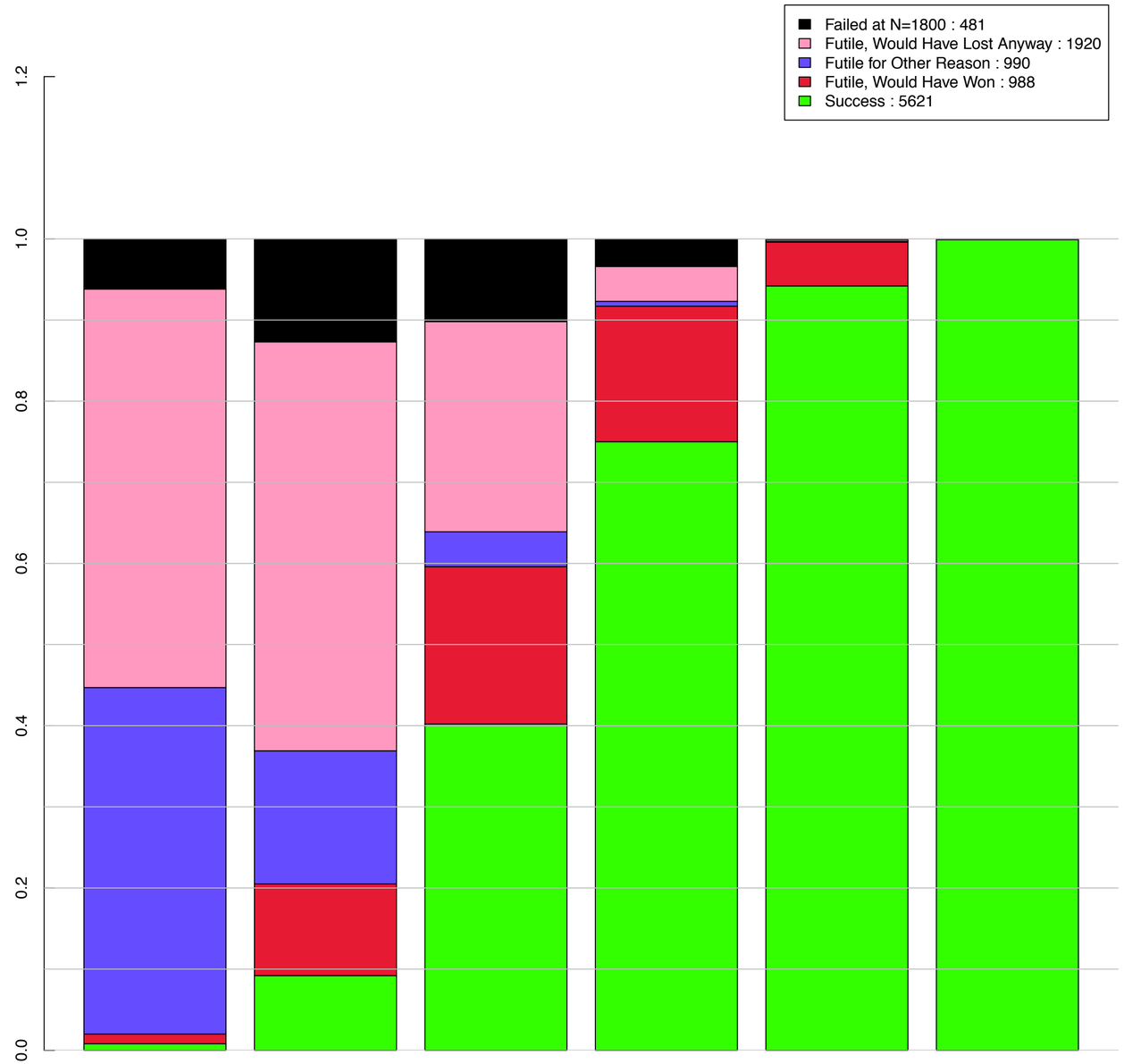
C
D
E


(Part 1 Rule = 0.05) Primary Endpoint, N=800 Futility = 0.75
Failed at N=1800 : 481
Success : 5621
Futile, Would Have Lost Anyway : 1920
Futile, Would Have Won : 988
Futile for Other Reason : 990
Morbidity Benefit
Mortality Benefit


Failed at N=1800 : 481
Futile, Would Have Lost Anyway : 1920
Futile for Other Reason : 990
Futile, Would Have Won : 988
Success : 5621
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0
A
B
C
D
E

Summary

- Adaptations allow more thorough exploration of dose range
  - RAR, Adaptive Decisions, Modeling
- Allow "dose-finding" to be larger if needed
- Able to use the subjects for dose-finding and confirmation
  - No need to take shot-in-the-dark for dose and go/no-go