Esmolol vs. Amiodarone for the treatment of refractory or recurrent out-of-hospital ventricular fibrillation

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Objectives

- Adults with OOHCA with VF/Pulseless VT refractory or recurrent following initial shock
- Compare Esmolol, Amiodarone and combination to control
- Primary Outcome: CPC 1,2 at 1-month
- Evaluator of CPC at 1-month blinded
- Clinically meaningful difference of improvement of 10%

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Design Details

- Fully factorial design
  - Control (neither)
  - Amiodarone only
  - Esmolol only
  - Combination

- All active arms compared to control

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Adaptations Considered

- Response adaptive randomization
- Early stopping for futility
- Early stopping for success

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Design characteristics

- Maximum sample size 1000
- Type I error threshold 0.025
- Reasonable power for 10% treatment difference

- Accrual rate 10 subjects per week
- No dropouts (for now)

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Trials Simulated

- Trial 1
  - Fixed trial (no adaptations)
- Trial 2
  - Response adaptive randomization
- Trial 3
  - Response adaptive randomization
  - Early stopping for futility
  - Early stopping for success

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Trial 1 – Fixed

- Randomization 1:1:1:1 (250 per arm)
- No early stopping
- Success if Pr(Best dose > control) > 0.99

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Trial 2 - RAR

- Burn-in 50 subjects per arm
- Response adaptive randomization begins at 200 subjects
  - Subjects allocated in proportion to probability that arm is the *best*

- Fixed allocation on control
- Allocation probabilities updated every 100 subjects
- Sample size always 1000
- Success if Pr(Best dose > control) > 0.99

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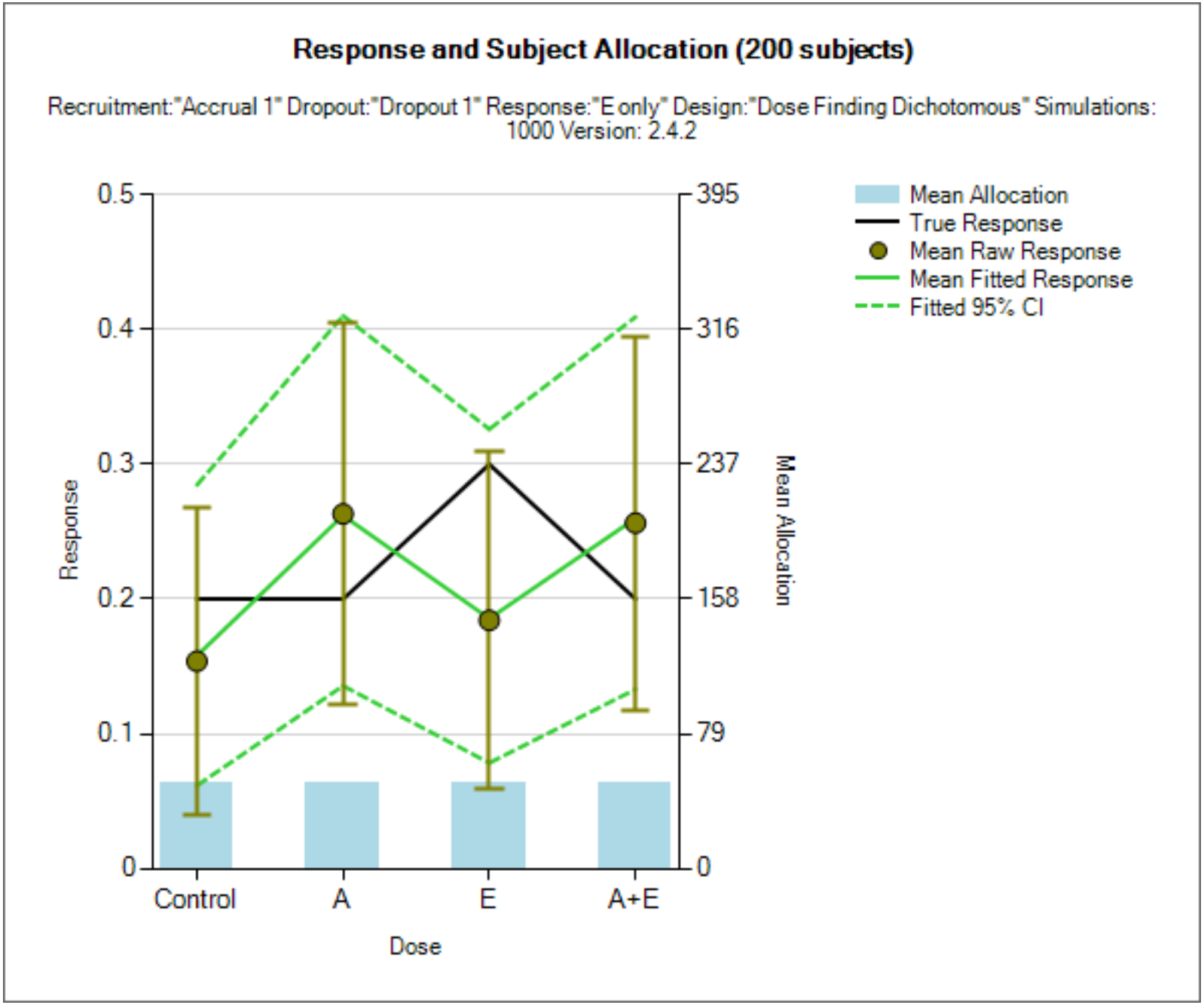
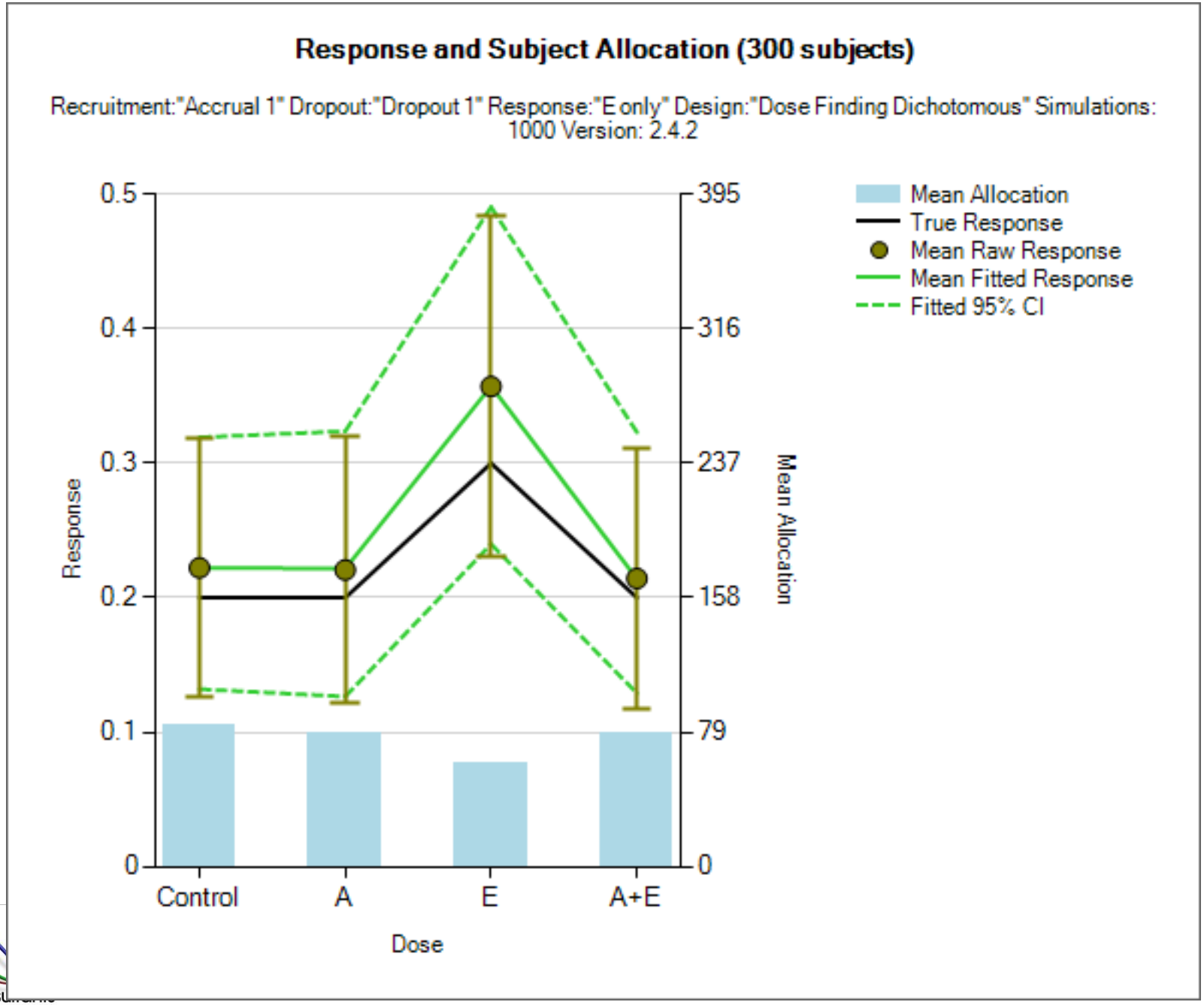
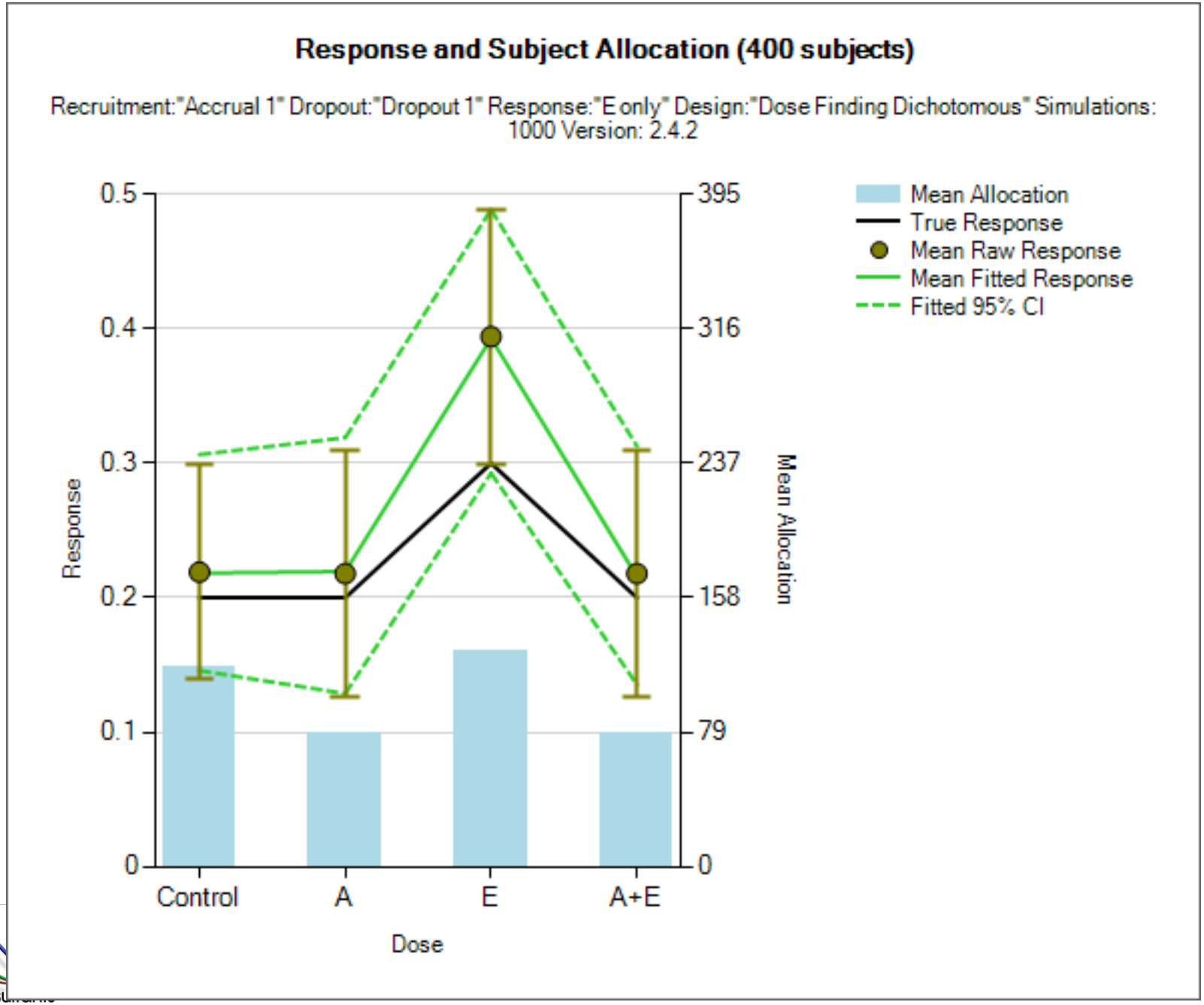
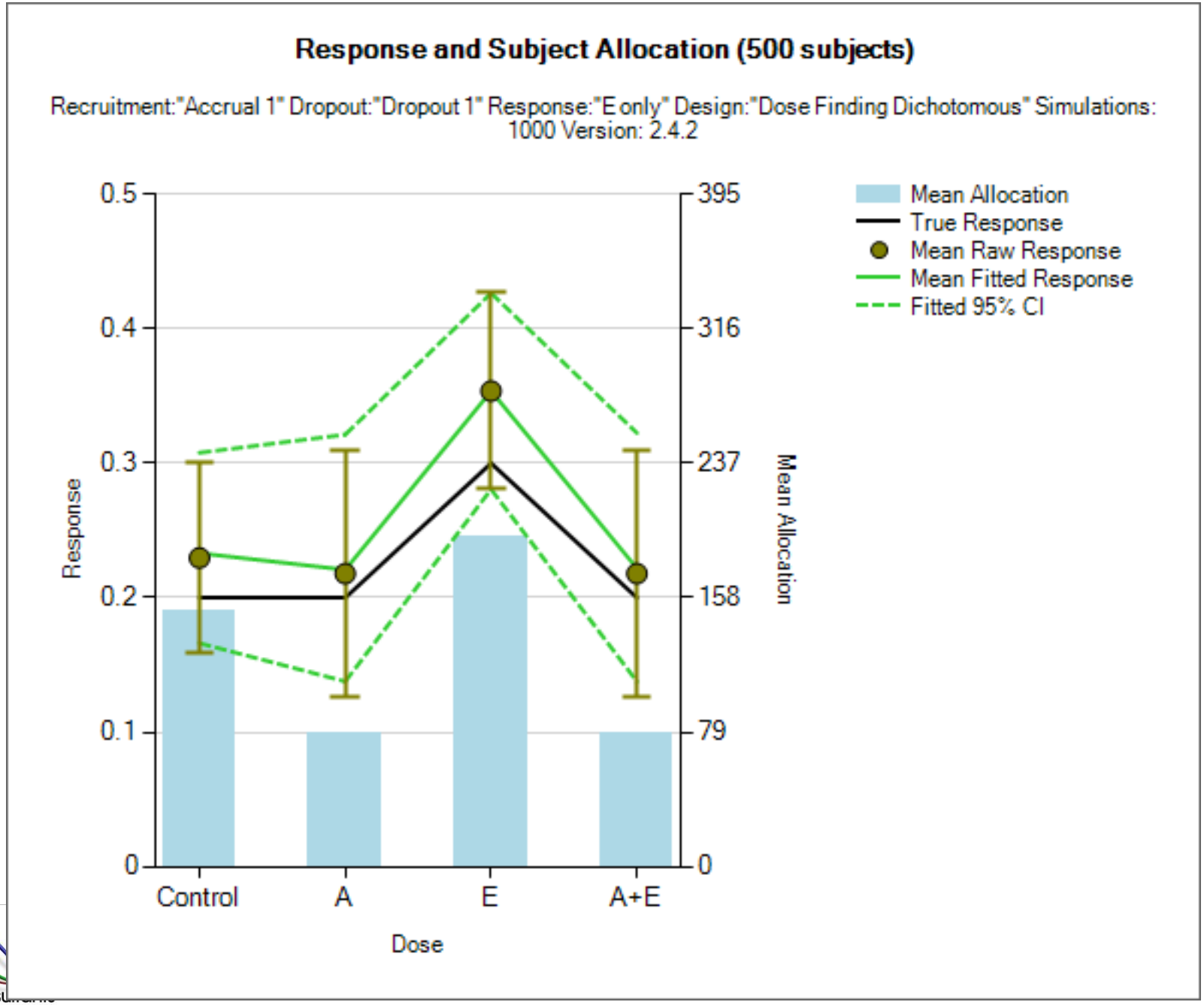
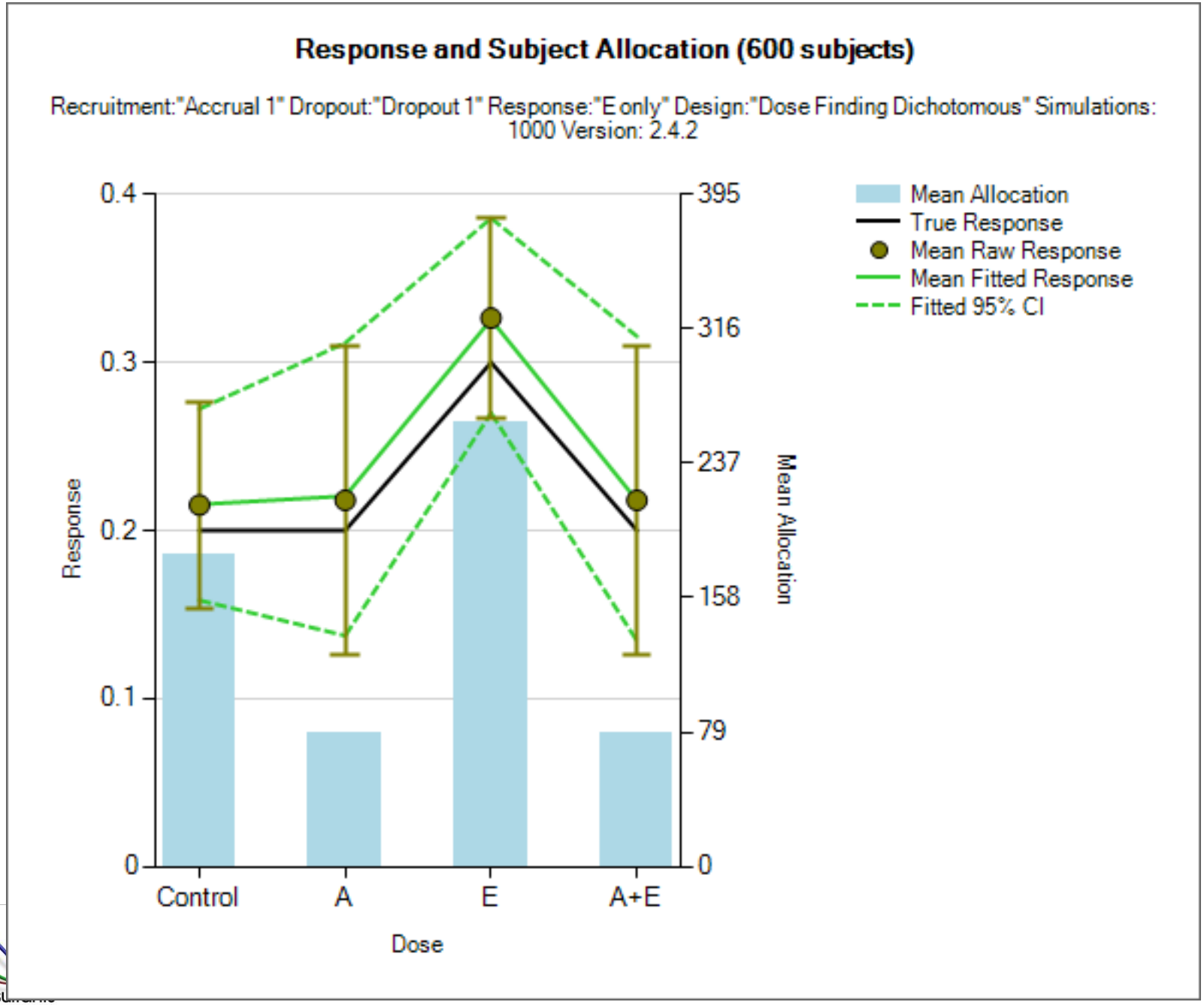
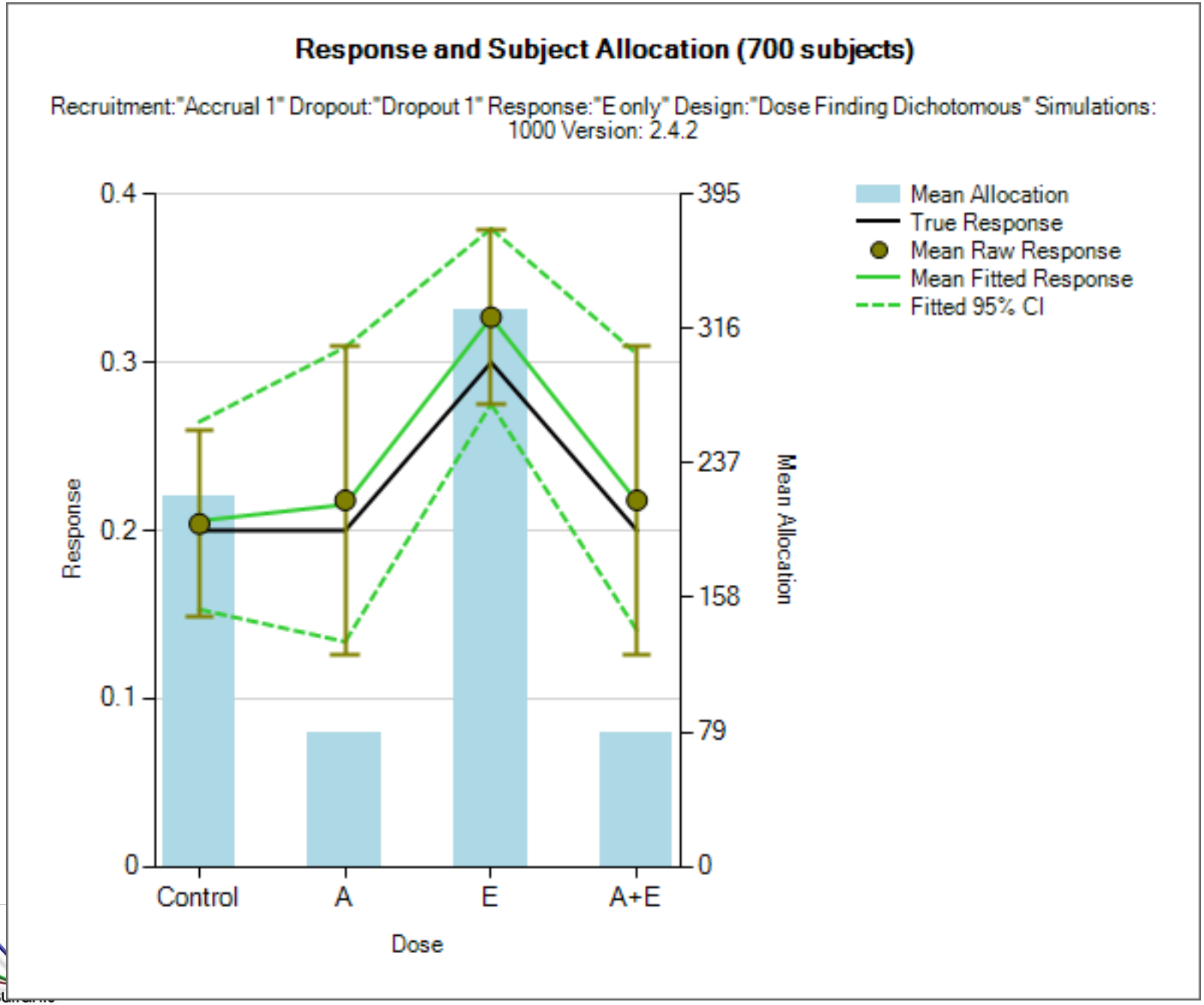

Response and Subject Allocation (200 subjects)
Recruitment:"Accrual 1" Dropout:"Dropout 1" Response:"E only" Design:"Dose Finding Dichotomous" Simulations: 1000 Version: 2.4.2
0.5
0.4
0.3
0.2
0.1
0
Response
395
316
237
158
79
0
Mean Allocation
Control
A
E
A+E
Dose
Mean Allocation
True Response
Mean Raw Response
Mean Fitted Response
Fitted 95% CI

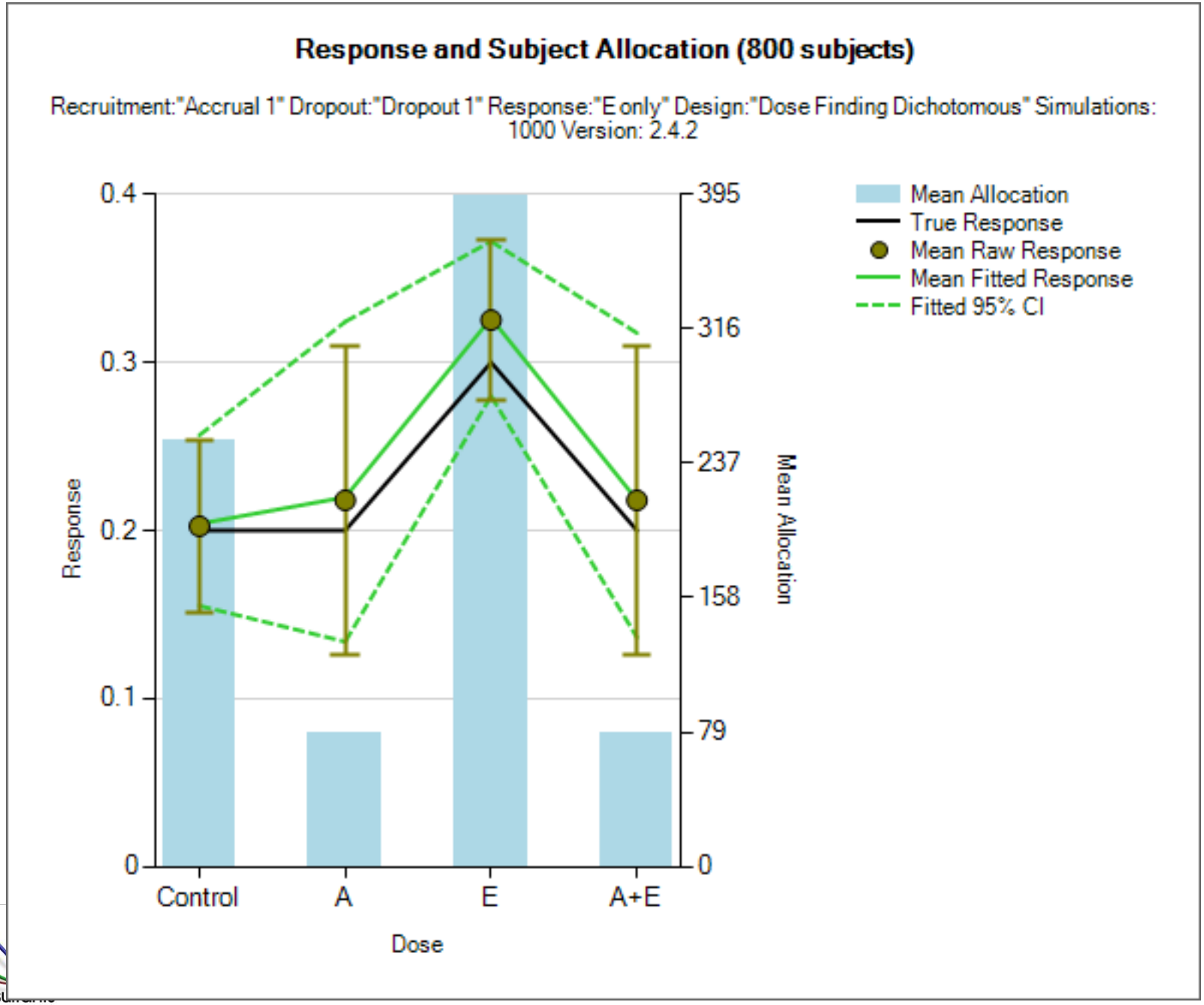











Response and Subject Allocation (800 subjects)
Recruitment:"Accrual 1" Dropout:"Dropout 1" Response:"E only" Design:"Dose Finding Dichotomous" Simulations: 1000 Version: 2.4.2
Mean Allocation
True Response
Mean Raw Response
Mean Fitted Response
Fitted 95% CI
Response
0.4
0.3
0.2
0.1
0
Mean Allocation
395
316
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Control
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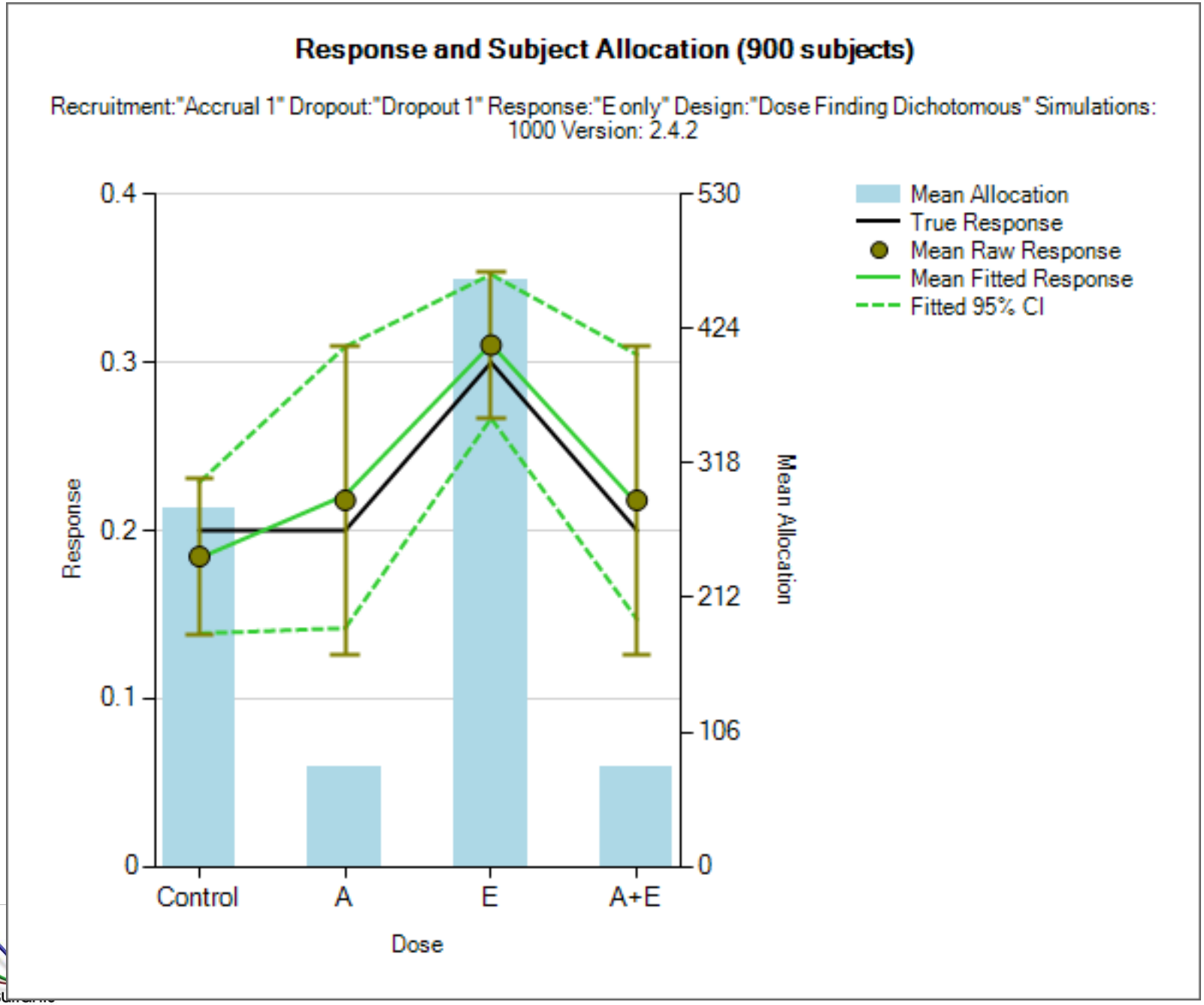
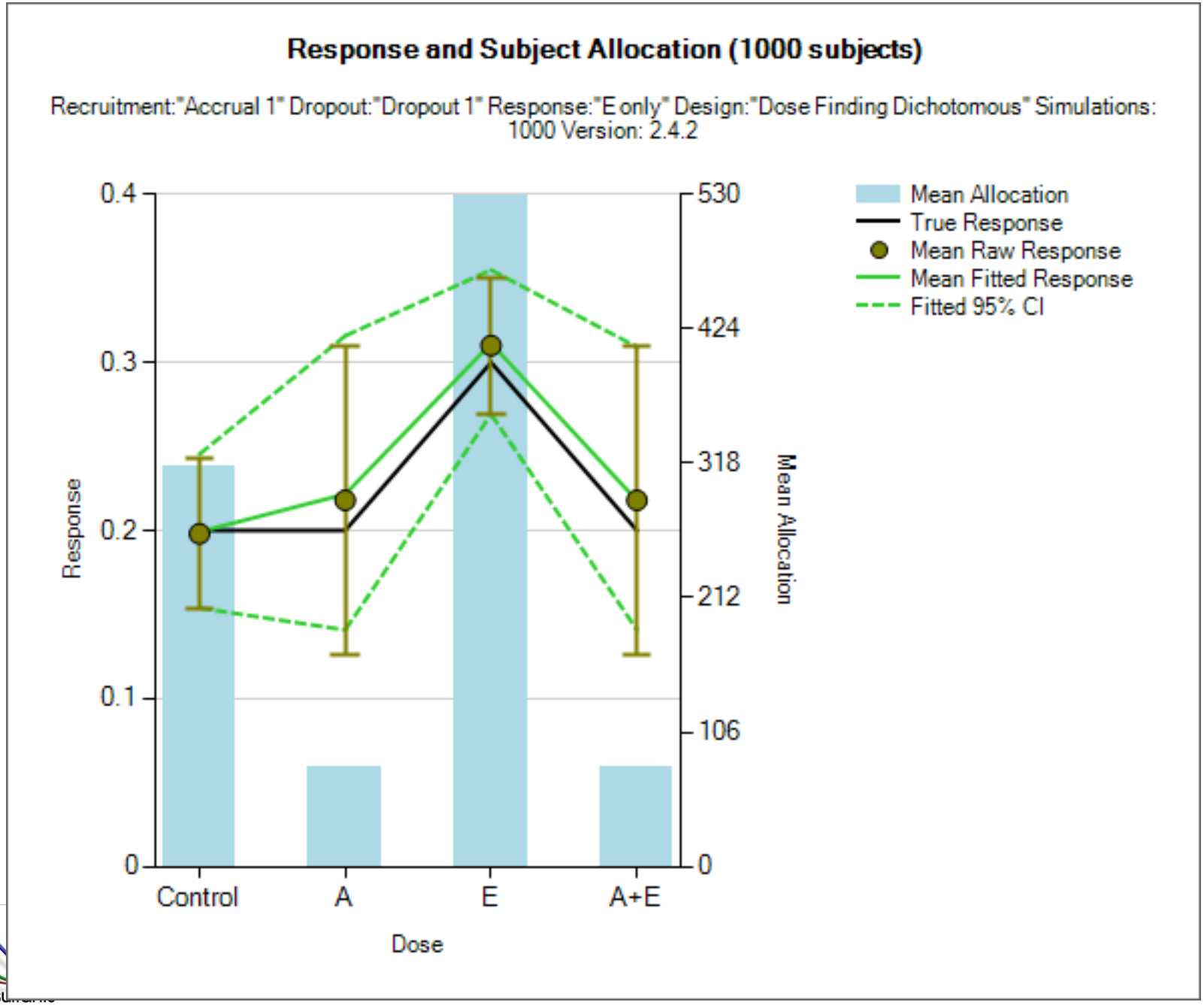
A+E
Dose





Trial 3 – RAR/Early Stopping

- Trial 2 plus early stopping
- Early stopping for futility
  - Pr(Best dose > control) < 0.20
- Early stopping for success
  - Pr(Best dose > control) > 0.999

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Simulation Scenarios

Scenario	Control	A only	E only	A+E combination
Null	0.20	0.20	0.20	0.20
E Worse	0.20	0.20	0.15	0.15
Only E	0.20	0.20	0.30	0.20
Combo only	0.20	0.20	0.20	0.30
E good	0.20	0.20	0.30	0.30

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Operating Characteristics

	Pr(Success)		
	Fixed	RAR	RAR/Stop
Null	0.033	0.025	0.025
E Harm	0.010	0.011	0.011
E only	0.619	0.803	0.775
Combo	0.620	0.802	0.785
E good	0.772	0.852	0.854

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Operating Characteristics (RAR/Early Stop)

	Pr(EarlySuccess)	Pr(LateSuccess)	Pr(EarlyFutility)	Pr(LateFutility)
Null	0.015	0.010	0.171	0.804
E Harm	0.008	0.003	0.413	0.576
E only	0.522	0.253	0.013	0.212
Combo	0.520	0.265	0.019	0.196
E good	0.627	0.227	0.002	0.144

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Operating Characteristics

		N			
	Total	Control	A Only	E Only	A+E combo
RAR					
Null	1000	317	231	227	226
E Harm	1000	317	395	145	143
E only	1000	317	97	491	95
Combo	1000	317	99	97	488
E good	1000	317	76	305	302
RAR/Stop					
Null	910	287	211	204	208
E Harm	779	243	299	117	119
E only	791	247	91	363	90
Combo	787	246	90	96	355
E good	746	232	71	220	223

Corners cut..need to be filled in

- Limited sleep
- More simulations (type I error control)
- Comparison to a group sequential design
- Dosing of Esmolol
- Can we drop the control arm?
- More scenarios, possibilities, etc.
- Enrichment (witnessed/not witnessed, etc.)