Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable1: Patient Sociodemographic Characteristics

	Overall	Guided Group	Usual Care Group
	N=1232 No. (%)	**N=614** No. (%)	**N=618** No. (%)
Employment status			
Employed	318 (25.8)	167 (27.2)	151 (24.4)
Unemployed	43 (3.5)	20 (3.3)	23 (3.7)
Disabled	99 (8.0)	45 (7.3)	54 (8.7)
Retired	660 (53.8)	327 (53.3)	333 (53.9)
Unknown/Not reported	112 (9.1)	55 (9.0)	57 (9.2)
Household median income			
Less than $50,000	709 (57.6)	355 (57.8)	354 (57.3)
$50,000 - $75,000	410 (33.3)	208 (33.9)	202 (32.7)
$75,000 or more	113 (9.2)	51 (8.3)	62 (10.0)
Health insurance			
Private	401 (32.6)	208 (33.9)	193 (31.2)
Public	831 (67.5)	406 (66.1)	425 (68.8)
Residency			
Missouri	661 (53.7)	332 (54.1)	329 (53.2)
Illinois	499 (40.5)	246 (40.0)	253 (40.9)
Other states	72 (5.8)	36 (5.9)	36 (5.8)
Living status			
Lives alone	289 (23.5)	136 (22.2)	153 (24.8)

eTable2: Pre-Operative Health Conditions: Comorbidities

	Overall	Guided Group	Usual Care Group
	N=1232 No. (%)	N=614 No. (%)	N=618 No. (%)
Charlson Comorbidity Index			
0-1	43 (3.5)	25 (4.1)	18 (2.9)
2-3	300 (24.4)	140 (22.8)	160 (25.9)
4-5	468 (38.0)	230 (37.5)	238 (38.5)
6+	421 (34.2)	219 (35.7)	202 (32.7)
Comorbidities			
Coronary artery disease	463 (37.6)	235 (38.3)	228 (36.9)
Congestive heart failure	251 (20.4)	139 (22.6)	112 (18.1)
Valvular heart disease	534 (43.3)	279 (54.4)	255 (41.3)
Atrial fibrillation	184 (14.9)	94 (15.3)	90 (14.6)
Cerebrovascular disease / Stroke / Transient ischemic attack	194 (15.8)	93 (15.2)	101 (16.3)
Peripheral artery disease	143 (11.6)	71 (11.6)	72 (11.7)
History of aortic aneurysm	100 (8.1)	52 (8.5)	48 (7.8)
History of deep venous thrombosis / Pulmonary embolism	115 (9.3)	61 (9.9)	54 (8.7)
Diabetes mellitus	367 (29.8)	189 (30.8)	178 (28.8)
Hypertension	913 (74.1)	462 (75.2)	451 (73.0)
Chronic kidney disease	283 (23.0)	144 (23.5)	139 (22.5)
Chronic obstructive pulmonary disease	252 (20.5)	130 (21.2)	122 (19.7)
Asthma	111 (9.0)	53 (8.6)	58 (9.4)
Cirrhosis	15 (1.2)	9 (1.5)	6 (1.0)
History or currently diagnosed with cancer	614 (49.8)	293 (47.7)	321 (51.9)
Gastroesophageal reflux disease	518 (42.0)	263 (42.8)	255 (41.3)
Anemia	355 (28.8)	186 (30.3)	169 (27.4)
Dementia / Cognitive impairment	5 (0.4)	3 (0.5)	2 (0.3)
History of delirium	157 (12.8)	78 (12.8)	79 (12.9)
History of post-operative delirium	115 (9.4)	56 (9.2)	59 (9.6)
Sensory impairment			
Hearing impairment	260 (21.1)	137 (22.3)	123 (19.9)
Hearing limits daily activities	158 (12.8)	79 (12.9)	79 (12.8)
Vision impairment	1127 (91.5)	557 (90.7)	570 (92.2)
Vision limits daily activities	145 (11.8)	72 (11.7)	73 (11.8)

eTable3: Patient Sociodemographic Characteristics and Pre-Operative Health Conditions by 30-day follow-up Response

	Overall N=1,209*	Respondents N=1036	Non-Respondents N=173
Age - median [IQR] years	69.3 [64.8 to 75.0]	69.3 [64.7 to 74.9]	69.2 [65.2 to 75.9]
Female sex – no. (%)	555 (45.9)	464 (44.8)	91 (52.6)
Body mass index – median [IQR] kg/m^2	29.0 [25.0 to 33.0]	28.0 [25.0 to 33.0]	29.0 [25.0 to 34.0]
Race[a] – no. (%)			
White	1090 (90.2)	948 (91.5)	142 (82.1)
African-American	107 (8.9)	79 (7.6)	28 (16.2)
Other	12 (1.0)	9 (1.0)	3 (1.7)
Education: attended college – no. (%)	399 (33.0)	356 (34.4)	43 (24.9)
Employed – no. (%)	317 (26.2)	276 (28.8)	41 (28.7)
Median-income less than $50,000 – no. (%)	695 (57.5)	577 (55.7)	118 68.2)
Public health insurance – no. (%)	814 (67.3)	693 (66.9)	121 (69.9)
Missouri resident – no. (%)	653 (54.0)	549 (53.0)	104 (60.1)
Lives alone – no. (%)	285 (23.6)	234 (22.6)	51 (29.5)
Lifetime tobacco use[b] – no. (%)	711 (58.8)	598 (57.7)	113 (65.3)
Current weekly alcohol use[c] – no. (%)	576 (47.6)	507 (48.9)	69 (39.9)
Current use of anticonvulsants – no. (%)	171 (14.1)	130 (12.5)	41 (23.7)
Regular use of opioids – no. (%)	298 (24.6)	238 (23.0)	60 (34.7)
Regular use of benzodiazepine – no. (%)	187 (15.5)	157 (15.2)	30 (17.3)
ASA physical classification[d] >3 – no. (%)	416 (34.4)	344 (33.2)	72 (41.6)
Marginal exercise tolerance (< 4 METs) – no. (%)	578 (47.8)	473 (47.5)	105 (65.2)
Pulmonary hypertension – no. (%)	187 (15.5)	161 (15.5)	26 (15.0)
Aortic stenosis – no. (%)	194 (16.0)	168 (16.2)	26 (15.0)

eTable3: Patient Sociodemographic Characteristics and Pre-Operative Health Conditions by 30-day follow-up Response (cont.)

	Overall N=1,209	Respondents N=1036	Non-Respondents N=173
History of delirium – no. (%)	151 (12.5)	128 (12.4)	23 (13.3)
Number of co-morbidities - median [IQR]	5.0 [3.0 to 6.0]	4.0 [3.0 to 6.0]	5.0 [3.0 to 7.0]
History of depression – no. (%)	163 (13.5)	125 (12.1)	38 (22.0)
PHQ8[e] – median [IQR]	3.0 [0.0 to 6.0]	3.0 [0.0 to 6.0]	4.0 [1.0 to 8.0]
Short Blessed Test for Cognition[f] – median [IQR]	2.0 [0.0 to 4.0]	2.0 [0.0 to 4.0]	2.0 [0.0 to 6.0]
8-item Interview to Differentiate Aging and Dementia[g] – median [IQR]	0.0 [0.0 to 1.0]	0.0 [0.0 to 1.0]	0.0 [0.0 to 1.0]
Barthel Activities of Daily Living Index[h] – median [IQR]	15.0 [15.0 to 15.0]	15.0 [15.0 to 15.0]	15.0 [14.0 to 15.0]
Grip strength in kg – mean (SD)	26.1 (10.9)	26.4 (10.7)	24.0 (11.7)
Timed Up and Go test – median [IQR] seconds	10.8 [9.3 to 13.2]	10.7 [9.2 to 13.0]	11.4 [10.0 to 14.9]
Lawton Instrumental Activities of Daily Living[i] – median [IQR]	8.0 [7.0 to 8.0]	8.0 [8.0 to 8.0]	8.0 [7.0 to 8.0]
VR-12 Physical Component Score[j] – mean (SD)	38.2 (11.8)	38.6 (11.8)	35.6 (11.6)
VR-12 Mental Component Score[j] – mean (SD)	53.6 (10.8)	54.1 (10.5)	50.1 (12.1)

IQR, interquartile range**.**

[a]Patient self reported.

[b]Lifetime tobacco use, which includes current use, was obtained from patients' electronic medical record. During their assessment prior to surgery, patients are asked whether they have ever smoked tobacco.

[c]Alcohol consumption was obtained from patients' electronic medical record. All surgical patients are asked about their average number of drinks per week if they respond that they consume alcoholic drinks.

[d]ASA: American Society of Anesthesiologists physical status classification system, (1 to 6), 1. Healthy patient, 2. Mild systemic disease, 3. Severe systemic disease, 4. Severe systemic disease that is a constant threat to life, 5. Not expected to survive without procedure, 6. Neurologically deceased organ donor. In this study, ASA was dichotomized with a threshold set at 3 or higher

[e]PHQ8: eight-item Personal Health Questionnaire Depression Scale (0 to 24): 10 or more indicates major depression, 20 or more indicates severe major depression

[f]Short Blessed Test for Cognition (0 to 28): 0-4 normal cognition, 5-9 questionable impairment, 10 or more impairment consistent with dementia.

[g]8-item Interview to Differentiate Aging and Dementia (0 to 8): 0-1 Normal cognition, 2 or greater cognitive impairment is likely to be present.

[h]Barthel Activities of Daily Living Index (0 to 100): <20 totally dependent, 20-39 very dependent, 40-59 partially dependent, 60-79 minimally dependent, 80-100 independent

[i]Lawton Instrumental Activities of Daily Living: scale ranges from 0 (low function, dependent) to 8 (high function, independent)

[j]VR-12, Veterans' Rand 12-item Health Survey: standardized 0-100 scale, where 50 represents population average

*Note: There were 23 patients who died within 30-days post-discharge, 1,232 – 23 = 1,209. The 30 day follow up response rate was 1036/1209 (85.7%)

Statistical differences were found in the following variables:

Sociodemographic: Race (minority) self-reported by patient, Education (did not attend college), and patients with an average median-income less than $50,000

Health related conditions: Current antoconvulsants & opioid use, ASA status, Marginal exercise tolerance (<4 METS), PHQ8 (depression screen) score, and VR-12 physical component score

eTable4: Laboratory Values

	Preoperative Laboratory Values[a]			Postoperative Laboratory Values[b]			
	Overall	**Guided Group**	**Usual Care Group**	**Overall**	**Guided Group**	**Usual Care Group**	
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	
Sodium	140.0 [138.0 to 142.0]	140 [138.0 to 142.0]	140 [138.0 to 142.0]	140.0 [138.0 to 142.0]	140 [138.0 to 142.0]	140 [138.0 to 142.0]	
Potassium	4.2 [3.9-4.5]	4.2 [3.9 to 4.9]	4.4 [4.0 to 4.5]	4.3 [4.0 to 4.7]	4.3 [4.0 to 4.7]	4.3 [4.0 to 4.7]	
BUN	18.0 [14.0 to 23.0]	18.0 [14.0 to 23.0]	18.0 [14.0 to 22.0]	16.0 [12.0 to 21.0]	16.0 [12.0 to 20.0]	16.0 [12.0 to 21.0]	
Creatinine	1.0 [0.8 to 1.2]	0.99 [0.79 to 1.21	0.97 [0.80 to 1.18]	0.9 [0.8 to 1.2]	0.94 [0.76 to 1.17]	0.94 [0.76 to 1.20]	
Glucose	102.0 [91.0 to 125.0]	102.0 [91.0 to 125.0]	102.0 [90.0 to 126.0]	156.0 [132.0 to 185.0]	155.0 [133.0 to 182.0]	156.0 [131.0 to 188.0]	
Albumin	4.2 [3.9 to 4.4]	4.2 [3.9 to 4.4]	4.1 [3.9 to 4.4]	3.5 [3.2 to 3.8]	3.5 [3.2 to 3.8]	3.5 [3.2 to 3.8]	
Hematocrit	38.7 [34.6 to 42.0]	38.5 [34.3 to 41.9]	38.8 [35.1 to 42.3]	32.7[29.2 to 36.1]	32.9 [29.2 to 36.2]	32.4 [29.4 to 35.9]	
Hemoglobin	12.7 [11.2 to 13.9]	12.6 [11.1 to 13.8]	12.7 [11.4 to 13.9]	10.7[9.6 to 12.7]	10.8 [9.6 to 11.6]	10.7 [9.6 to 11.9]	

IQR, interquartile range. BUN, blood urea nitrogen.

[a]Preoperative laboratory values were those documented closest prior to surgery but no more than 30 days prior.

[b]Postoperative lab values were the first values documented following the procedure.

The units for sodium and potassium are mmol/L. BUN, creatinine, glucose and albumin are reported as mg/dL. Hematocrit is a percent, and hemoglobin and albumin are in g/dL.

eTable5: Surgery Information

	Overall	Guided Group	Usual Care Group
	N=1232 No. (%)	**N=614** No. (%)	**N=618** No. (%)
Preoperative admission status			
Inpatient	318 (25.8)	156 (25.4)	162 (26.2)
Outpatient	912 (74.0)	457 (74.4)	455 (73.6)
Type of anaesthesia			
General without regional	1189 (96.5)	594 (96.7)	595 (96.3)
General plus regional	43 (3.5)	20 (3.3)	23 (3.7)
Surgery type[a]			
Cardiac	475 (38.6)	237 (38.6)	238 (38.5)
Gastrointestinal	148 (12.0)	74 (12.1)	74 (12.0)
Gynecologic	94 (7.6)	37 (6.0)	57 (9.2)
Hepatobiliary-pancreatic	165 (13.4)	87 (14.2)	78 (12.6)
Thoracic	97 (7.9)	51 (8.3)	46 (7.4)
Urologic	120 (9.7)	55 (9.0)	65 (10.5)
Vascular	123 (10.0)	61 (9.9)	62 (10.0)
Other	292 (23.7)	89 (14.5)	92 (14.9)

[a]Patients who underwent combined procedures are reported under multiple surgery types.

eTable6: Intraoperative Drug Administration

	Guided Group	Usual Care Group
	N=614 No. (%)	**N=618** No. (%)
Hypnotic agents		
Ketamine	33 (5.4)	19 (3.1)
Dexmedetomidine	40 (6.5)	41 (6.6)
Opioids		
Morphine	5 (<1.0)	4 (<1.0)
Hydromorphone	310 (50.5)	315 (51.0)
Methadone	31 (5.0)	31 (5.0)
Fentanyl	608 (99.0)	615 (99.5)
Sufentanil	1 (<1.0)	1 (<1.0)
Remifentanil	1 (<1.0)	1 (<1.0)
Neuromuscular blockade		
Atracurium	12 (2.0)	16 (2.6)
Cisatracurium	58 (9.4)	67 (10.8)
Rocuronium	415 (67.6)	398 (64.4)
Vecuronium	100 (16.3)	93 (15.0)
Vasopressors and inotropes		
Phenylephrine	501 (81.6)	513 (83.0)
Ephedrine	180 (29.3)	199 (32.2)
Epinephrine	68 (11.1)	102 (16.5)
Norepinephrine	252 (41.0)	254 (41.1)
Dobutamine	102 (16.6)	98 (15.9)
Milrinone	22 (3.6)	25 (4.0)

eTable7: Intraoperative Cumulative Durations of Low/High Mean Arterial Pressure and Heart Rate

	Guided Group N=613	Usual Care Group N=617	*P*-Value	Difference In Medians	95% CI
	Median minutes [IQR]	Median minutes [IQR]			
MAP threshold					
BP <55	3.0 [0.0 to 9.0]	2.0 [0.0 to 8.0]	0.36	1.0	-0.1 to 1.9
BP <60	7.0 [2.0 to 19.0]	7.0 [1.0 to 19.0]	0.62	0.0	-1.7 to 1.7
BP <65	20.0 [6.0 to 45.0]	20.0 [6.0 to 46.0]	0.77	0.0	-4.9 to 4.9
BP <70	42.0 [15.0 to 89.0]	43.0 [17.0 to 93.0]	0.17	-1.0	-9.8 to 7.8
BP <75	76.0 [31.0 to 142.0]	81.0 [41.0 to 145.0]	0.09	-5.0	-17.2 to 7.2
BP >110	8.0 [2.0 to 17.0]	6.0 [2.0 to 15.0]	0.004	2.0	-0.6 to 3.4
BP >115	5.0 [1.0 to 12.0]	4.0 [0.0 to 10.0]	0.007	1.0	-0.1 to 2.1
BP >120	3.0 [0.0 to 8.0]	3.0 [0.0 to 7.0]	0.002	0.0	-0.9 to 0.9
HR threshold					
HR <40	0.0 [0.0 to 0.0]	0.0 [0.0 to 0.0]	0.73	0.0	–
HR <50	0.0 [0.0 to 11.0]	0.0 [0.0 to 10.0]	0.93	0.0	-0.6 to 0.6
HR >100	1.0 [0.0 to 11.0]	1.0 [0.0 to 9.0]	0.97	0.0	-0.9 to 0.9

IQR, interquartile range; BP, blood pressure; HR, heart rate; MAP, mean arterial pressure.

eTable8: Number of Delirium Assessments Completed		
	CAM/CAM-ICU Completed	**Chart Review Completed**
	No./total no. (%)[a]	**No./total No. (%)[a]**
Postoperative day 1	1057/1194 (88.5)	1194/1194 (100.0)
Postoperative day 2	1013/1157 (87.6)	1157/1157 (100.0)
Postoperative day 3	861/1061 (81.1)	1061/1061 (100.0)
Postoperative day 4	717/895 (80.1)	895/895 (100.0)
Postoperative day 5	580/756 (76.7)	756/756 (100.0)

CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the intensive care unit.
[a]Denominators are the number of patients eligible for an assessment on each postoperative day. Patients were eligible if they were alive, in the hospital and had RASS score >-4.
At least one CAM or CAM-ICU assessment was performed in 1188 patients while chart review was completed on all eligible patients. A total of 1213 of the 1232 randomized patients had the delirium outcome assessed during postoperative days 1-5 using one of these modalities. Of the 19 remaining patients, one patient died during surgery, 3 patients withdrew from the study the day of surgery, 11 patients were heavily sedated over the entire assessment period, and 4 patients were discharged prior to the afternoon of postoperative day 1.

eTable9: Reasons CAM or CAM-ICU Assessments Were Not Conducted

Reasons for Ineligibility	Postoperative Day 1	Postoperative Day 2	Postoperative Day 3	Postoperative Day 4	Postoperative Day 5
Discharged[a]	13	73	211	363	521
Died[a]	1	2	3	4	6
Reasons not assessed					
Refused	81	72	83	83	70
Undergoing medical procedure	11	7	12	6	7
Sedation or coma (RASS < -3)	43	33	30	24	23
Other[b]	26	32	32	35	25
Total not completed – no./total no. (%)[c]	161/1194 (13.5)	144/1157 (12.4)	157/1061 (14.8)	148/895 (16.5)	125/756 (16.5)

CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the intensive care unit; RASS, Richmond Agitation and Sedation Scale.
[a]Cumulative values.
[b]Other may include family or nursing request, or patient withdrew.
[c]Denominators are the number of patients eligible for an assessment on each postoperative day. Patients were eligible if they were alive, in the hospital and had RASS score >-4.

eTable10: Logistic Regression and Covariate Adjustment for Delirium

The purpose of the logistic regression and adjustment for prognostic covariates was to improve the power of the trial to detect a beneficial effect attributable to the intervention (minimization of electroencephalographic suppression) or to usual anesthesia care on the outcome of interest, postoperative delirium. The covariates included were pre-selected and considered likely to be associated with postoperative delirium.

Logistic Regression

	Coefficient	*P-V*alue	Odds Ratio	95% CI
Guided group	0.192	0.21	1.21	0.90 to 1.64
Age	0.039	<0.001	1.04	1.02 to 1.06
Male	-0.012	0.94	0.99	0.71 to 1.38
White	-0.784	<0.001	0.46	0.28 to 0.74
Living alone	-0.091	0.62	0.91	0.63 to 1.32
Hearing aid use	-0.197	0.40	0.82	0.52 to 1.30
Number of comorbidities (1-10)	0.078	0.03	1.08	1.01 to 1.16
ASA[a] (> 3)	0.683	0.003	1.98	1.27 to 3.09
Marginal exercise tolerance (< 4 METS)	0.190	0.27	1.21	0.86 to 1.70
Falls in previous 6 months	0.221	0.21	1.25	0.88 to 1.76
History of delirium	0.603	0.004	1.83	1.21 to 2.76
Preoperative PHQ8	0.029	0.12	1.03	0.99 to 1.07
Preoperative Lawton	-0.053	0.45	0.95	0.83 to 1.09
Preoperative Barthel	-0.048	0.56	0.95	0.81 to 1.12
Preoperative opioids	0.236	0.20	1.27	0.88 to 1.82
Preoperative benzodiazepines	0.249	0.24	1.28	0.85 to 1.94
Preoperative sodium level	-0.016	0.52	0.98	0.94 to 1.03
Preoperative creatinine level	0.055	0.47	1.06	0.91 to 1.22
Preoperative hemoglobin level	-0.007	0.88	0.99	0.91 to 1.08
Cardiac surgery	-0.089	0.70	0.92	0.58 to 1.44
Intercept	-0.916	0.81	-	-

Observations[b]	ROC Area	Standard Error	95% CI
n=1,051	0.6951	0.0188	0.66 to 0.73
Pearsons chi2 = 1043.46		Hosmer-Lemeshow chi2 = 7.79	
Prob > chi2 = 0.3783		Prob > chi2 = 0.4542	

CI, Confidence Interval; PHQ8, eight-item Patient Health Questionnaire depression scale; ROC, receiver operating characteristic.

[a]ASA: American Society of Anesthesiologists physical status classification system, 1-6, 1. Healthy patient, 2. Mild systemic disease, 3. Severe systemic disease, 4. Severe systemic disease that is a constant threat to life, 5. Not expected to survive without procedure, 6. Neurologically deceased organ donor. In this study, ASA was dichotomized with a threshold set at 3 or higher.

The logistic regression adjusted odds ratio for delirium was 1.21 (95% CI, 0.90 to 1.64; *P*=0.21) in the guided group with reference to the usual care group.

[b]No imputation was performed. The amount of missing data for any individual characteristic included in this model was less than 10%. The overall percentage of patients excluded from this analysis was 13.4% (N=162/1213).

Standardized Adjustment Method with Bootstrapped Standard Error

Parameters	dy/dx	Delta-Method Standard Error	Z	P> |z|	95% CI
Logit (n=1051)	0.032	0.0253	1.25	0.210	-0.018 to 0.081

Parameters	Observed Coefficient	Bootstrap Standard Error	Z	P> |z|	95% CI
Bootstrap (n=1000)	0.032	0.0258	1.23	0.218	-0.019 to 0.082

CI, confidence interval.

Using the standardized estimator method with bootstrapping, the standardized marginal effect was 0.032 (P=0.22; 95% CI, -0.019 to 0.082).

eTable11: Sensitivity Analyses – Treating Patients with Missing Assessments as All Positive or All Negative

	Guided Group	Usual Care Group	Difference[a] (95%CI)	*P*-Value[b]
Analysis with no imputation of missing delirium assessments (for the purpose of reference)				
- Delirium incidence – no./total (%)	157/604 (26.0)	140/609 (23.0)	3.0% (-2.0 to 8.0)	0.22
Analyses with imputed missing delirium assessments				
- All missing imputed as +ve – no./total (%)	167/614 (27.2)	148/617 (24.0)	3.2% (-2.0 to 8.2)	0.22
- All missing imputed as -ve – no./total (%)	157/614 (25.6)	140/617 (22.7)	2.9% (-2.0 to 7.8)	0.26

CI, confidence interval.
[a]Absolute difference between groups. All 95%CIs for difference between medians were computed using Hodges-Lehmann estimator with asymptotic standard error.
[b]P values were calculated with the use of the chi-square test with Fisher's exact test.
[c]Note: One patient died on the day of surgery.

eTable12: Sensitivity Analysis – Actual Treatment Received (Per Protocol Analysis) and Per Protocol Analyses with Imputation of Missing Delirium Assessments

	Guided Group	Usual Care Group	Difference[a] (95%CI)	*P*-Value[b]
Per protocol analysis with no imputation of missing delirium assessments				
Delirium incidence – no./total no. (%)	161/608 (26.5)	136/605 (22.5)	4.0% (-1.0 to 8.8)	0.11
Per protocol analyses with imputed missing delirium assessments				
- All missing imputed as +ve – no./total (%)[c]	172/619 (27.8)	143/612 (23.4)	4.4% (-0.6 to 9.4)	0.08
- All missing imputed as -ve – no./total (%)[c]	161/619 (26.1)	136/612 (22.2)	3.9% (-1.1 to 8.7)	0.13

CI, confidence interval.
[a]Absolute difference between groups. All 95%CIs for difference between medians were computed using Hodges-Lehmann estimator with asymptotic standard error.
[b]P values were calculated with the use of the chi-square test with Fisher's exact test.
[c]Note: One patient died on the day of surgery

eTable13: Frequency of All Serious Adverse Events by Body System and Preferred Term

	Total	Guided Group	Usual Care Group
	N=398 No. (%)	**N=198** No. (%)	**N=209** No. (%)
Hematologic	**16 (4.0)**	**5 (2.5)**	**11 (5.2)**
Bleeding/anemia requiring unexpected transfusion	3 (0.7)	1 (0.5)	2 (0.9)
Embolus (e.g., PE)	2 (0.5)	1 (0.5)	1 (0.4)
Thrombocytopenia	4 (1.0)	1 (0.5)	3 (1.4)
Thrombosis without embolus (e.g., DVT)	6 (1.5)	1 (0.5)	5 (2.3)
Other hematologic event	1 (0.2)	1 (0.5)	0 (0.0)
Cardiac event	**58 (14.5)**	**21 (10.6)**	**37 (17.7)**
Cardiac arrest (CPR)	13 (3.2)	1 (0.5)	12 (5.7)
Cardiac tamponade	1 (0.2)	1 (0.5)	0 (0.0)
Congestive heart failure	6 (1.5)	4 (2.0)	2 (0.9)
Myocardial infarction	8 (2.0)	3 (1.5)	5 (2.3)
Unexpected atrial fibrillation	4 (1.0)	2 (1.0)	2 (0.9)
Unexpected cardiogenic shock	8 (2.0)	2 (1.0)	6 (2.8)
Unexpected heart block	6 (1.5)	3 (1.5)	3 (1.4)
Other unexpected abnormal heart rhythms	5 (1.2)	0 (0)	5 (2.3)
Endocrine and metabolic	**10 (2.5)**	**4 (2.0)**	**6 (2.8)**
Unexpected hypo- or hyperkalemia	1 (0.2)	1 (0.5)	0 (0.0)
Unexpected hypo- or hypernatremia	1 (0.2)	0 (0.0)	1 (0.4)
Other endocrine or metabolic event	8 (2.0)	3 (1.5)	5 (2.3)
Gastrointestinal	**72 (18.0)**	**39 (19.6)**	**33 (15.7)**
Anastomotic leak	3 (0.7)	0 (0.0)	3 (1.4)

eTable13: Frequency of All Serious Adverse Events by Body System and Preferred Term (cont.)			
	Total	**Guided Group**	**Usual Care Group**
	N=398 No. (%)	**N=198** No. (%)	**N=209** No. (%)
Gastrointestinal (cont.)	**72 (18.0)**	**39 (19.6)**	**33 (15.7)**
Nausea and/or vomiting	11 (2.7)	8 (4.0)	3 (1.4)
GI bleed	6 (1.5)	5 (2.5)	1 (0.4)
Ileus/bowel obstruction	20 (5.0)	12 (6.0)	8 (3.8)
Other GI event	32 (8.0)	14 (7.0)	18 (8.6)
Immune or infectious event	**59 (14.8)**	**26 (13.1)**	**33 (15.7)**
Anaphylaxis	3 (0.7)	2 (1.0)	1 (0.4)
Infectious colitis	5 (1.2)	1 (0.5)	4 (1.9)
Sepsis	20 (5.0)	9 (4.5)	11 (5.2)
UTI	3 (0.7)	2 (1.0)	1 (0.4)
Wound infection	24 (6.0)	11 (5.5)	13 (6.2)
Other immune or infectious event	4 (1.0)	1 (0.5)	3 (1.4)
Neurological event	**24 (6.0)**	**15 (7.5)**	**9 (4.3)**
Anoxic encephalopathy	1 (0.2)	0 (0.0)	1 (0.4)
Stroke	14 (3.5)	10 (5.0)	4 (1.9)
Pain	2 (0.5)	2 (1.0)	0 (0.0)
Other neurological event	7 (1.7)	3 (1.5)	4 (1.9)
Pulmonary event	**79 (19.8)**	**42 (21.2)**	**37 (17.7)**
Hemothorax	4 (1.0)	3 (1.5)	1 (0.4)
Pleural effusion	4 (1.0)	1 (0.5)	3 (1.4)
Pneumonia	13 (3.2)	10 (5.0)	3 (1.4)

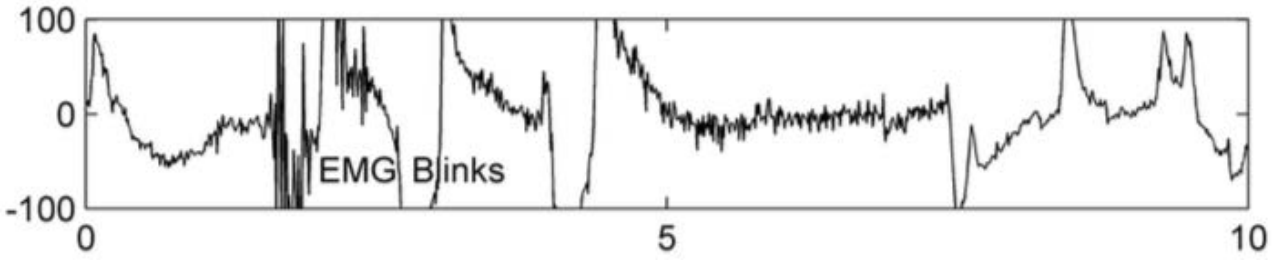
eTable13: Frequency of All Serious Adverse Events by Body System and Preferred Term (cont.)			
	Total	**Guided Group**	**Usual Care Group**
	N=398 No. (%)	**N=198** No. (%)	**N=209** No. (%)
Pneumothorax	2 (0.5)	1 (0.5)	1 (0.4)
Respiratory failure	48 (12.0)	21 (10.6)	27 (12.9)
Other respiratory event	8 (2.0)	6 (3.0)	2 (0.9)
Renal system	**27 (6.7)**	**11 (5.5)**	**16 (7.6)**
Acute kidney injury	7 (1.7)	1 (0.5)	6 (2.8)
Renal failure requiring dialysis	13 (3.2)	6 (3.0)	7 (3.3)
Urinary retention	1 (0.2)	1 (0.5)	0 (0.0)
Other renal event	6 (1.5)	3 (1.5)	3 (1.4)
Vascular system	**27 (6.7)**	**14 (7.0)**	**13 (6.2)**
Non-cardiogenic shock	6 (1.5)	3 (1.5)	3 (1.4)
Unexpected hypotension	5 (1.2)	4 (2.0)	1 (0.4)
Other vascular event	16 (4.0)	7 (3.5)	9 (4.3)
Other body system event	**26 (6.5)**	**12 (6.0)**	**14 (6.6)**

eTable14: Causes of Death up to 30 Days After Surgery			
	Total*	**Guided Group**	**Usual Care Group**
	N=23	**N=4**	**N=19**
Cardiac event	**9**	**2**	**7**
Cardiac arrest	2	0	2
Cardiogenic shock	3	0	3
Congestive heart failure	3	1	2
Unexpected atrial fibrillation	1	1	0
Gastrointestinal	**3**	**0**	**3**
Anastomotic leak	1	0	1
Perforated abdominal viscus	2	0	2
Immune or infectious event	**2**	**1**	**1**
Sepsis	2	1	1
Neurological event	**1**	**0**	**1**
Stroke	1	0	1
Pulmonary event	**1**	**0**	**1**
Respiratory failure	1	0	1
Renal event	**1**	**0**	**1**
Acute kidney injury	1	0	1
Other	**6**	**1**	**5**
Hemorrhagic shock	1	0	1
Abdominal aortic aneurysm	1	0	1
Cancer	2	0	2
Hemothorax	1	1	0
Unknown	1	0	1

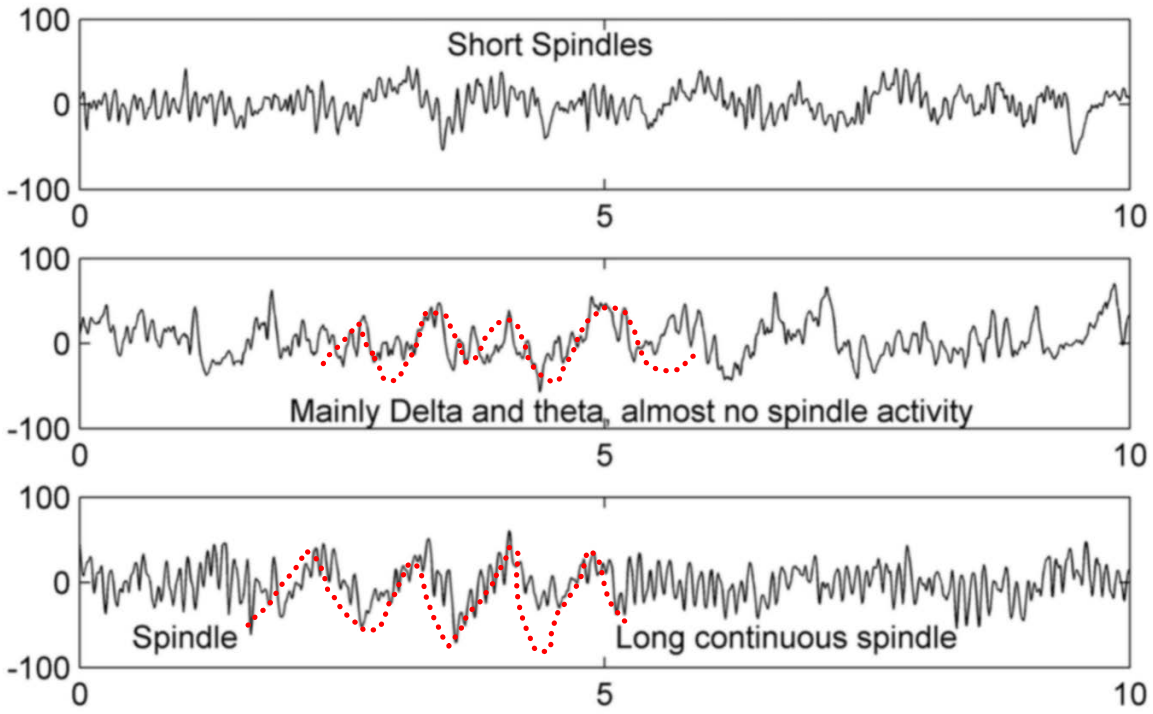
eFigure1: ENGAGES Study Electroencephalography (EEG) Guided Protocol Quick Reference Guide

This guide was provided to anesthesia clinicians caring for patients in the Guided arm on the day of surgery to assist with EEG guidance of anesthesia.

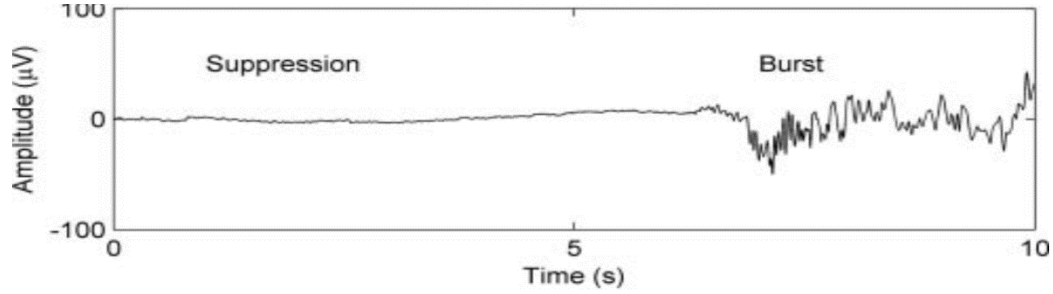
1) **EEG-guided protocol monitor setup**
    a. **Set the EEG wave to display at both 50 mm/second and 6.25 mm/second sweep speeds.** The faster 50 mm/s sweep is good for appreciating higher frequency waves while the 6.25 mm/s sweep is good for appreciating delta waves.
    b. **Set the EEG amplitude scale to 50 µV**. Adjust as needed for optimal display on each patient.
    c. **Turn EEG filter off** to prevent low frequency filtering (i.e., delta wave filtering).
    d. **EEG alarms:** BIS alarm range is set to low/high limits of 40/60 by default. Adjust according to clinical discretion.
    e. **Numeric values:** The BIS (bispectral index), SQI (signal quality index), SR (suppression ratio), EMG (electromyographic strength), and SEF (spectral edge frequency 95%) should be displayed on the monitor.
2) **Important EEG frequency ranges include gamma (>30 Hz), high beta (20-30 Hz), low beta (12-20 Hz), alpha (8-12 Hz), theta (4-8 Hz), and delta (0.5-4 Hz).**
3) **The EEG of the awake patient:** The awake EEG is dominated by high-frequency (i.e., high beta and gamma) activity, usually of low amplitude, producing a fuzzy-appearing wave on the faster 50 mm/s tracing. High-frequency, high-amplitude activity (EMG) may be seen. Additionally, periodic high-amplitude deviations (from blinking) may be observed.



4) **The EEG during general anesthesia:** The key EEG features that indicate appropriate anesthetic depth are the presence of delta (0.5-4 Hz) waves, absence of high beta (20-30 Hz) waves, and absence of any periods of burst suppression. Waves in the alpha (8-12 Hz), theta (4-8 Hz) or low beta (12-20 Hz) frequency ranges, often termed spindles, may or may not be superimposed. In the absence of contrary information or an artifactual EEG wave, BIS values below 40 also suggest that anesthesia is too deep. If delta activity is absent and other data support that anesthetic depth may be inadequate, increasing anesthetic administration might be indicated.
    In the following figures, the dotted red trace demonstrates waves in the delta range (~1 Hz).



5) **EEG suppression**: Any flattened interval on the EEG tracing (EEG suppression) indicates excessive anesthetic depth or suggests the presence of other suppressive stimuli (e.g., cerebral ischemia). Any amount of EEG suppression should be avoided as a part of the ENGAGES EEG-guided protocol, unless clinically required. EEG suppression is frequently observed after boluses of induction agents, including small doses given intraoperatively (e.g., propofol 20-50mg). For example, anesthetic boluses are sometimes administered to hypertensive patients whose EEG and anesthetic concentrations indicate adequate anesthesia, thus triggering EEG suppression. EEG suppression is also variably observed with anesthetic induction. The duration of such suppression should be minimized if possible.



6) Age-adjusted concentrations for volatile agents to achieve 0.5 MAC / 0.75 MAC / 1.0 MAC:

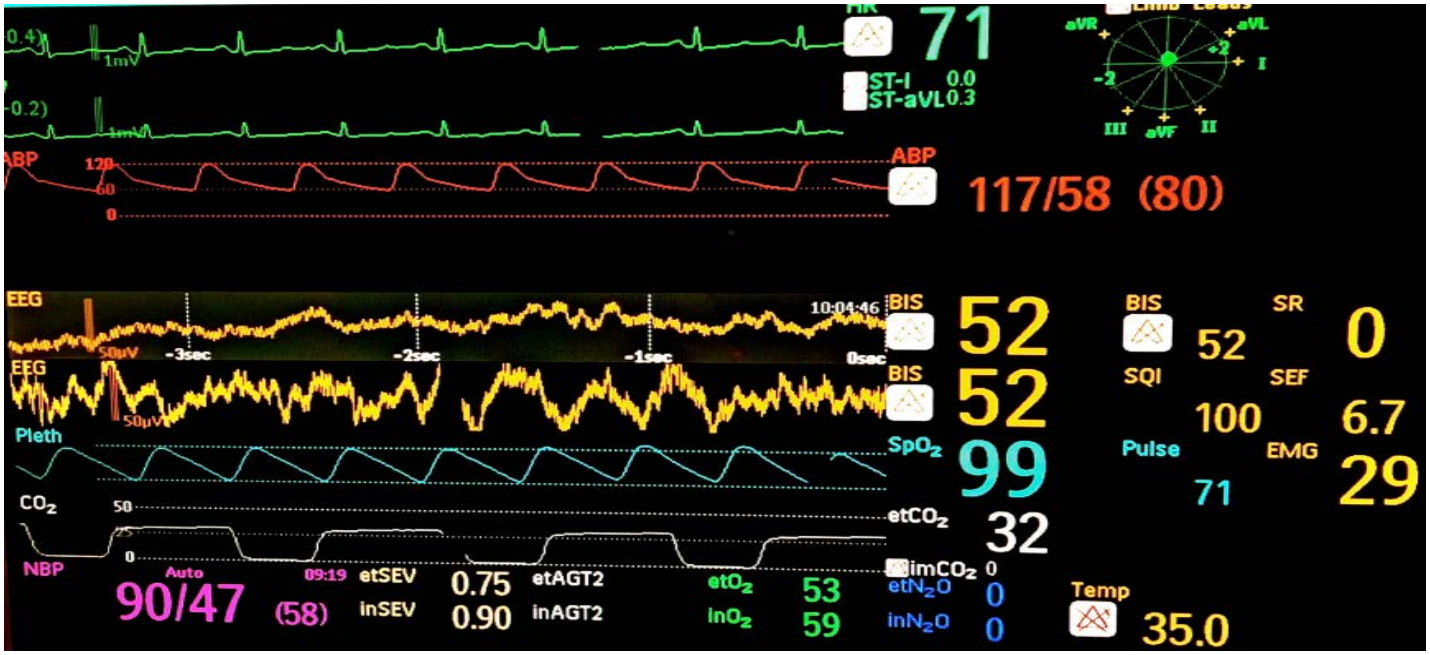
	Desflurane (% atm)			**Isoflurane (% atm)**			**Sevoflurane (% atm)**		
Age	0.5 MAC	0.75 MAC	1.0 MAC	0.5 MAC	0.75 MAC	1.0 MAC	0.5 MAC	0.75 MAC	1.0 MAC
65	2.8%	4.2%	5.7%	0.5%	0.8%	1.0%	0.8%	1.2%	1.5%
75	2.7%	4.0%	5.3%	0.5%	0.7%	0.9%	0.7%	1.1%	1.4%
85	2.5%	3.7%	5.0%	0.4%	0.7%	0.9%	0.7%	1.0%	1.4%
95	2.3%	3.5%	4.7%	0.4%	0.6%	0.8%	0.6%	1.0%	1.3%

References: Individual EEG tracings from: Bennett, C., Voss, L. J., Barnard, J. P. M. & Sleigh, J. W. Practical Use of the Raw Electroencephalogram Waveform During General Anesthesia: The Art and Science. *Anesth Analg* **109,** 539–550 (2009).

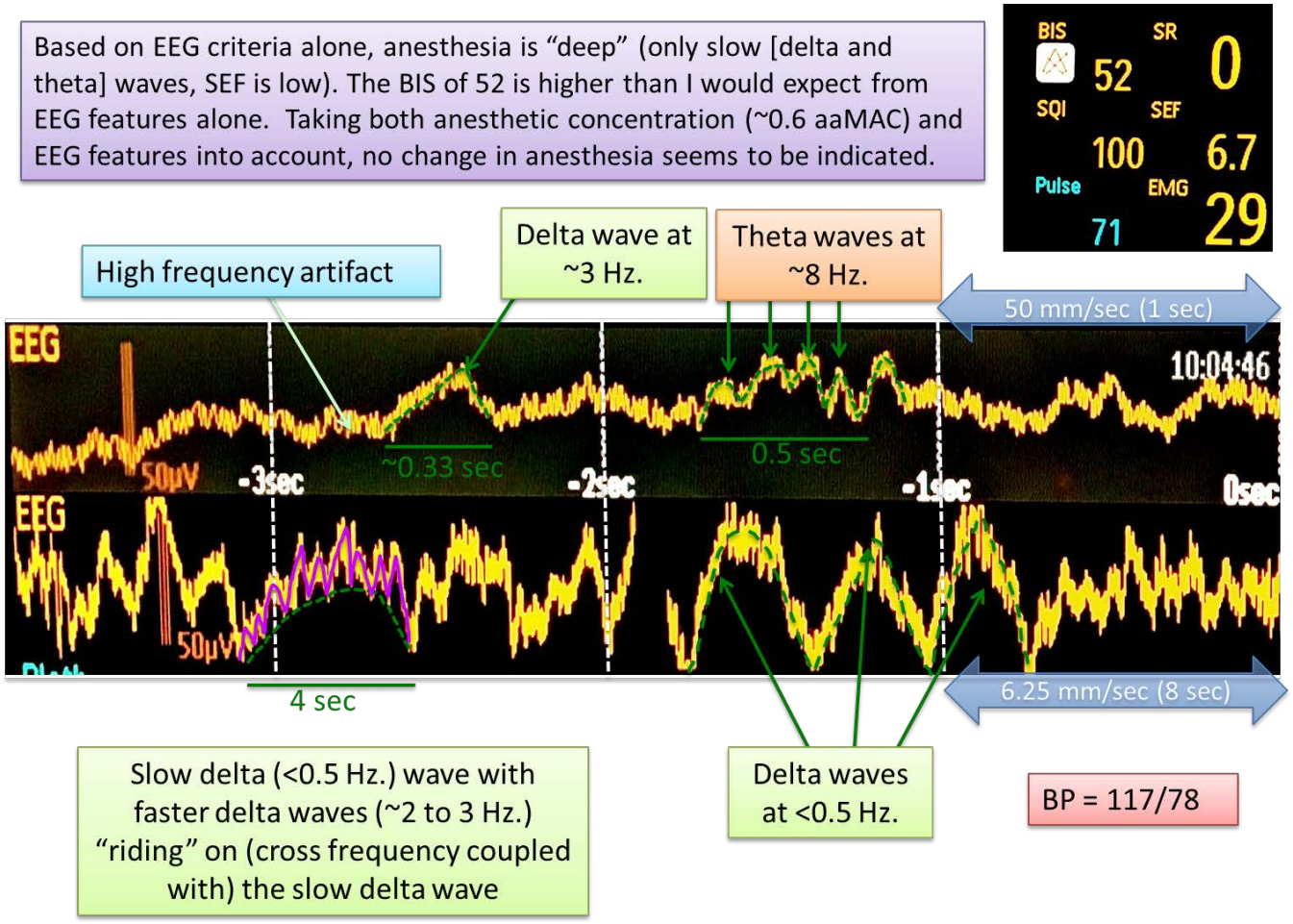
eFigure2: Real-Time Clinician Feedback.

Example 1: An example of the real time feedback provided to the anesthesia provider in the operating room during the procedure for patients in the guided group.

Photograph of the anesthesia monitor during the procedure:

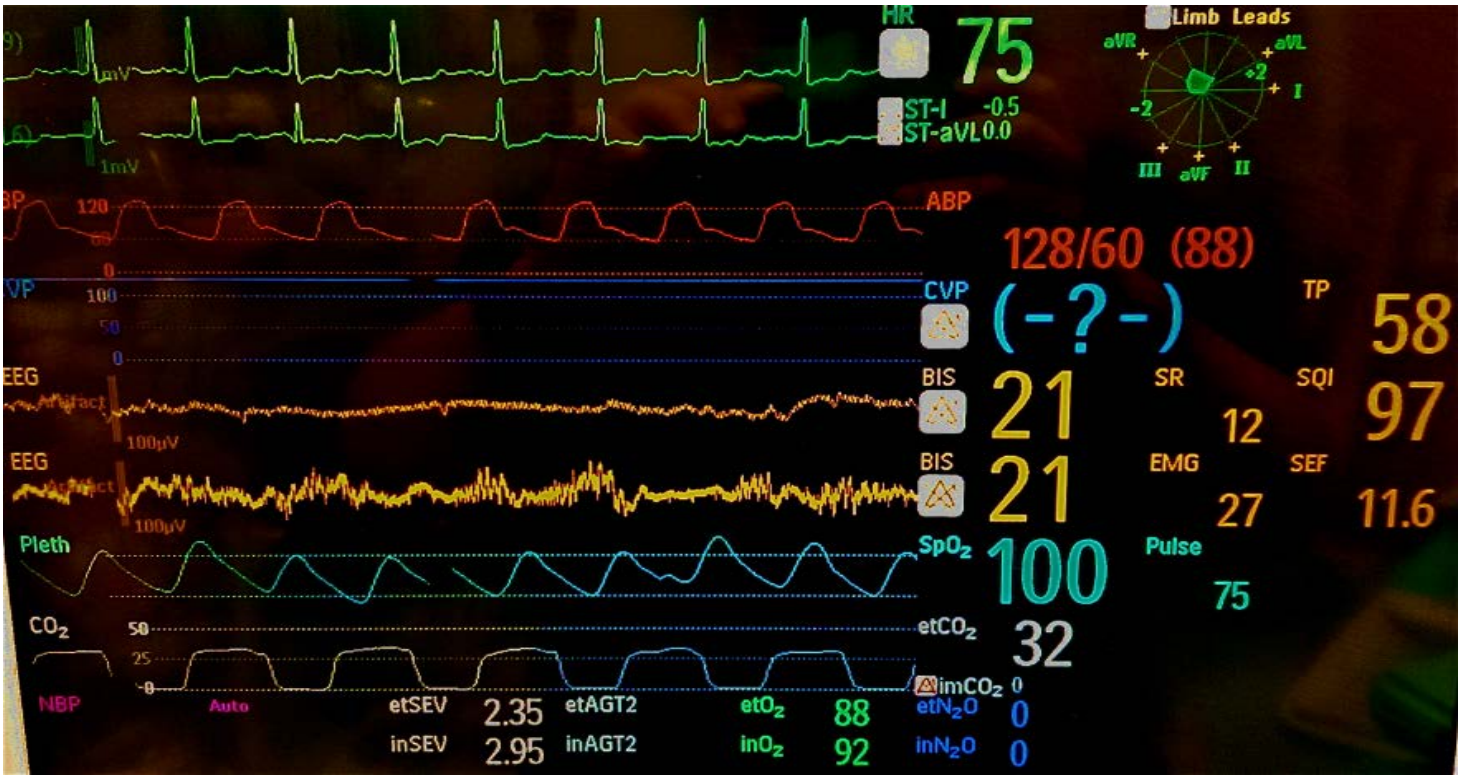


Feedback on the electroencephalogram features that was provided to the anesthesia clinicians:

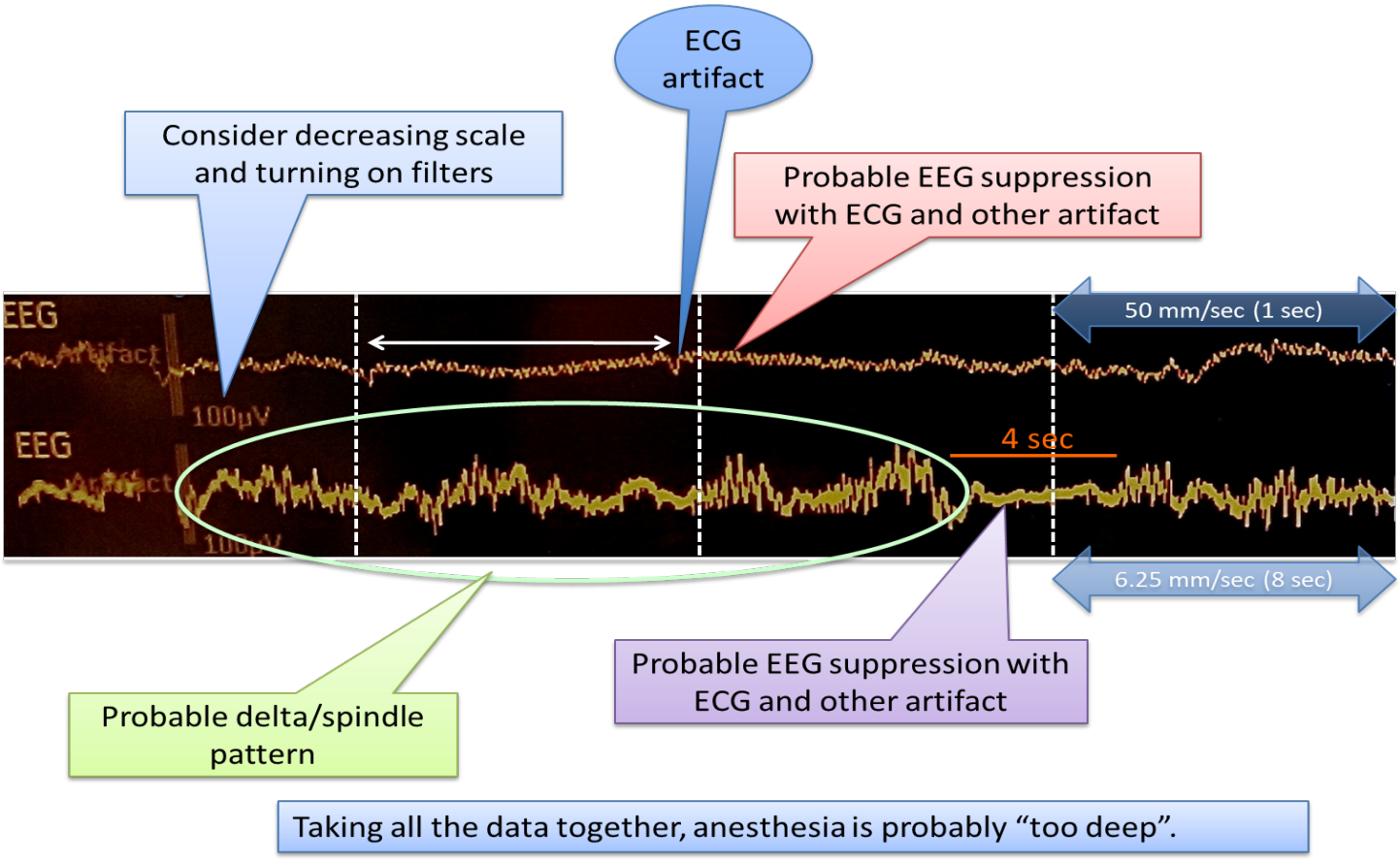


Example 2: An example of the real time feedback provided to the anesthesia provider in the operating room during the procedure for patients in the guided group.

Photograph of the anesthesia monitor during the procedure:

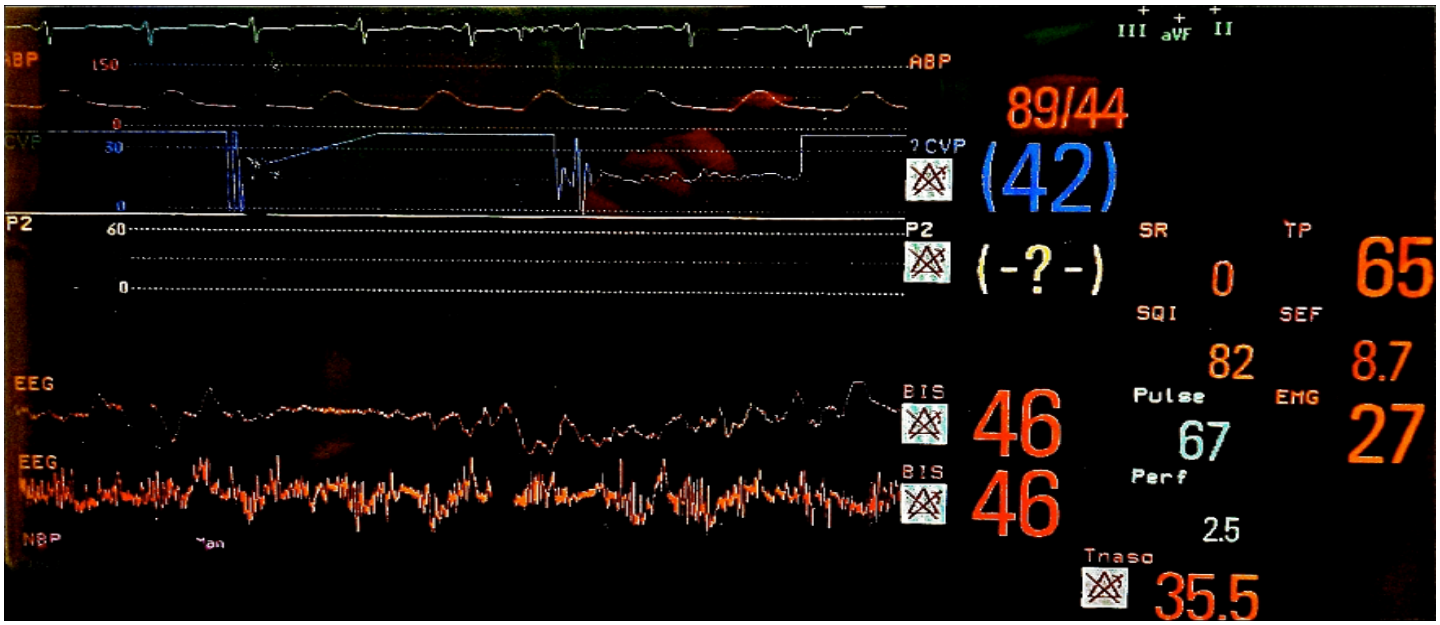


Feedback on the electroencephalogram features that was provided to the anesthesia clinicians:

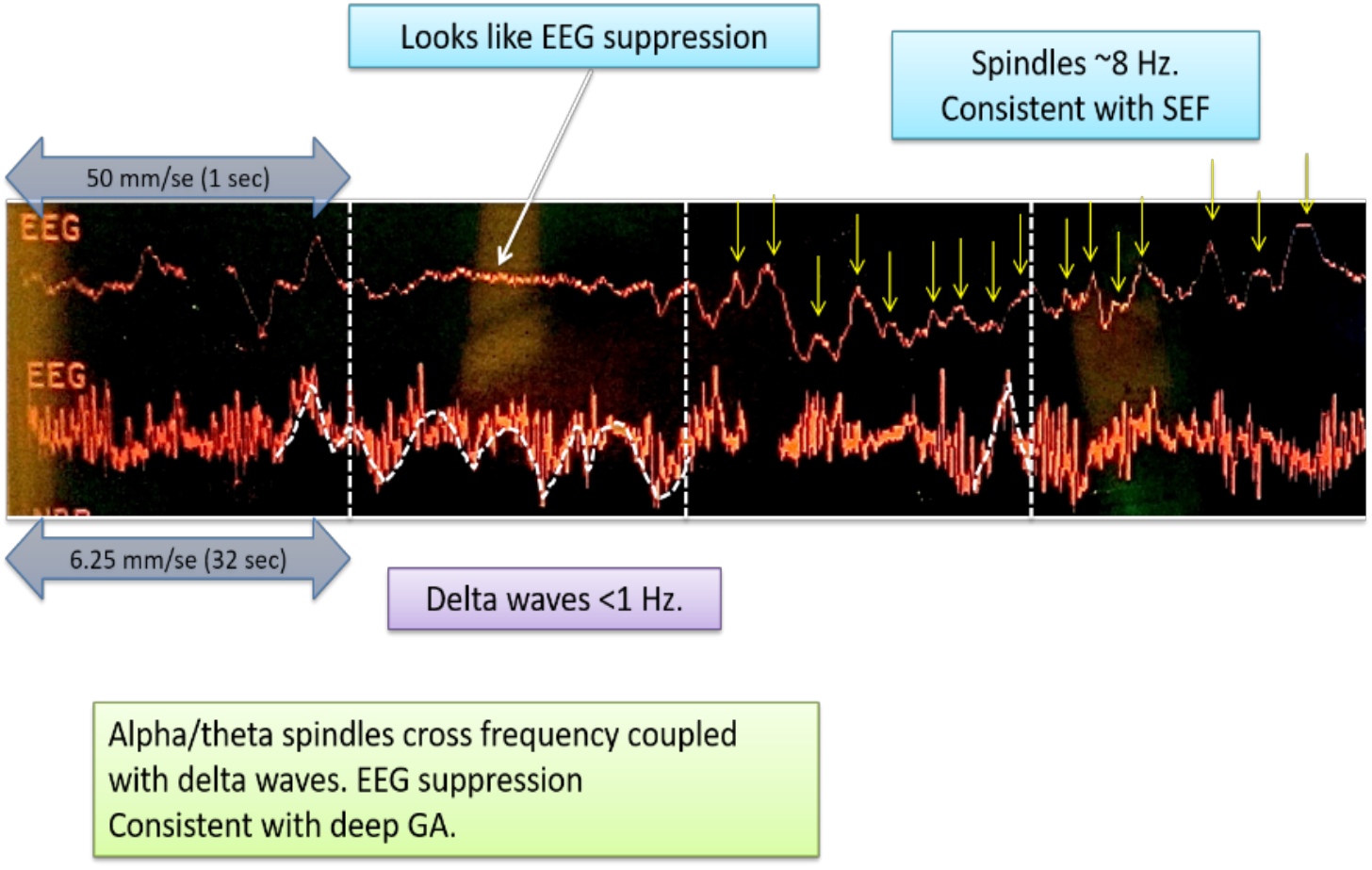


Example 3: An example of the real time feedback provided to the anesthesia provider in the operating room during the procedure for patients in the guided group.

Photograph of the anesthesia monitor during the procedure:



Feedback on the electroencephalogram features that was provided to the anesthesia clinicians:



BIS, bispectral index; EMG, electromyography; GA, general anesthesia; MAC, minimum alveolar concentration; SEF, spectral edge frequency; SQI, signal quality index; SR suppression ratio; TP, total power; Hz, hertz

eFigure3: Anesthesia Fidelity Checklist

Fidelity checklists were provided to all anesthesia clinicians during the surgery to complete and sign. A checklist was completed for 1227 of the 1232 patients in the ENGAGES trial.

Patient enrollment ID:_____

ENGAGES
Anesthesia Fidelity Checklist – Guided Group

Yes

No

	Yes	No
1. Was a quality EEG waveform visible for the duration of the case (excluding discrete periods of artifact or probe adjustment)?		
2. Was the EEG filter turned OFF for the duration of the surgery?		
3. Were you trained to interpret EEG by the ENGAGES team?		
4. Did you use the EEG-guided anesthetic protocol to guide your anesthetic (only deviating from it when you thought it was clinically necessary)?		

Did the patient have any undesired intraoperative movement or breathing during the surgery?

☐ No

Frequency

☐ Yes (check all that apply)

- ☐ Mild: Undesired spontaneous breathing or non-purposeful movement with no impact on the surgery or patient outcome. _____ times
- ☐ Moderate: Movement that mildly impacted the surgery (e.g., required a pause in the surgery for coughing or straining) and required deepening of anesthesia, deepening of analgesia, or increased muscle relaxant _____ times
- ☐ Severe: Movement with a marked negative impact on the surgery (e.g., a patient injury, loss of sterility of the surgical field, purposeful movements suggestive of awareness, or other surgical complication) _____ times

Comments:_____

Name:_____ ☐ Attending ☐ CRNA ☐ Fellow ☐ Resident

Signature:_____ Date:_____

Name:_____ ☐ Attending ☐ CRNA ☐ Fellow ☐ Resident

Signature:_____ Date:_____

Name:_____ ☐ Attending ☐ CRNA ☐ Fellow ☐ Resident

Signature:_____ Date:_____

EEG, electroencephalography.

Patient enrollment ID:_____

ENGAGES
Anesthesia Fidelity Checklist – Usual Care Group


Yes


No

1. Did the BIS maintain a SQI >50 for the duration of the surgery (excluding discrete periods of artifact or probe adjustment)?		
2. Was the anesthesia team blinded to all EEG data (except for SQI) for the duration of the surgery?		

Did the patient have any undesired intraoperative movement or breathing during the surgery?

☐ No

Frequency

☐ Yes (check all that apply)

- ☐ Mild: Undesired spontaneous breathing or non-purposeful movement with no impact on the surgery or patient outcome. _____ times
- ☐ Moderate: Movement that mildly impacted the surgery (e.g., required a pause in the surgery for coughing or straining) and required deepening of anesthesia, deepening of analgesia, or increased muscle relaxant _____ times
- ☐ Severe: Movement with a marked negative impact on the surgery (e.g., a patient injury, loss of sterility of the surgical field, purposeful movements suggestive of awareness, or other surgical complication) _____ times

Comments:_____

Name:_____ ☐ Attending ☐ CRNA ☐ Fellow ☐ Resident

Signature:_____ Date:_____

Name:_____ ☐ Attending ☐ CRNA ☐ Fellow ☐ Resident

Signature:_____

Date:_____

Name:_____ ☐ Attending ☐ CRNA ☐ Fellow ☐ Resident

Signature:_____ Date:_____

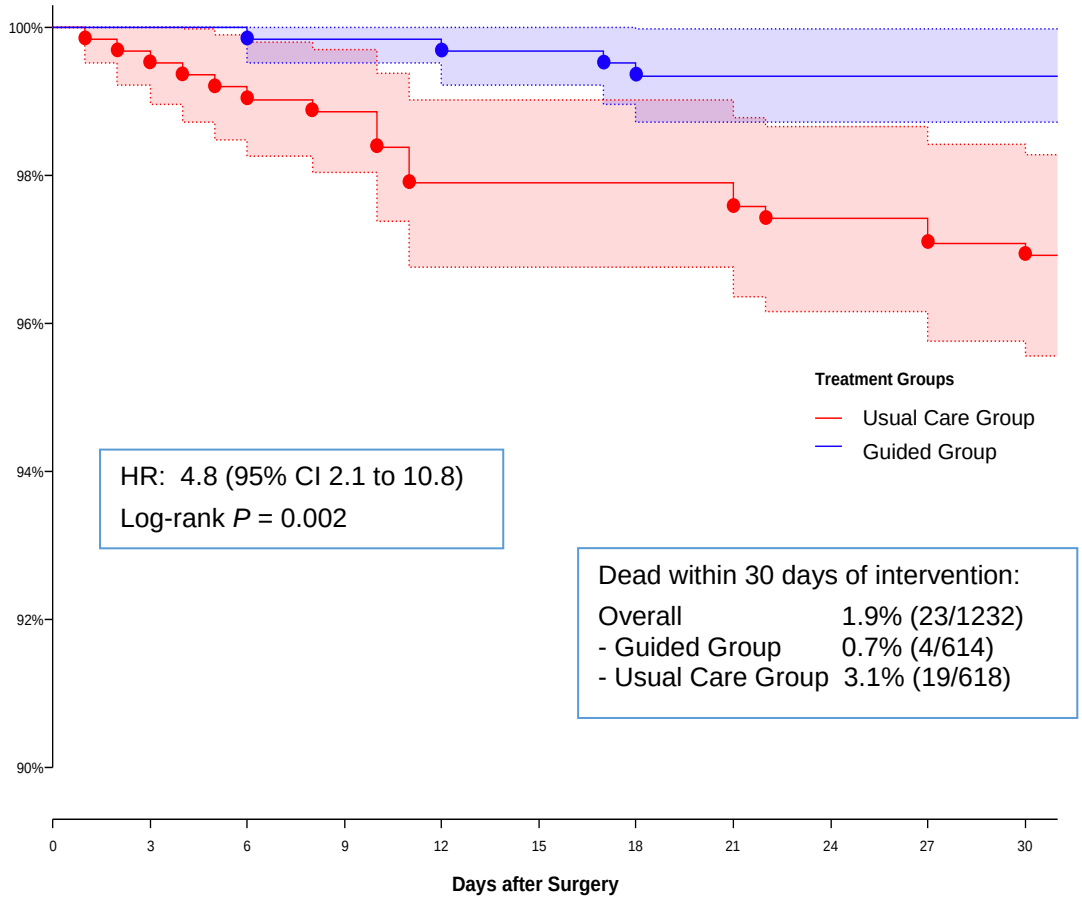
Name:_____ ☐ Attending ☐ CRNA ☐ Fellow ☐ Resident

Signature:_____ Date:_____

EEG, electroencephalography; BIS, Bispectral Index; SQI, Signal Quality Index

eFigure4: Kaplan-Meier Curve: 30 Day Survival

Kaplan-Meier curves of 30-day survival with 95% confidence intervals (CI), by treatment groups.

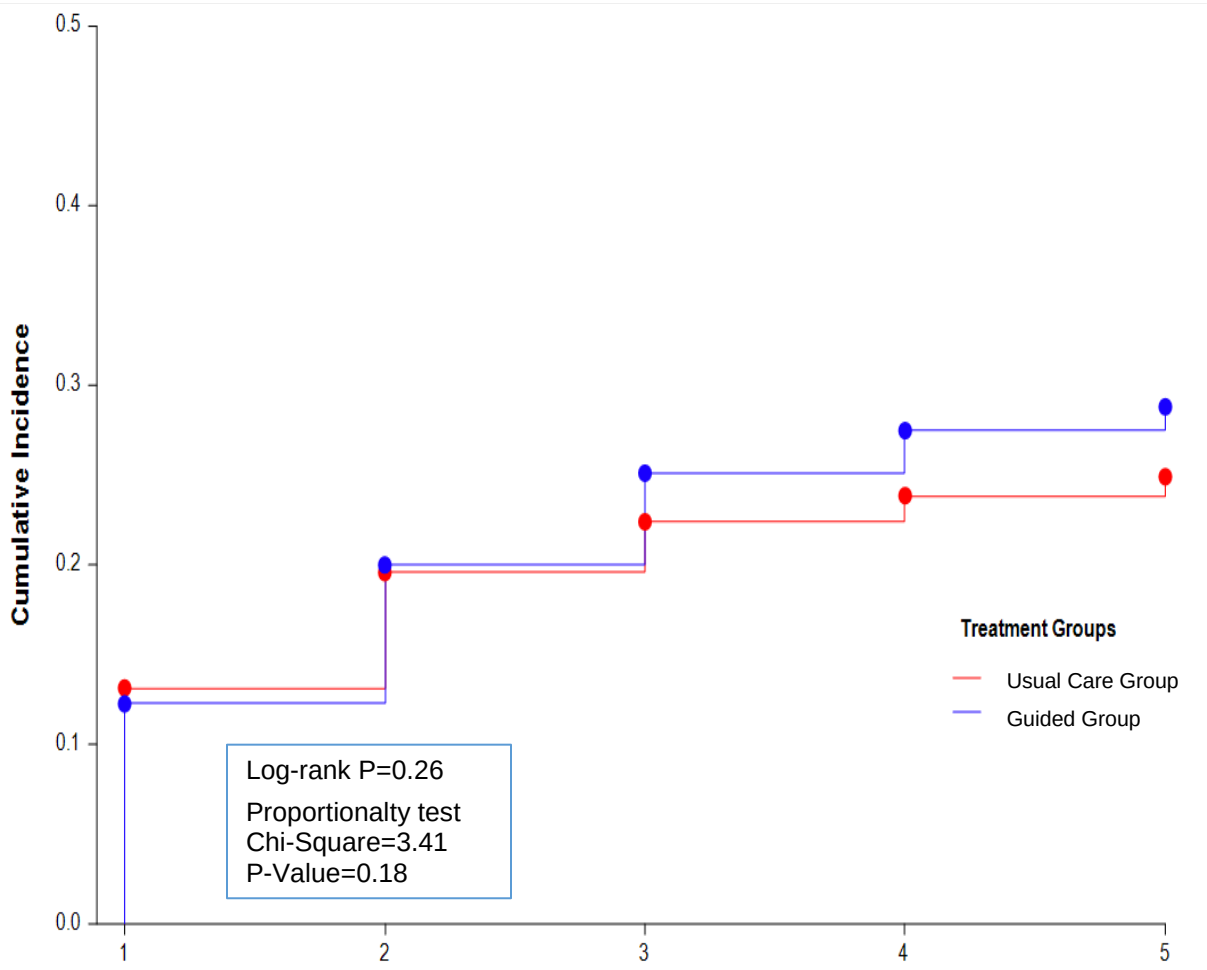


Number at Risk

Guided Group	614	614	613	613	612	612	610	610	610	610	610
Usual Care Group	618	614	610	607	604	604	604	602	602	600	599

eFigure5: Kaplan-Meier Curve: Cumulative Incidence of Delirium

Kaplan-Meier curves showing cumulative delirium incidence over postoperative days 1 to 5, by treatment group.



Number At Risk					
Guided	74/592	41/573	25/537	11/451	6/373
Usual Care	80/602	34/584	14/524	7/444	5/383

Percentage of Patients with Delirium by Post-operative Day

	Overall percentage of patients with delirium on each POD			Percentage of patients with new onset delirium on each POD		
	Total	Guided Group	Usual Care Group	Total	Guided Group	Usual Care Group
	No./total no. (%)	No./total no. (%)	No./total no. (%)	No./total no. (%)	No./total no. (%)	No./total no. (%)
POD 1	154/1194 (12.9)	74/592 (12.5)	80/602 (13.3)	154/1194 (12.9)	74/592 (12.5)	80/602 (13.3)
POD 2	146/1157 (12.6)	72/573 (12.6)	74/584 (12.6)	75/1157 (6.5)	41/573 (7.2)	34/584 (5.8)
POD 3	118/1061 (11.1)	69/537 (12.8)	49/524 (9.3)	39/1061 (3.7)	25/537 (4.7)	14/524 (2.7)
POD 4	87/895 (9.7)	51/451 (11.3)	36/444 (8.1)	18/895 (2.0)	11/451 (2.4)	7/444 (1.6)
POD 5	60/756 (7.9)	37/373 (9.9)	23/383 (6.0)	11/756 (1.5)	6/373 (1.6)	5/383 (1.3)

POD, postoperative day.
The overall number with delirium is based on the number of patients positive by CAM, CAM-ICU or chart review for that day. New delirium onset is the number of *new* positive patients by CAM, CAM-ICU or chart review for that day.

eFigure6: Delirium Incidence by Comorbidity

Incidence of postoperative delirium in the ENGAGES study segregated by Charlson Comorbidity Index