The ENGAGES Pragmatic Trial and the Power of Negative Thinking

Funded by a NIH grant to support pragmatic trials (1 UH2 HL125141, 5 UH3 AG050312)

Also funded by NIH NIDUS Grant (NIAR24AG054259) and Dr. Seymour and Rose T. Brown Endowed Chair at Washington University

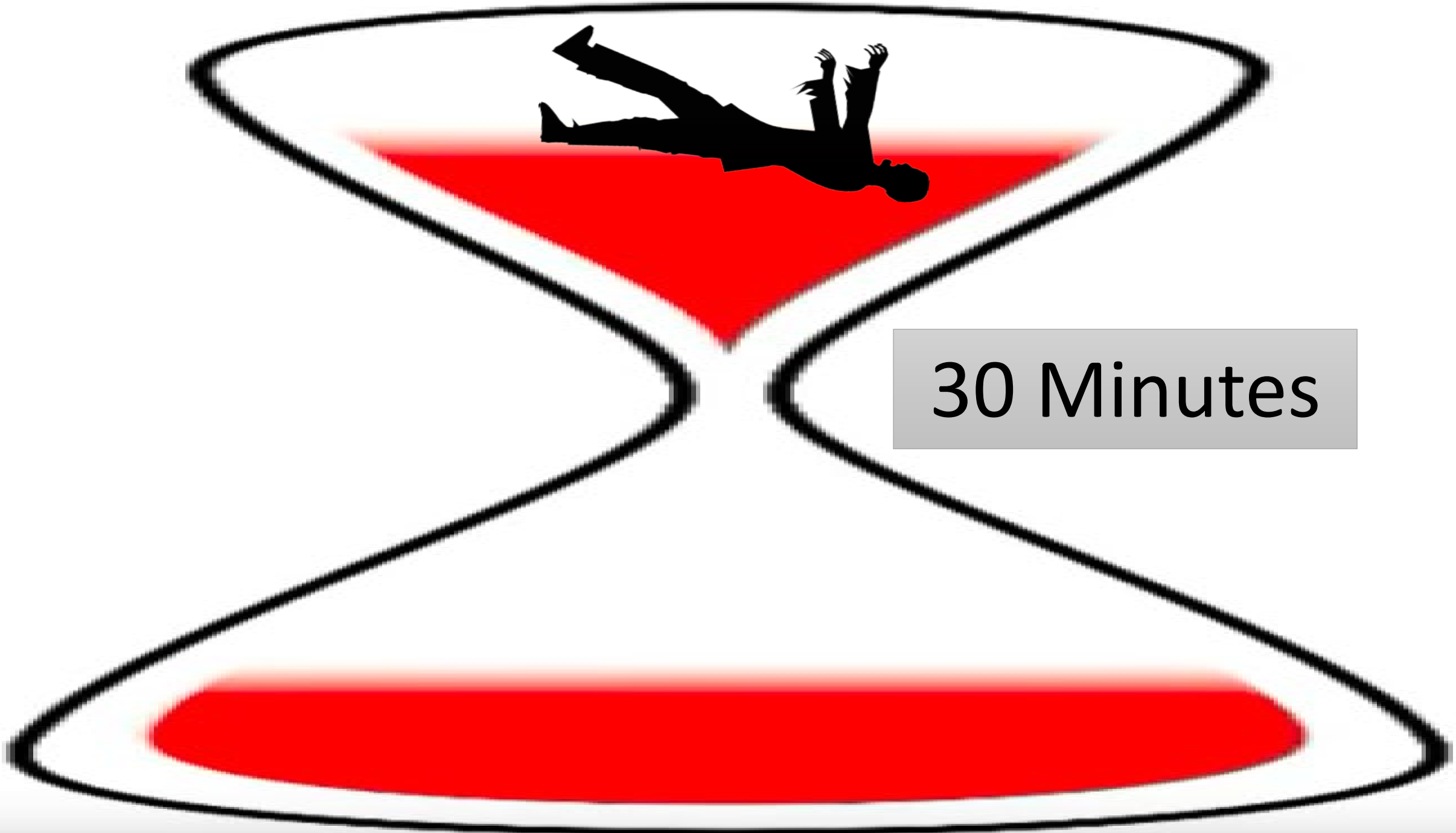
5th April 2019

Michael S. Avidan MBBCh FCASA

Dr. Seymour and Rose T. Brown Professor of Anesthesiology

NIH National Institute on Aging

Washington University in St. Louis


30 Minutes

Acknowledgements

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National Institute of General Medical Sciences
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Canadian Institute of Health Research
Institute of Clinical and Translational Science
National Institute of Nursing Research

I have no conflicts of interest to declare.

James S. McDonnell Foundation

NIH National Institute on Aging

NIH Collaboratory

Health Care Systems Research Collaboratory

pcornet

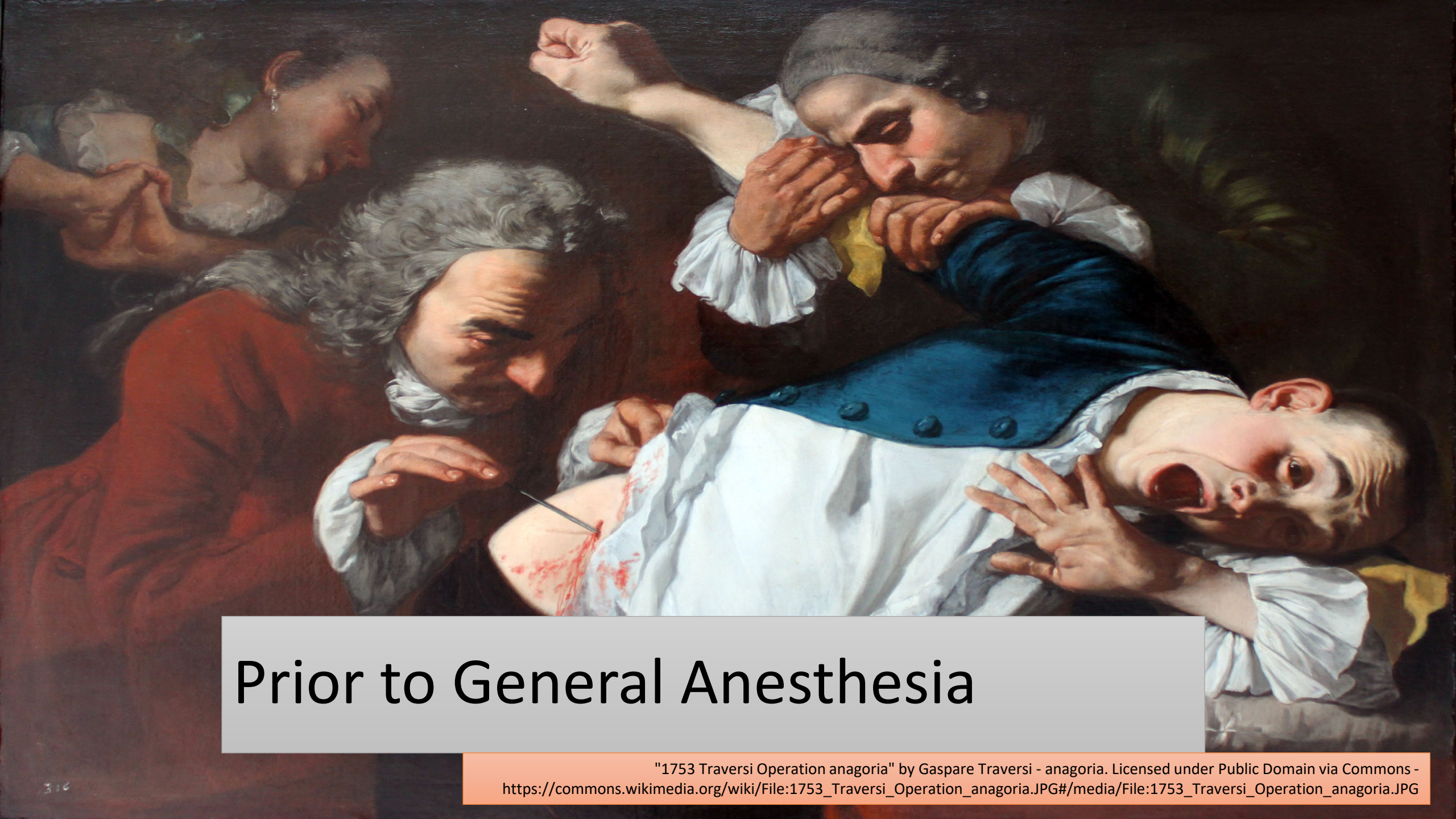
The National Patient-Centered Clinical Research Network

Grand Rounds: A Shared Forum of the NIH Collaboratory and PCORnet

Rethinking Clinical Trials®

https://rethinkingclinicaltrials.org/

Prologue



Prior to General Anesthesia

A Promethean Event

"The crucial **spark of transformation** — the moment that changed not just the future of surgery but of medicine as a whole — was the publication on November 18, 1846, of Henry Jacob Bigelow's groundbreaking report, 'Insensibility during Surgical Operations Produced by Inhalation'"

Gawande A. Two hundred years of surgery. *N Engl J Med*. 2012 May 3;366(18):1716-23.

Painting by Robert Cutler Hinckley

Brandt AM. *N Engl J Med* 2012;366:1-7.

Paradise Found

THE

BOSTON MEDICAL AND SURGICAL JOURNAL.

VOL. XXXV. WEDNESDAY, NOVEMBER 18, 1846. No. 16.

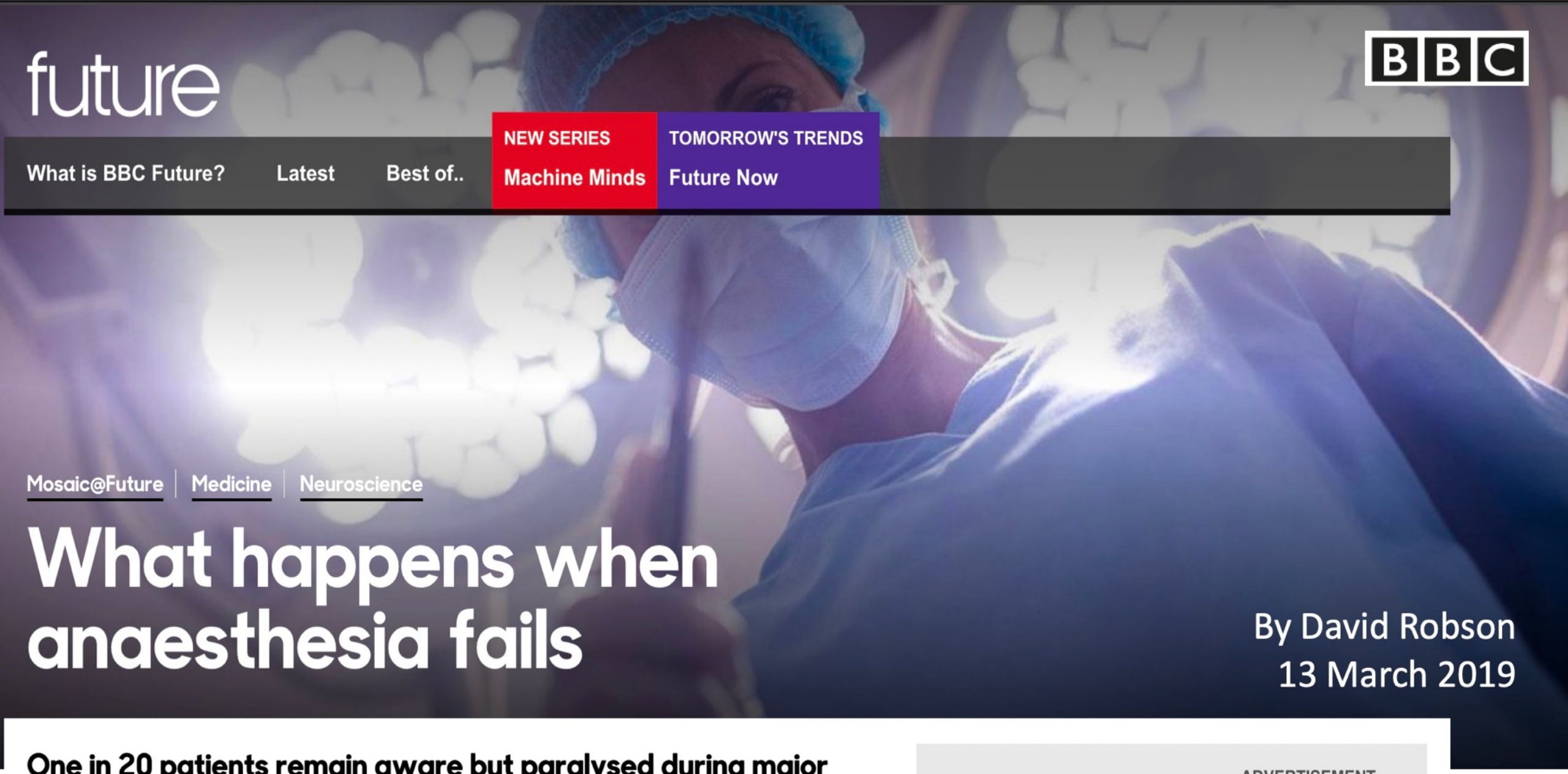
INSENSIBILITY DURING SURGICAL OPERATIONS PRODUCED BY INHALATION.

Read before the Boston Society of Medical Improvement, Nov. 9th, 1846, an abstract having been previously read before the American Academy of Arts and Sciences, Nov. 3d, 1846.

By Henry Jacob Bigelow, M.D., one of the Surgeons of the Massachusetts General Hospital.

[Communicated for the Boston Medical and Surgical Journal.]

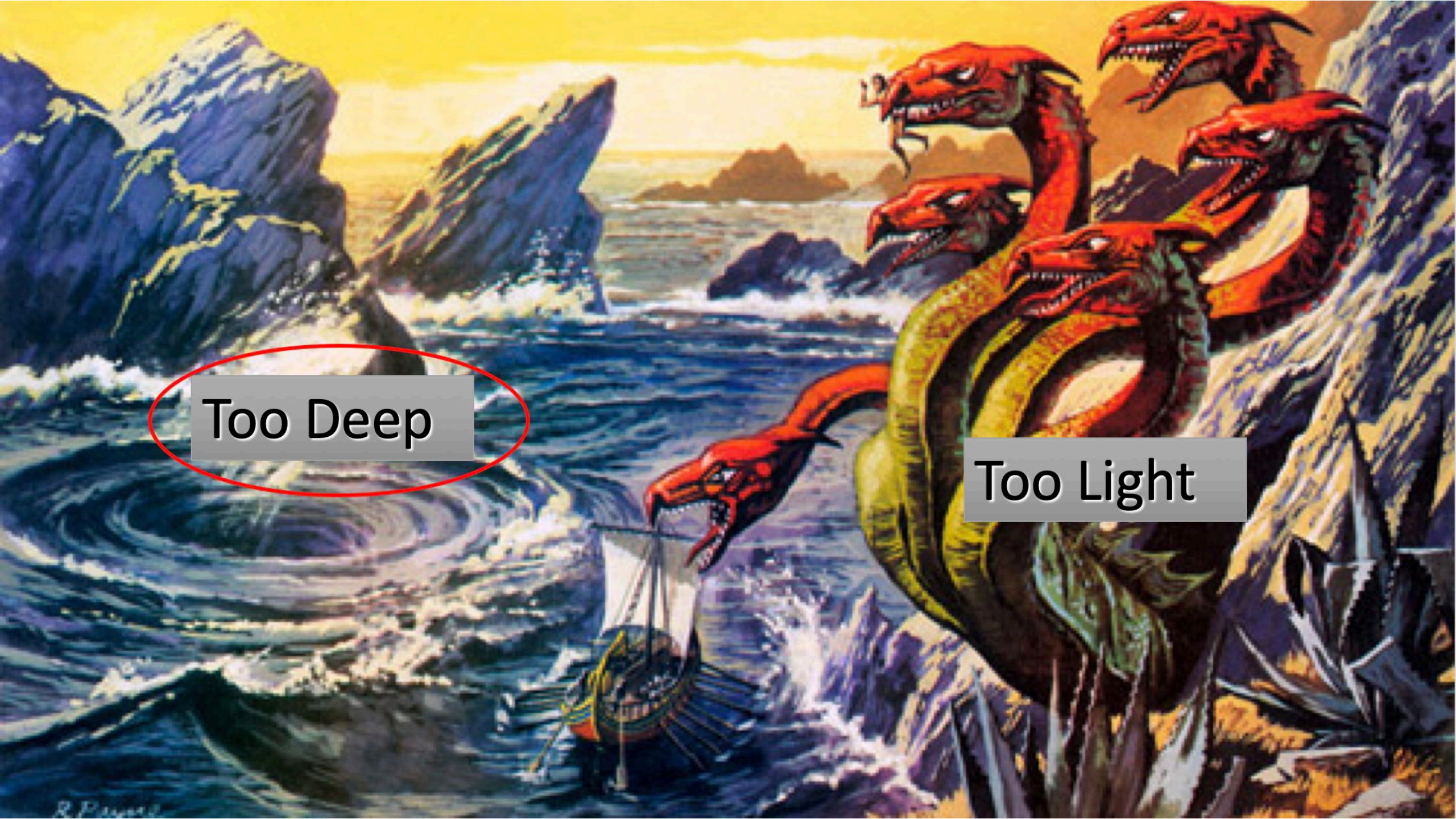
IT has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An efficient agent for this purpose has at length been discovered. A patient has been rendered completely insensible during an amputation of the thigh, regaining consciousness after a short interval. Other severe operations have



What happens when anaesthesia fails

By David Robson
13 March 2019

One in 20 patients remain aware but paralysed during major medical procedures - though the vast majority will not remember it afterwards. Why?


Too Deep
Too Light

National Institutes of Health

"Pragmatic clinical trials are performed in **real-world clinical settings** with **highly generalizable populations** to generate **actionable clinical evidence** at a **fraction of the typical cost and time** needed to conduct a traditional clinical trial. They present an opportunity to **efficiently address critical knowledge gaps** and generate high-quality **evidence to inform medical decision-making**."

https://rethinkingclinicaltrials.org/

ENGAGES

1. Why ENGAGES
2. Patient Centered
3. Efficient
4. Pragmatic
5. Successes
6. Limitations
7. Next Steps

Aim and Elements of CER

- The aim of CER is to improve decisions that affect medical care at the levels of both policy and the individual.

- The key elements of CER are
  (a) head-to-head **comparisons of active treatments**,
  (b) study **populations typical of day-to-day clinical practice**,
  (c) a focus on **evidence to inform care tailored to the characteristics of individual patients**.

Sox HC, Goodman SN. The methods of comparative effectiveness research. Annu Rev Public Health. 2012 Apr;33:425-45.

Objectives

We designed the pragmatic Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial to investigate whether minimizing anesthetic administration and electroencephalogram suppression during surgical anesthesia would

- Decrease the incidence of postoperative **delirium**.
- Secondary outcomes were **quality of life, functional status, and postoperative falls**, assessed one month after the procedure.
- **Safety considerations** were undesirable intraoperative patient **movement, hypotension, and intraoperative awareness**.

A Dash of Delirium

Delirium is a pathophysiologically obscure, underdiagnosed, common, and serious neurological complication of surgery.

The field of anesthesiology should therefore prioritize its prevention, diagnosis, and treatment, while concurrently investigating its underlying mechanisms.

Mashour and Avidan. Anesthesiology. 2014;121(2):214-216.

What is delirium?

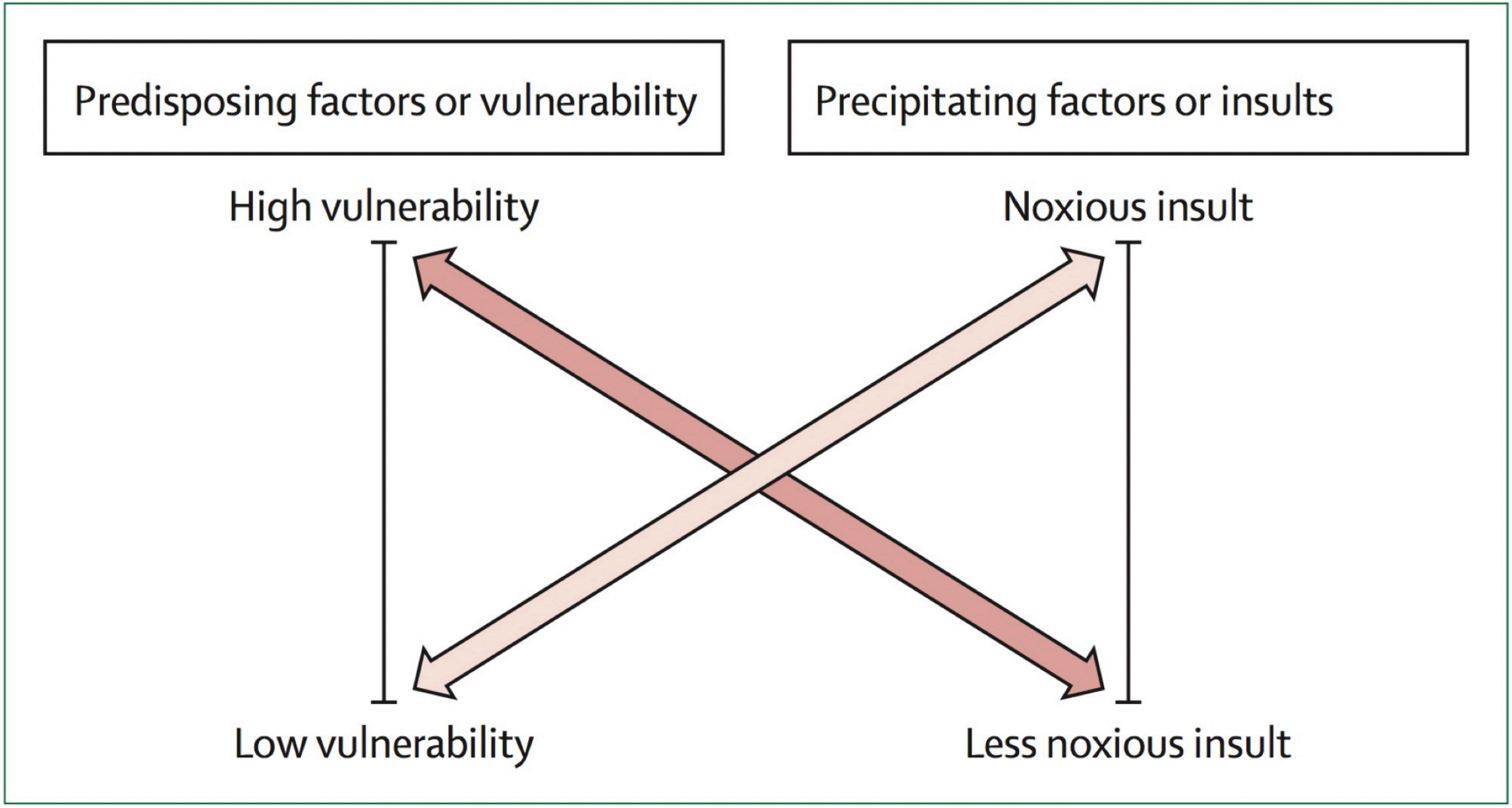
Disturbance in consciousness	• Reduced awareness of environment • Inattention
Change in cognition	• Memory deficit • Disorientation • Hallucinations
Short period of time	• Hours to days • Tends to fluctuate
Medical illness	• Results from the direct physiological consequences of a general medical condition

DSM-IV TR criteria

~25% to 50% of older adults experience delirium after major surgery.

The number is even higher for ICU patients.

Rudolph JL. Circulation 2009;119(2):229-36.
Robinson TN. Annals of surgery 2009;249(1):173-8.
Robinson TN. American journal of surgery 2008;196(5):670-4.



Inouye SK. Lancet 2014; 383: 911–22

Does it matter?

Increased ICU LOS	8 vs. 5 days
Increased Hosp. LOS	21 vs. 11 days
Increased time on vent	9 vs. 4 days
Higher costs	$22 000 vs. $13 000

3 fold increased risk of death

Possible long term cognitive impairment

Ely ICM 2001;27,1892-1900,

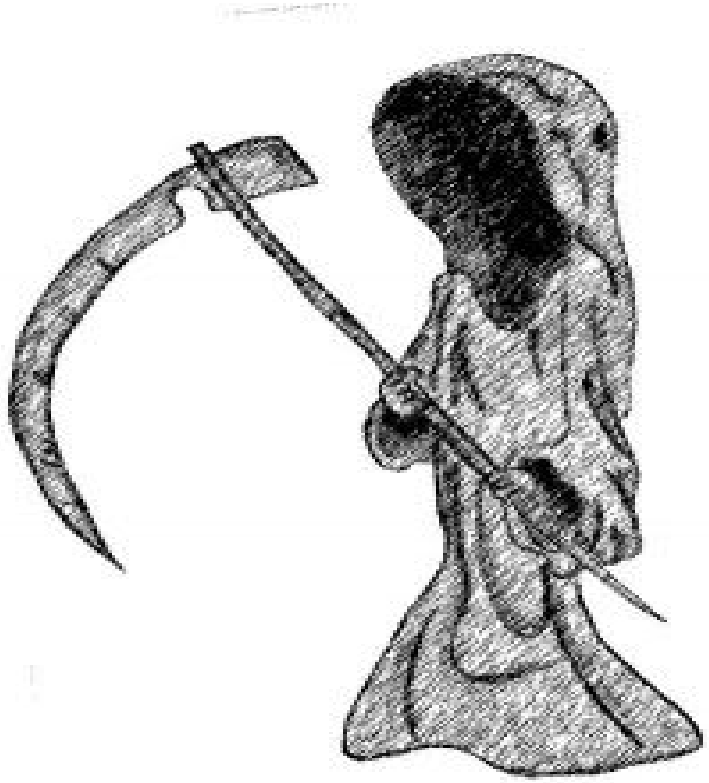
Ely JAMA 2004;291:1753-1762,

Lim SM, CCM 2004;32:2254-2259,

Milbrandt E, CCM 2004;32:955-962,

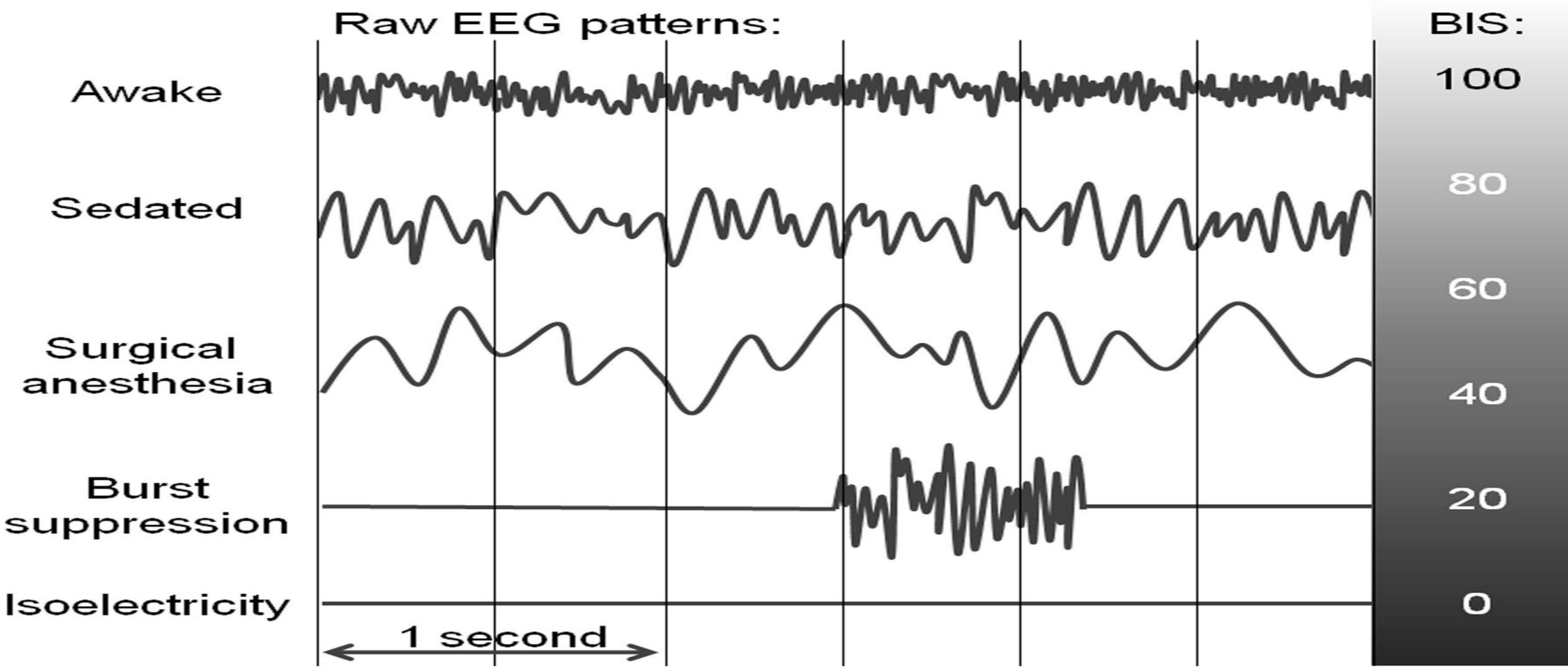
Jackson Neuropsychology Review 2004;14:87-98

Association

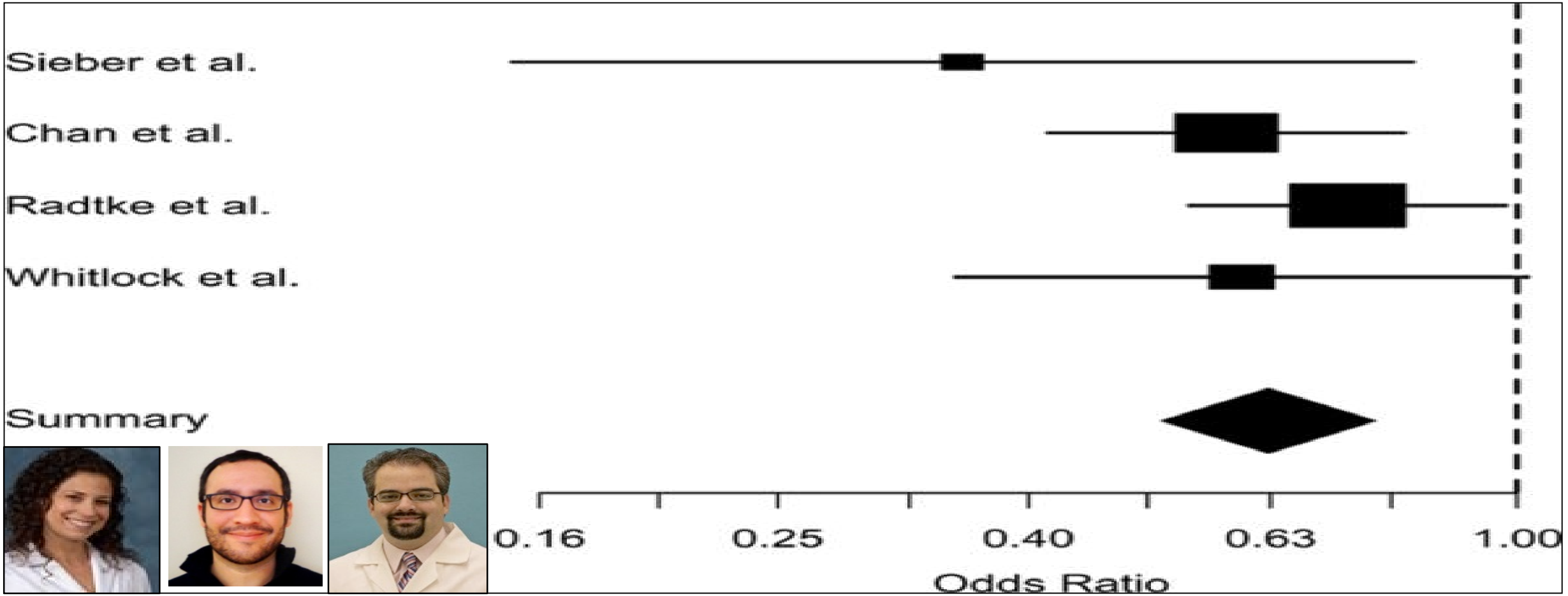


Deliriogenicity of Deep Anesthesia

Brain Monitoring



Kertai MD, Whitlock EL, Avidan MS. Anesth Analg. 2012 Mar;114(3):533-46.



Meta-analysis of randomized controlled trials assessing postoperative delirium with intraoperative Bispectral Index (BIS) guidance of anesthesia compared with an alternative approach (i.e., usual care or an alternative protocol). Odds ratios <1 favor BIS guidance.

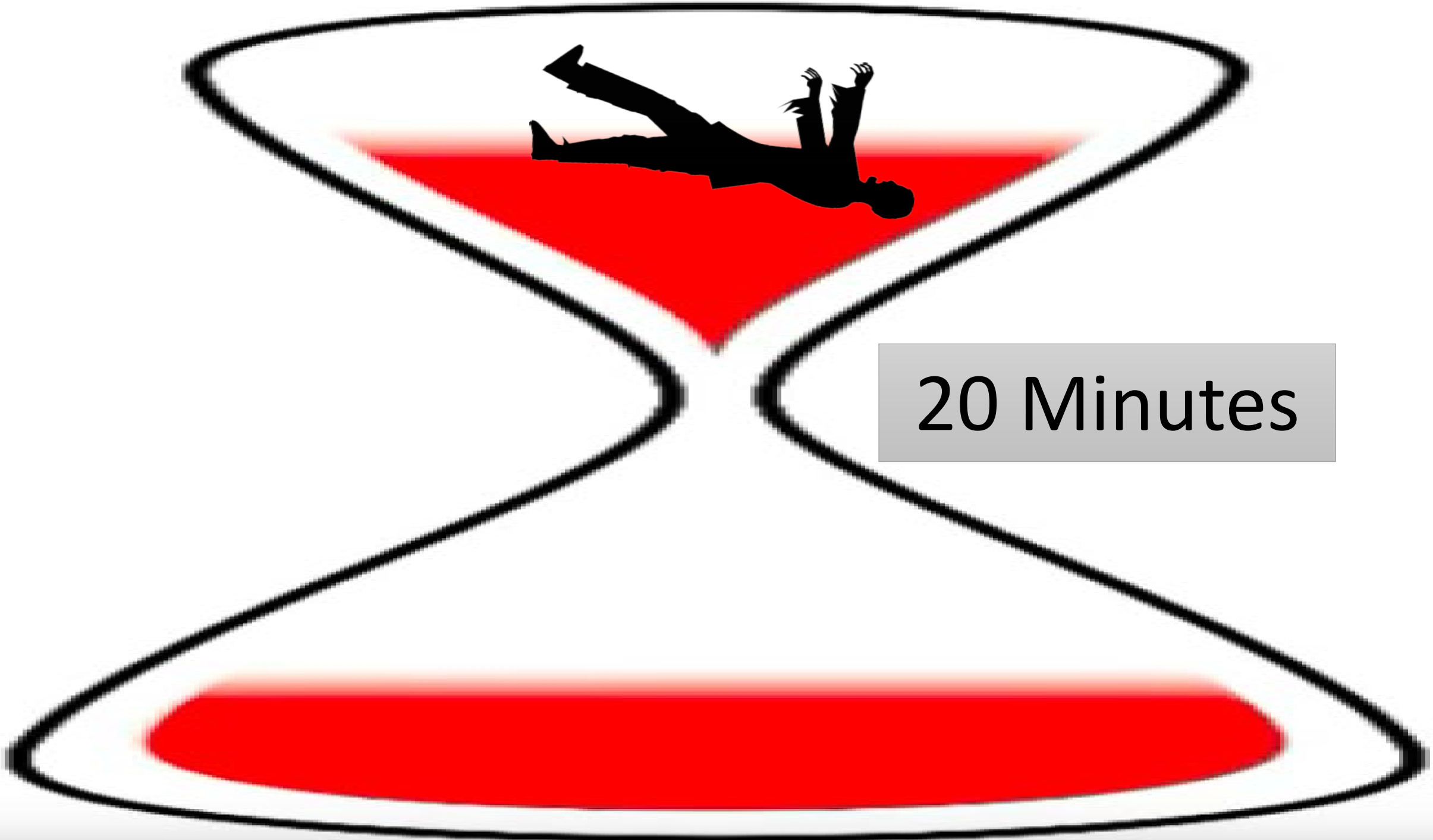
ANESTHESIA & ANALGESIA®

Anesthesia & Analgesia. 118(4):809-817, April 2014.

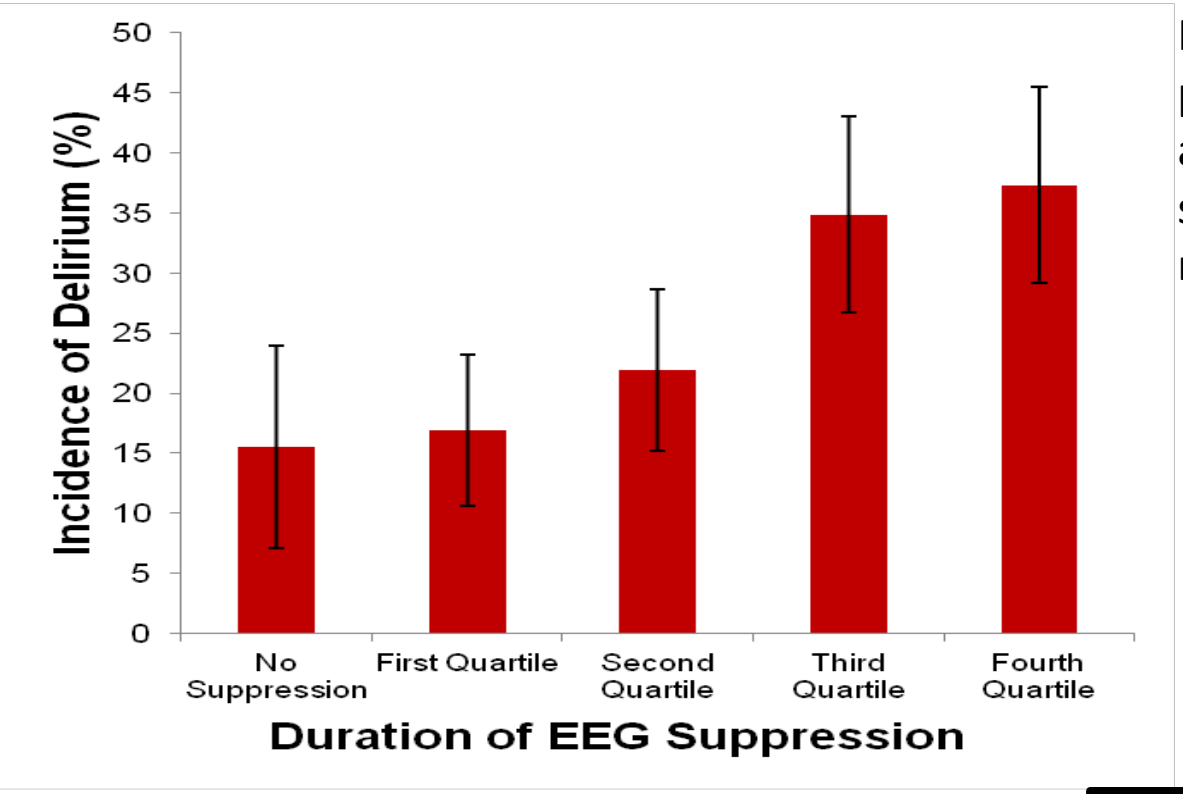
Burst Suppression

With very deep general anesthesia burst suppression occurs, which is characterized by periods of suppression lasting seconds to minutes, punctuated with bursts of high voltage electrical activity over a few seconds.

Ching S et al. PNAS 2012;**109**(8):3095-100.
Lewis LD et al. Brain 2013;**136**(Pt 9):2727-37.


20 Minutes

EEG suppression predicts delirium



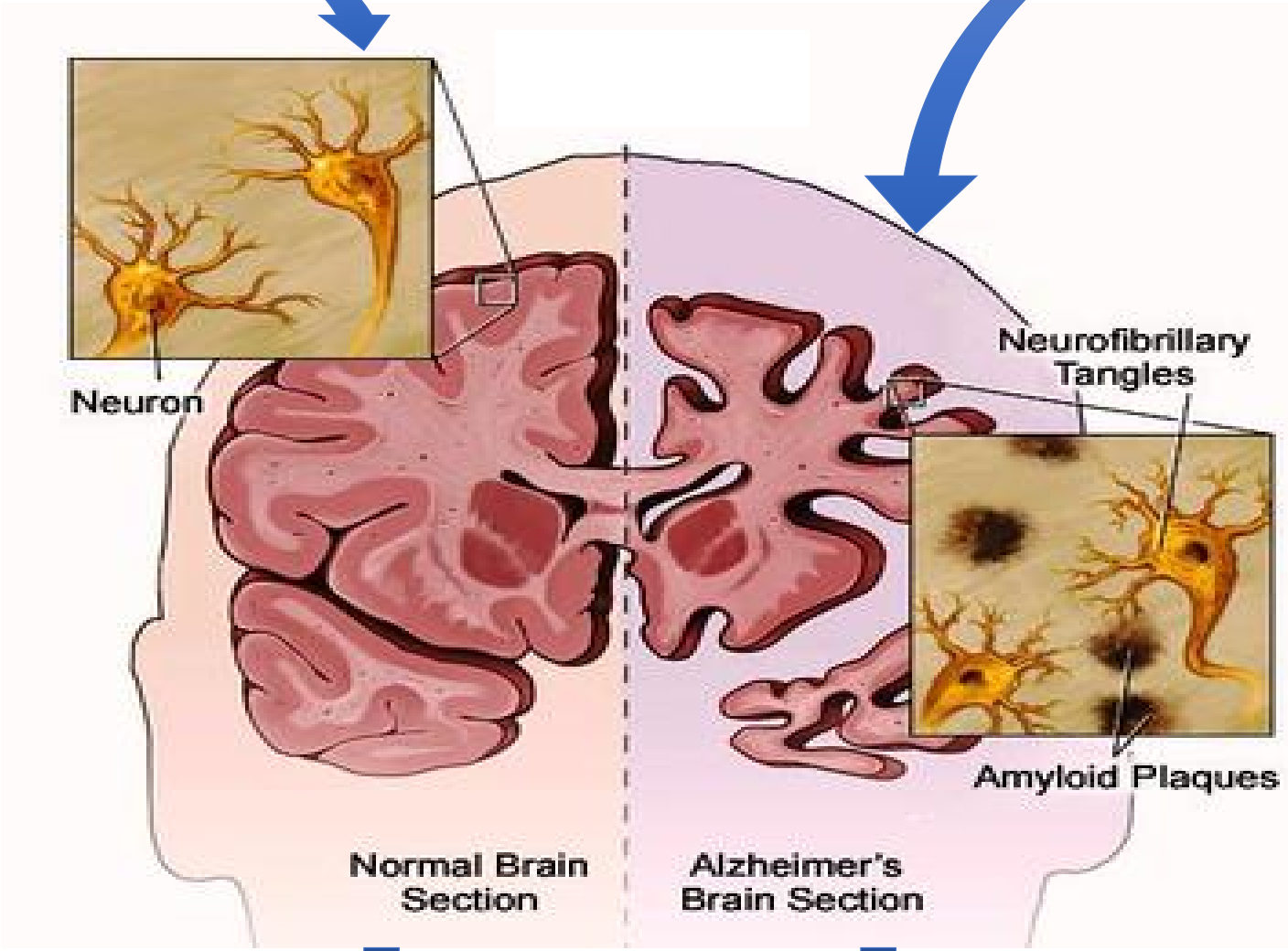
Postoperative delirium was observed in 162 (26%) of 619 patients assessed. Burst suppression predicted delirium after adjusting for potential confounders (odds ratio for log(EEG suppression) 1.22 [99% CI 1.06 to 1.40, p = 0.0002] per 1-minute increase in suppression).

$\chi^2(4) = 25, p < 0.0001$

Anesthesia & Analgesia

Typical Anesthesia: burst suppression is unlikely

Postoperative delirium is unlikely whether or not there was burst suppression



Typical Anesthesia: burst suppression is likely

Postoperative delirium is likely whether or not there was burst suppression

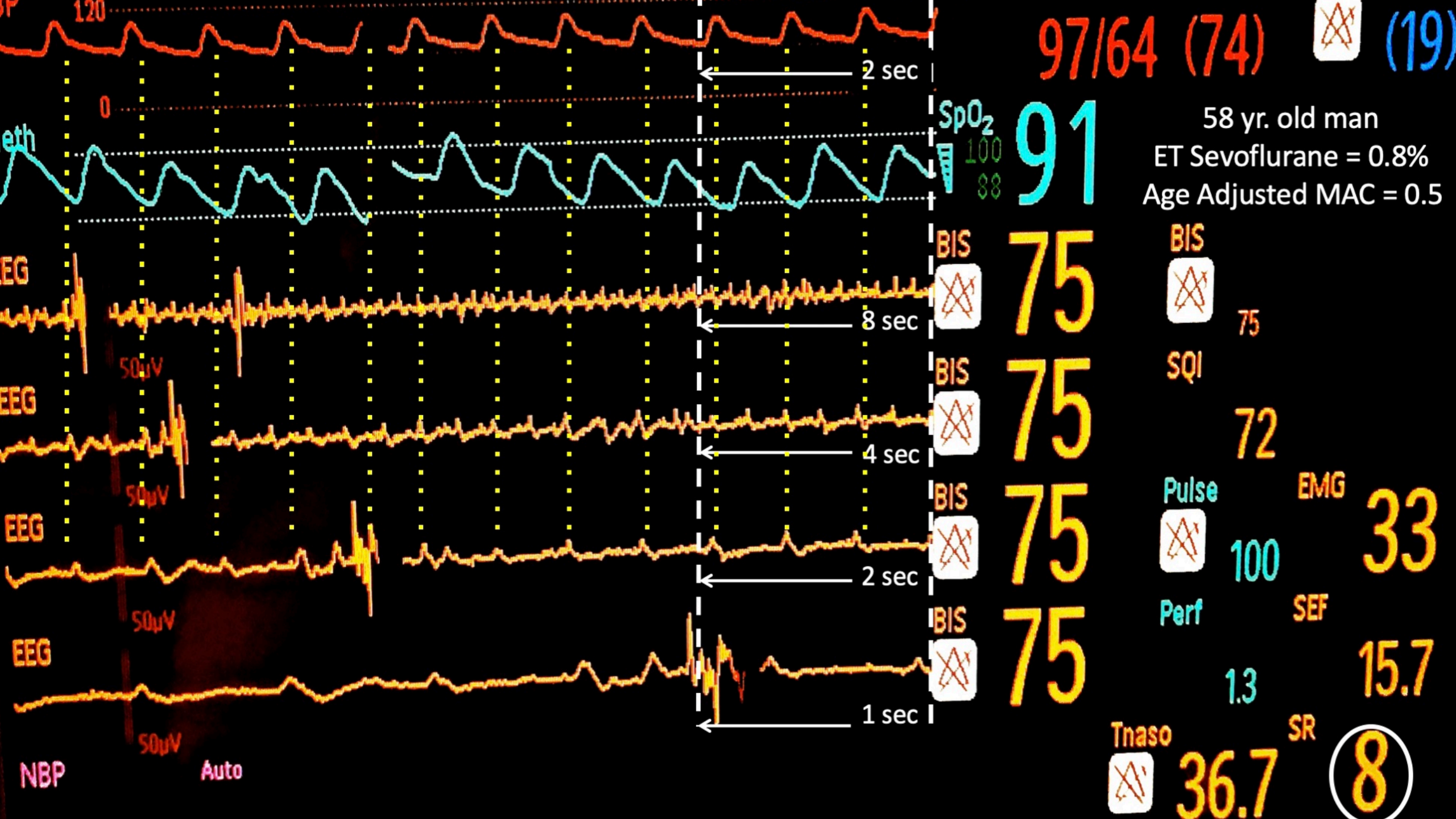
Intraoperative electroencephalogram suppression at lower volatile anaesthetic concentrations predicts postoperative delirium occurring in the intensive care unit

B. A. Fritz*, H. R. Maybrier and M. S. Avidan

Department of Anesthesiology, Washington University School of Medicine in St. Louis, St. Louis, MO, USA

*Corresponding author. E-mail: bafritz@wustl.edu

This article is accompanied by an editorial: Overlapping cognitive disintegration of anaesthesia and delirium by Lindroth & Sanders, *Br J Anesth* 2018:121:193–196, doi: 10.1016/j.bja.2018.01.013.


120
0
eth
2 sec
97/64 (74)
(19)
SpO2
100
88
91
58 yr. old man
ET Sevoflurane = 0.8%
Age Adjusted MAC = 0.5
EEG
50µV
8 sec
BIS
75
BIS
75
SQI
72
EEG
50µV
4 sec
EEG
50µV
2 sec
Pulse
100
EMG
33
Perf
1.3
SEF
15.7
EEG
50µV
1 sec
Tnaso
36.7
SR
8
NBP
Auto

British Journal of Anaesthesia Page 1 of 8
doi:10.1093/bja/aeu105

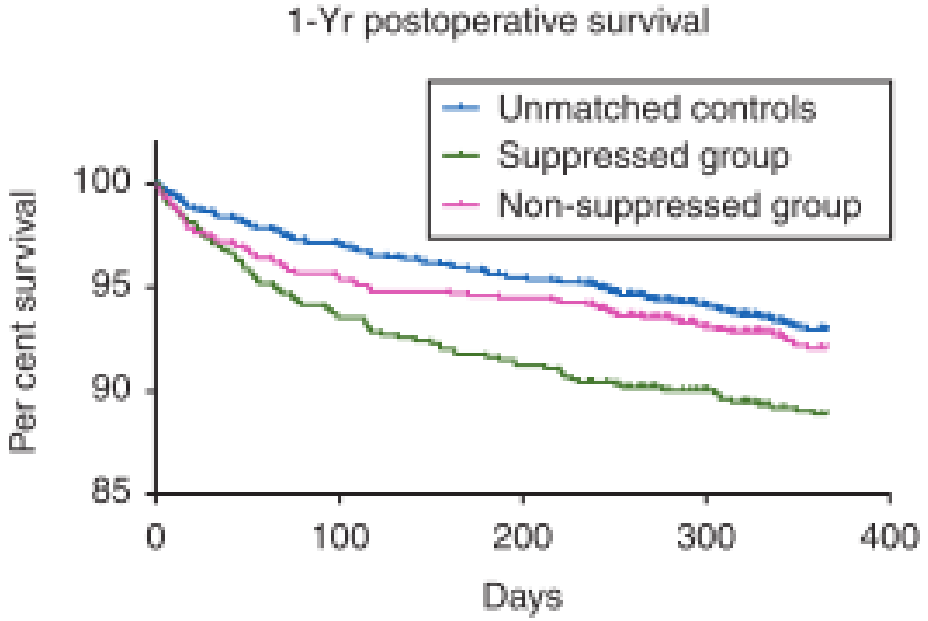
BJA

Association between intraoperative electroencephalographic suppression and postoperative mortality

M. Willingham[1†], A. Ben Abdallah[1], S. Gradwohl[1], D. Helsten[1], N. Lin[2], A. Villafranca[3], E. Jacobsohn[3], M. Avidan[1] and H. Kaiser[1*†]

Time to Mortality (up to 1 yr follow-up)

(Log-Rank Tests)



All patients (prior to matching):

Green curve vs blue curve

Shorter time to death:

Log-Rank $x^2(1) = 14.09$, $p < 0.001$

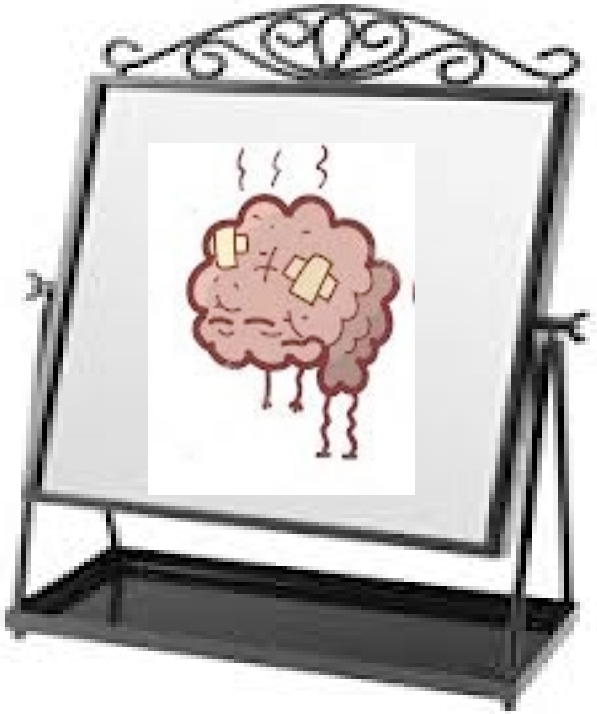
Matched cohorts:

Green curve vs pink curve

No difference:

Log-Rank $x^2(1) = 2.13$, $p = 0.14$

Murderer, Mediator or Mirror?



ENGAGES

Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes Study

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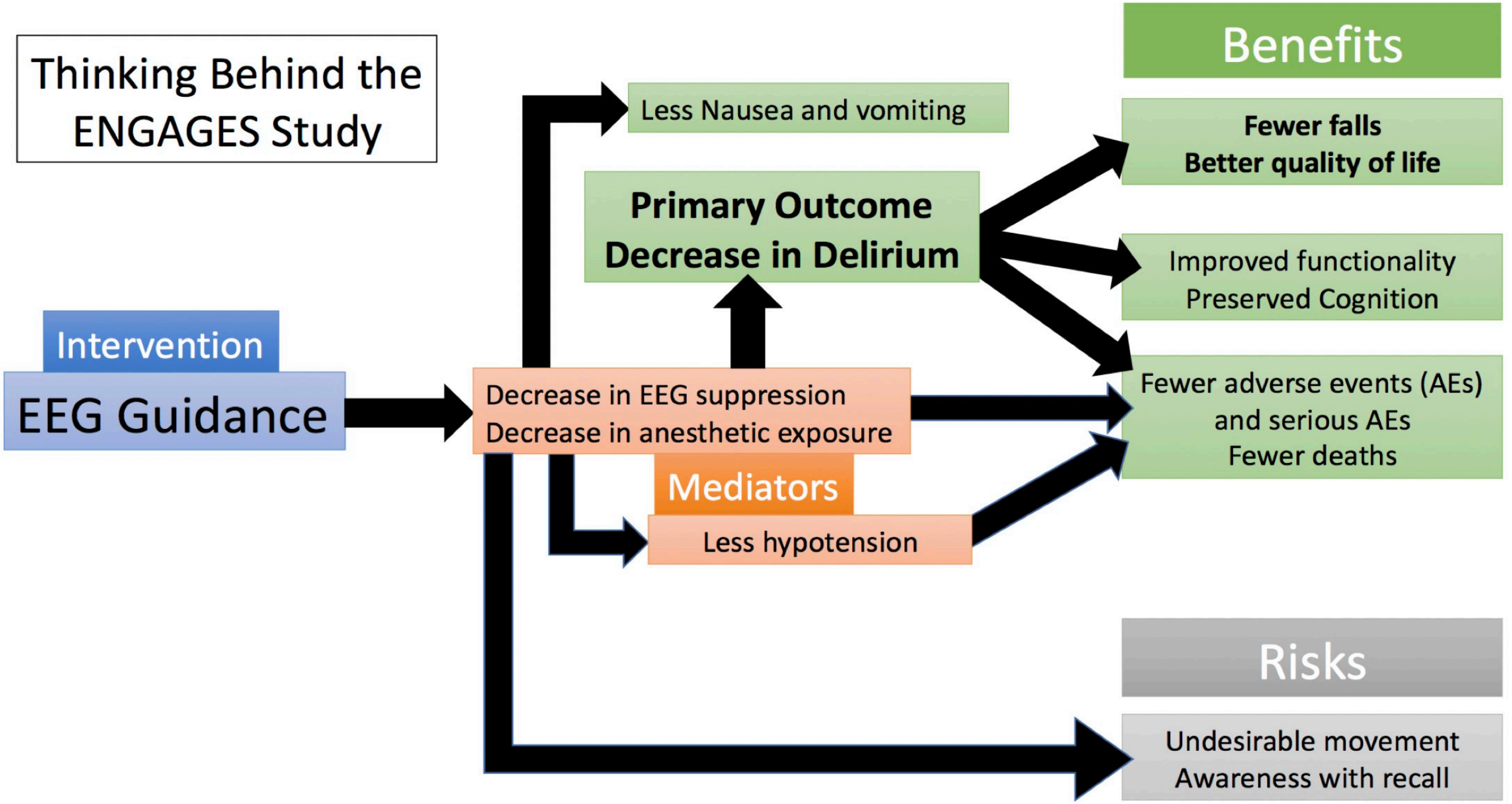
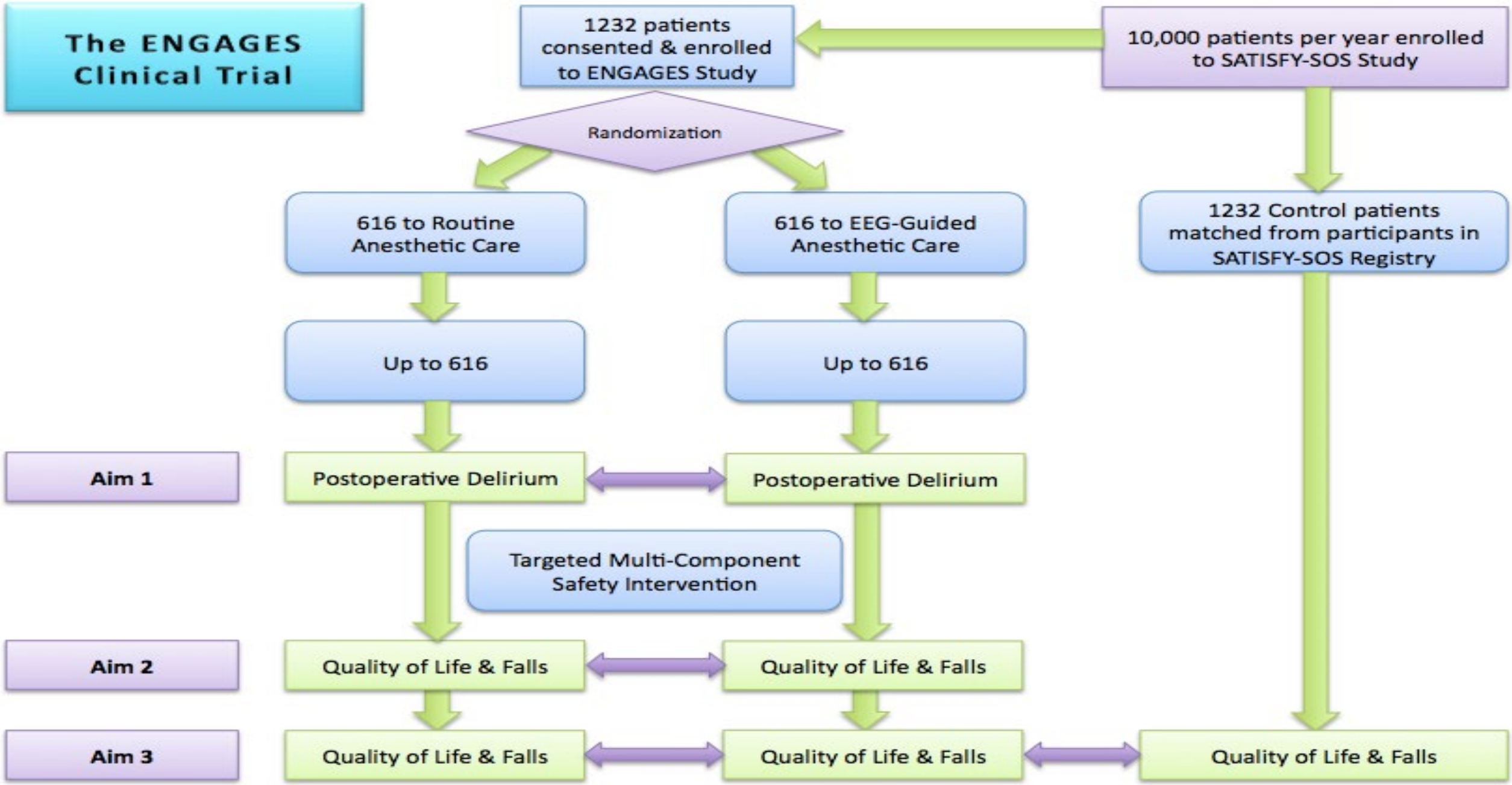
SCHOOL OF MEDICINE

Thinking Behind the ENGAGES Study




The ENGAGES Clinical Trial
1232 patients consented & enrolled to ENGAGES Study
10,000 patients per year enrolled to SATISFY-SOS Study
Randomization
616 to Routine Anesthetic Care
616 to EEG-Guided Anesthetic Care
1232 Control patients matched from participants in SATISFY-SOS Registry
Up to 616
Up to 616
Aim 1
Postoperative Delirium
Postoperative Delirium
Targeted Multi-Component Safety Intervention
Aim 2
Quality of Life & Falls
Quality of Life & Falls
Aim 3
Quality of Life & Falls
Quality of Life & Falls
Quality of Life & Falls

Patient Centered

Outcomes patients care about:

- Delirium
- Falls
- Quality of Life

Active patient involvement:

- Home safety assessment
- Patient self-assessment
- FAM-CAM
- PROs

Efficient

Institute of Quality Improvement Research & Informatics (INQUIRI)

SATISFY

Surgical Outcomes Surveys

TRACKING YOUR HEALTH & WELL-BEING AFTER SURGERY

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BJC HealthCare

Washington University in St. Louis
School of Medicine

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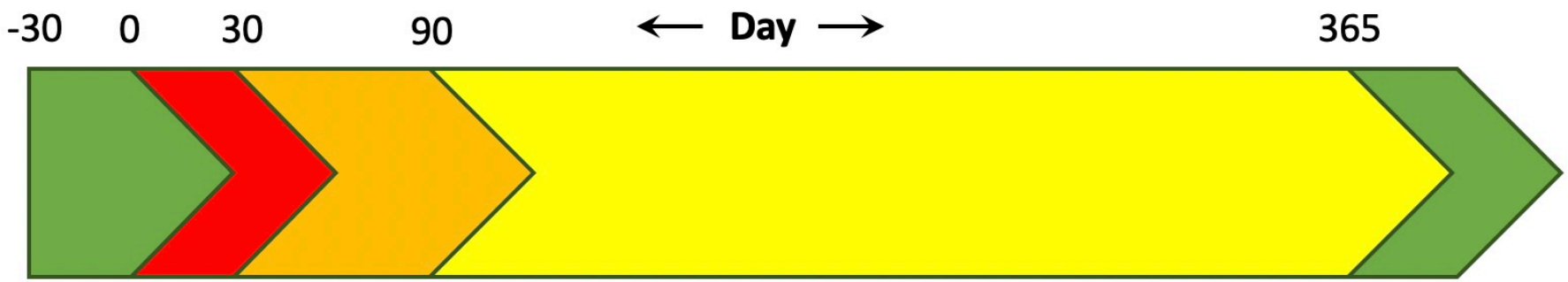
Patient Timeline for SATISFY-SOS

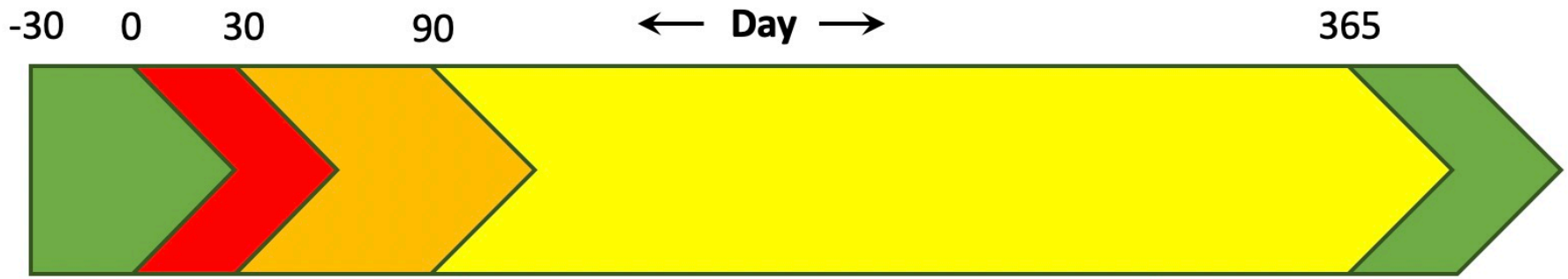


Preoperative clinic

Detailed History	Recruitment and consent
Extensive Co-morbidities	Baseline Quality of Life (VR-12)
Physical Examination	Employment Status
Special Investigations	Falls History
Baseline Pain	Pain (current and expectations)
Dementia Screen	Motivation for surgery
Functional dependence	

Helsten et al. Anesthesiology. 2016. 125: 495.

Patient Timeline for SATISFY-SOS

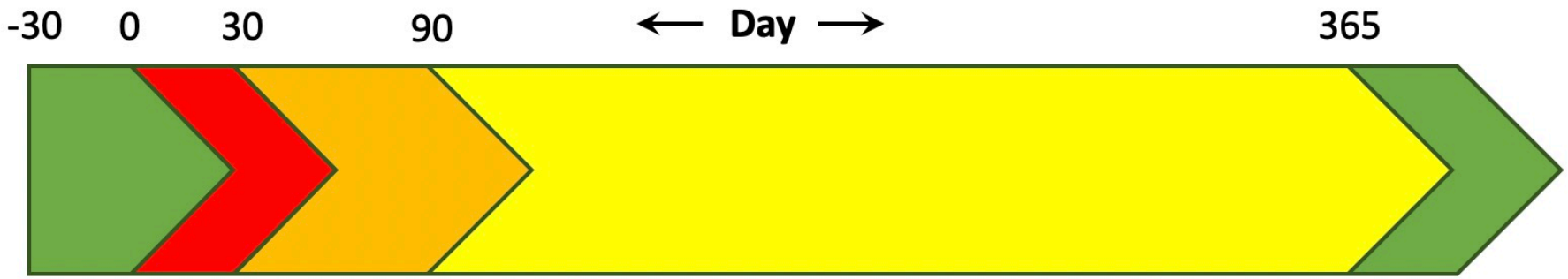


Intra-op and In-hospital

Detailed intraoperative records
Data from EMRs for inpatient care and complications

Helsten et al. Anesthesiology. 2016. 125: 495.

Patient Timeline for SATISFY-SOS



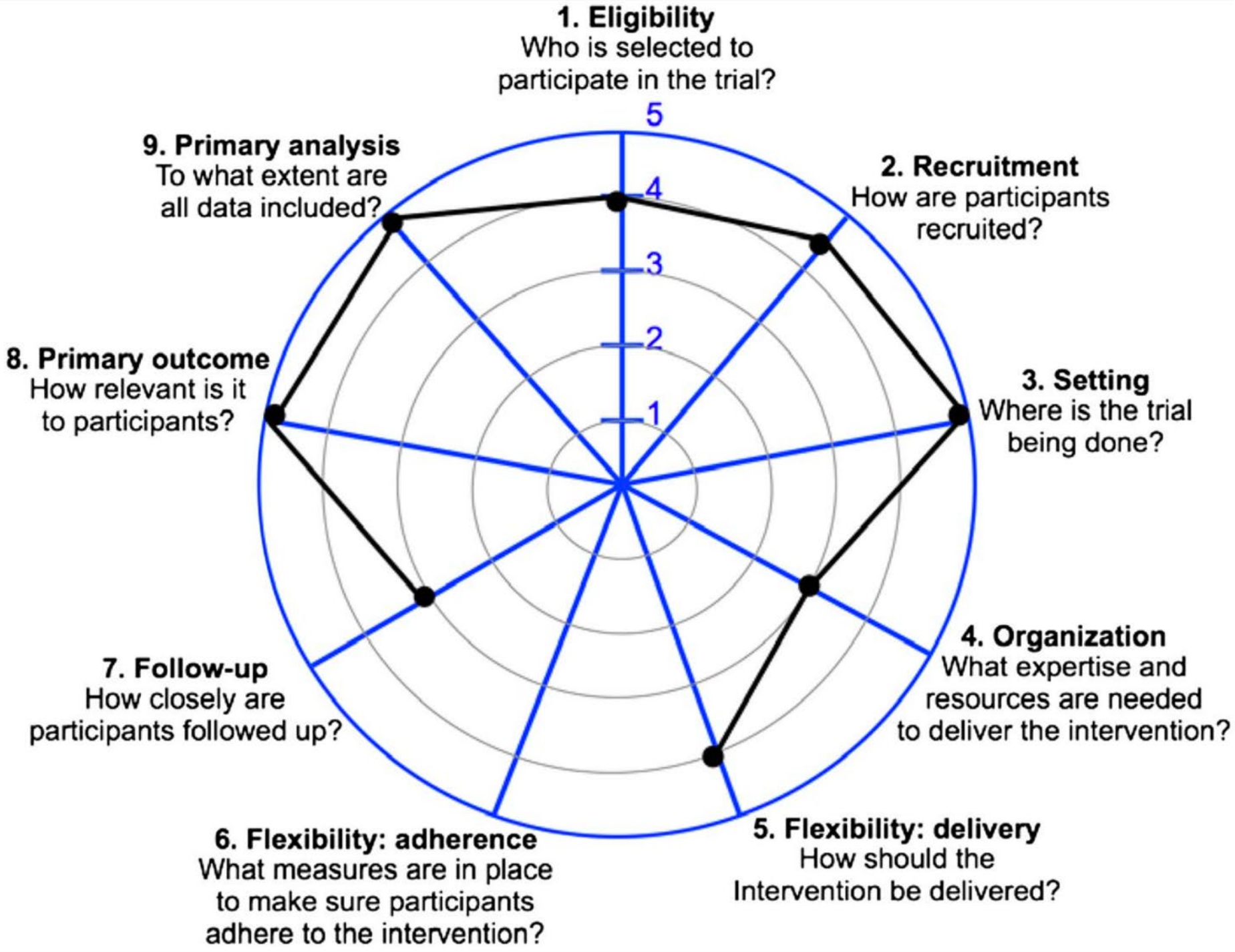
Post-operative PROs (30-90 day & 1 year)

x 3,
✉ x 2,
☎ x 5

- Subjective perceptions
- Quality of Life
- Pain
- Independent function
- Return to work
- Intraoperative awareness
- Subjective cognition
- In-hospital complications (NSQIP-inspired)
- Post discharge complications (NSQIP-inspired)
- Falls & injurious falls

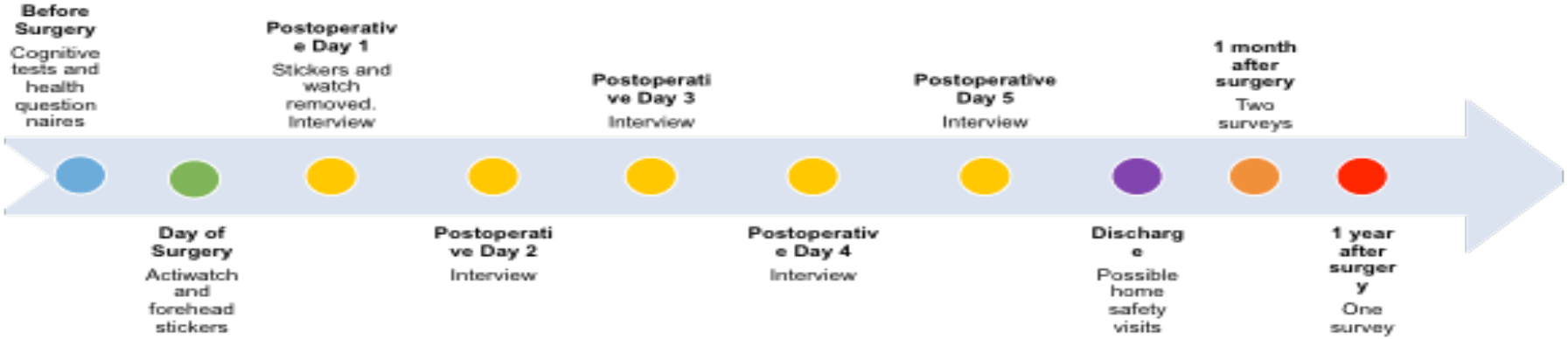
Helsten et al. Anesthesiology. 2016. 125: 495.

BMJ Open



BMJ Open. 2016 Jun 15;6(6):e011505.

ENGAGES Trial Participation Schedule



	Timeframe	What to expect
Before Surgery	At least one day before surgery (60-90 min)	An ENGAGES researcher will ask you a series of questions about your health.
Day of Surgery	Just before surgery Between 4 PM and 8 PM (10 min)	An ENGAGES researcher will place stickers on your forehead and a watch on your wrist before surgery. You may or may not be awake. A researcher will visit you after surgery to ask questions about your thinking and pain.
Postoperative Days One to Five	Between 4 PM and 8 PM (10 min)	An ENGAGES researcher will visit you in the hospital and ask questions about how you are thinking and your pain.
Discharge	After you leave the hospital (2 or 3 visits lasting one hour each)	Occupational therapy might visit your home and suggest changes to reduce your risk of falls.
One month after surgery	Around 30 days after surgery (2 surveys lasting 15 min each)	You will receive two surveys. One will be given over the phone with an ENGAGES researcher. Another will be given as part of the SATISFY-SOS study by phone, mail, or email.
One year after surgery	Around one year after surgery (10 min)	You will receive one SATISFY-SOS survey by phone, mail, or email.

Challenges

- Representative enrollment
- Baseline Assessment
- Altering anesthetic management
- Avoiding trial-related temporal change in practice
- Home safety intervention

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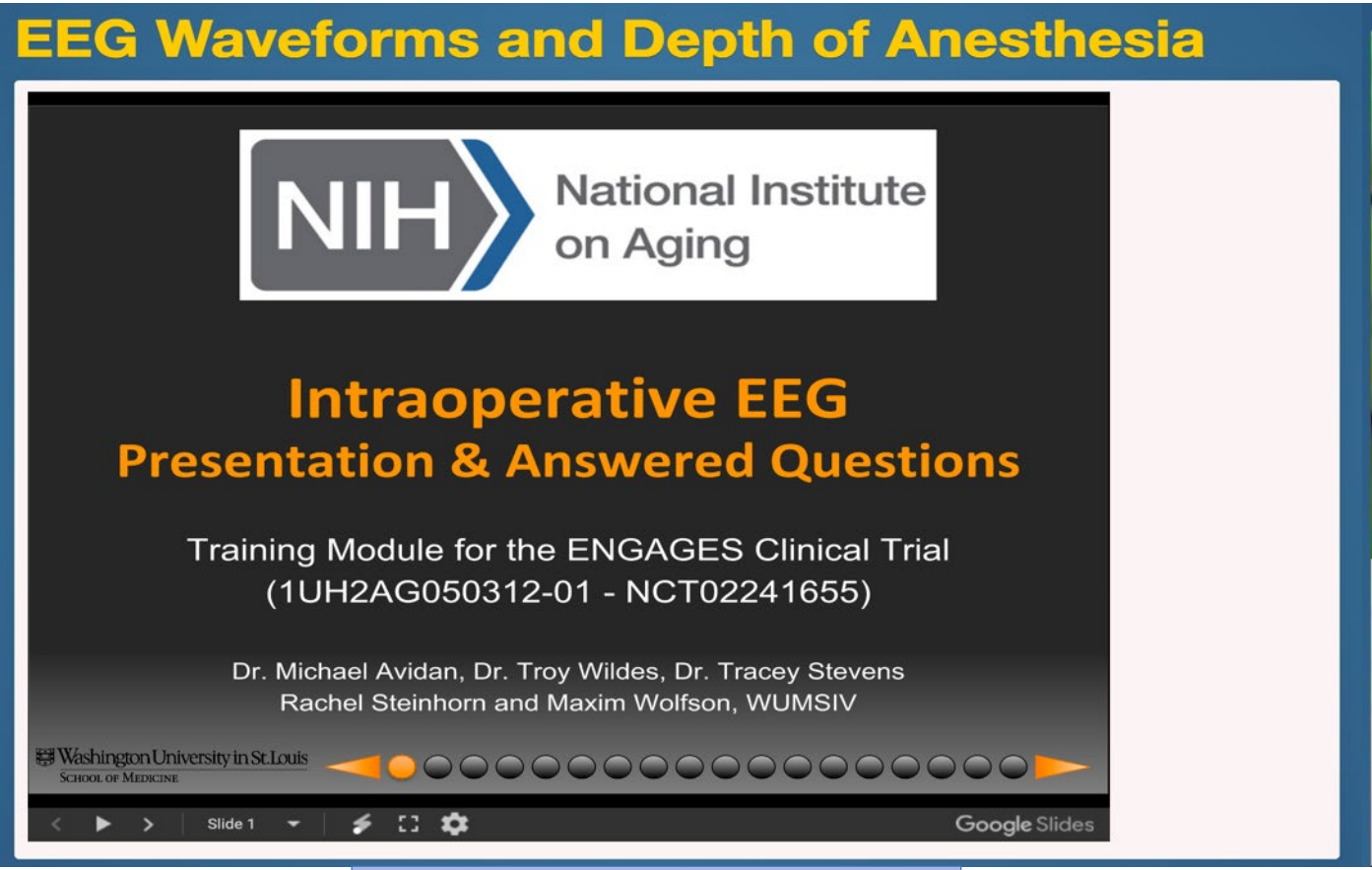
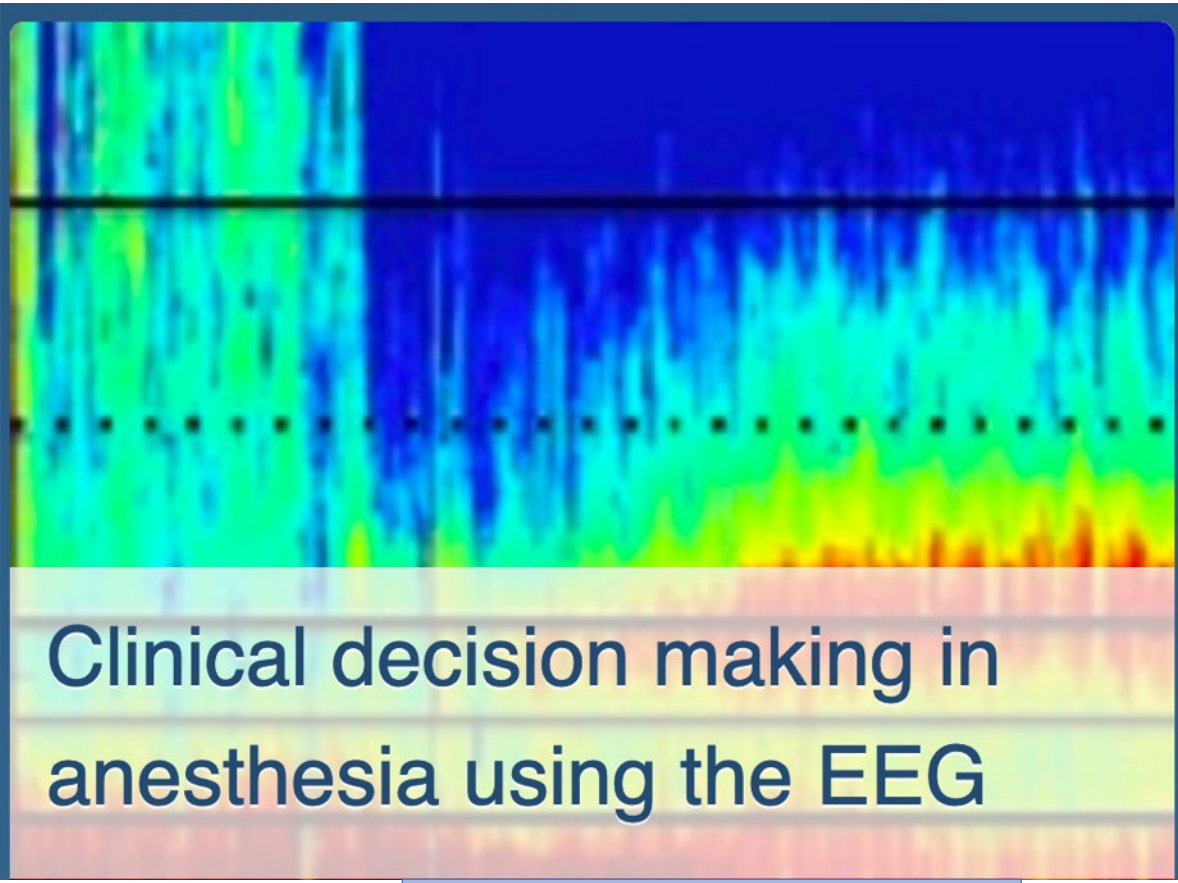
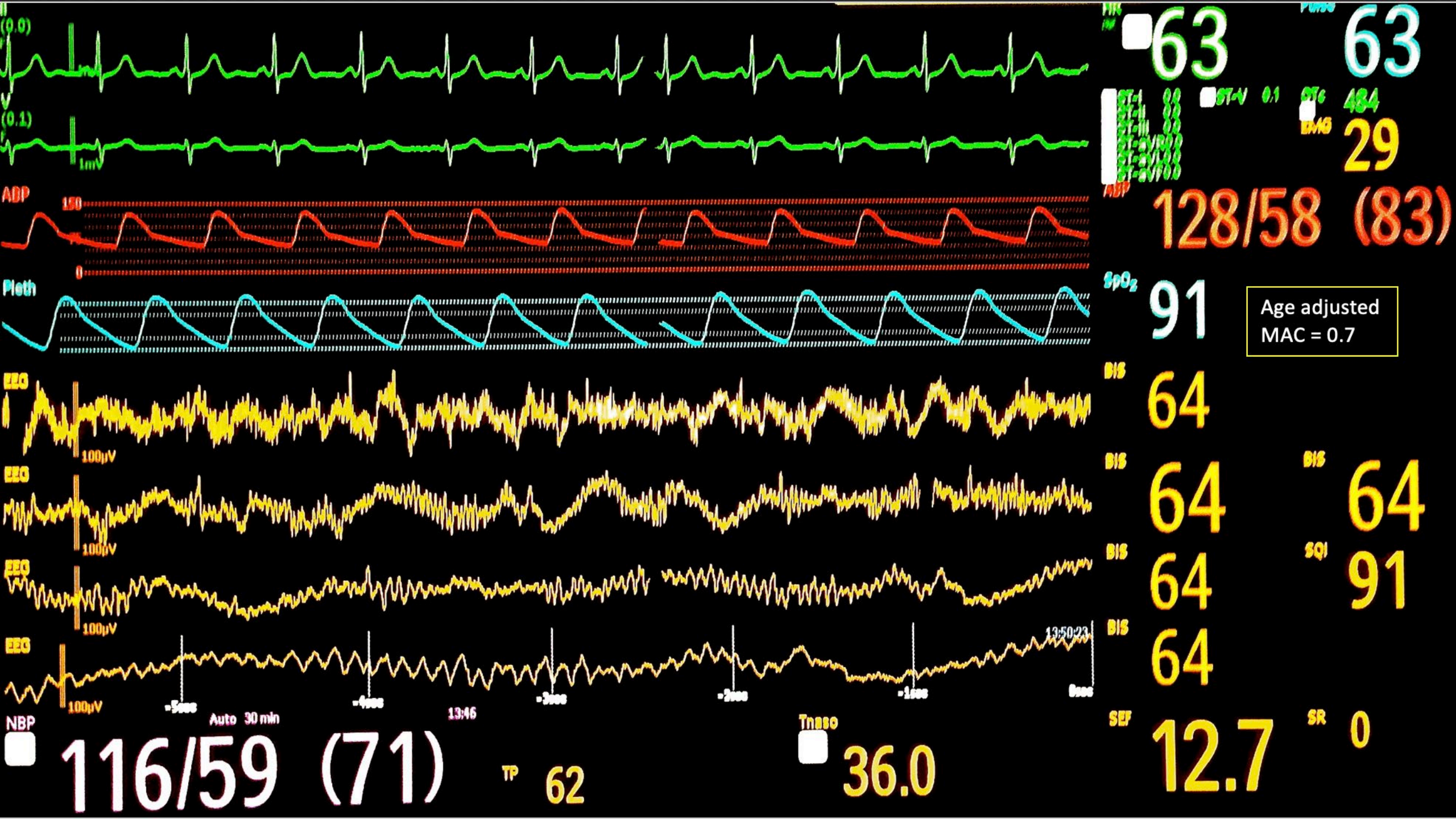


>3,000 Views



>5,000 Views


63
63
ST-I
ST-II
ST-III
ST-aVR
ST-aVL
ST-aVF
ST-V
0.1
STc
484
EMG
29
ADP
150
0
128/58 (83)
Pleth
SpO2
91
Age adjusted
MAC = 0.7
EEG
100µV
BIS
64
BIS
64
BIS
64
SQI
91
BIS
64
13:50:23
-5sec
-4sec
-3sec
-2sec
-1sec
0sec
NBP
Auto 30 min
13:46
116/59 (71)
TP
62
Tnasp
36.0
SEF
12.7
SR
0


SpO2 LOW PERF
II
F
1mV
V
F
1mV
ABP
180
90
0
EEG
50µV
EEG
50µV
EEG
50µV
EEG
50µV
BIS
100
80
60
40
20
0
90min
60min
30min
NBP
Auto
HR
0
?Pulse
150
QTc
-?-
ST-I -?-
ST-II -?-
ST-III -?-
ST-aVF -?-
?SpO2
98
PAP
9/6
(7)
ABP
63/59
(61)
BIS
25
BIS
25
SvO2 -?-
BIS
25
C.O.
C.I.
BIS
25
Tblood 33.3
BIS
25
SR 35
SEF 14.5
SQI 94
EMG 25
TP 60
Temp 33.7

Less anesthesia during surgery doesn't prevent post-op delirium

The National Institute on Aging funded ENGAGES trial reported in JAMA that electroencephalography guided general anesthesia does not appear to prevent postoperative delirium.

Read More

See All News...

31st Annual C. R. Stephen Lecture will be delivered by John P.A. Ioannidis, M.D., DSc

Less anesthesia during surgery doesn't prevent post-op delirium

Dr. Robert Gereau honored With Election as Fellow into AAAS

Cox named Wise Endowed Chair in Pediatric Anesthesiology

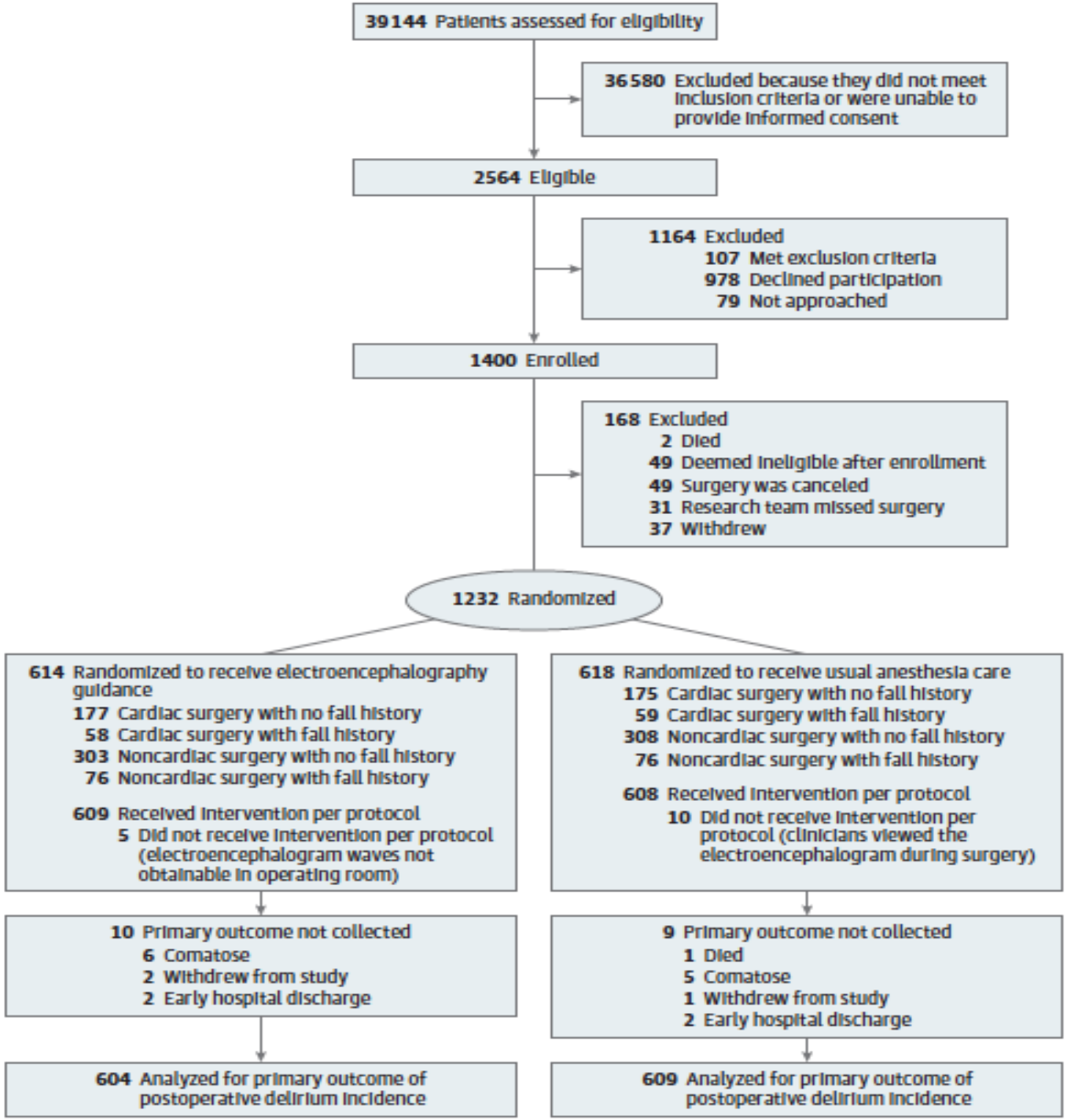

39144 Patients assessed for eligibility
36580 Excluded because they did not meet inclusion criteria or were unable to provide informed consent
2564 Eligible
1164 Excluded
107 Met exclusion criteria
978 Declined participation
79 Not approached
1400 Enrolled
168 Excluded
2 Died
49 Deemed ineligible after enrollment
49 Surgery was canceled
31 Research team missed surgery
37 Withdrew
1232 Randomized
614 Randomized to receive electroencephalography guidance
177 Cardiac surgery with no fall history
58 Cardiac surgery with fall history
303 Noncardiac surgery with no fall history
76 Noncardiac surgery with fall history
609 Received intervention per protocol
5 Did not receive intervention per protocol (electroencephalogram waves not obtainable in operating room)
618 Randomized to receive usual anesthesia care
175 Cardiac surgery with no fall history
59 Cardiac surgery with fall history
308 Noncardiac surgery with no fall history
76 Noncardiac surgery with fall history
608 Received intervention per protocol
10 Did not receive intervention per protocol (clinicians viewed the electroencephalogram during surgery)
10 Primary outcome not collected
6 Comatose
2 Withdrew from study
2 Early hospital discharge
9 Primary outcome not collected
1 Died
5 Comatose
1 Withdrew from study
2 Early hospital discharge
604 Analyzed for primary outcome of postoperative delirium incidence
609 Analyzed for primary outcome of postoperative delirium incidence

Table 1. Preoperative Patient Characteristics

	No. (%)	
	Guided (n = 614)	Usual Care (n = 618)
Age, median (IQR), y	69.5 (65.0-74.7)	69.4 (64.7-75.8)
Women	282 (45.9)	281 (45.5)
Men	332 (54.1)	337 (54.5)
BMI, median (IQR)	29.0 (25-33)	29.0 (25-33)
Race		
White	555 (90.4)	558 (90.3)
Black	54 (8.8)	53 (8.6)
Other	5 (0.8)	7 (1.1)
Attended college	198 (36.3)	208 (37.3)
Lifetime tobacco use[a]	376 (61.2)	349 (56.8)
Current weekly alcohol use[b]	289 (47.1)	297 (48.1)
Current use of anticonvulsants	94 (15.3)	81 (13.1)
Regular use of opioids	154 (25.1)	149 (24.1)
Regular use of benzodiazepines	86 (14.0)	102 (16.5)
ASA physical classification >3[c]	209 (34.0)	221 (35.8)
Marginal exercise tolerance (<4 METs)	297 (50.3)	295 (50.4)
Pulmonary hypertension	97 (15.8)	95 (15.4)
Aortic stenosis	90 (14.7)	108 (17.5)
History of or high risk for obstructive sleep apnea	230 (37.5)	219 (35.4)
History of delirium	78 (12.8)	79 (12.9)
No. of comorbidities, median (IQR)	5 (3-6)	5 (3-6)
History of depression	85 (13.8)	83 (13.4)
PHQ8, median (IQR)[d]	3 (1-6)	3 (0-6)
Short Blessed Test for cognition score, median (IQR)[e]	2 (0-4)	2 (0-4)
8-item Interview to Differentiate Aging and Dementia, median (IQR)[f]	0 (0-1)	0 (0-1)
Barthel Activities of Daily Living index, median (IQR)[g]	15 (15-15)	15 (15-15)
Handgrip strength score, mean (SD), kg	26.4 (11.0)	25.7 (10.7)
Timed up-and-go score, median (IQR), s	10.5 (9.2-13.1)	11.0 (9.4-13.4)
Lawton Instrumental Activities of Daily Living, median (IQR)[h]	8 (7-8)	8 (8-8)
VR-12 Component Score, mean (SD)[i]		
Physical	38.1 (11.9)	38.2 (11.8)
Mental	53.6 (10.6)	53.6 (11.0)

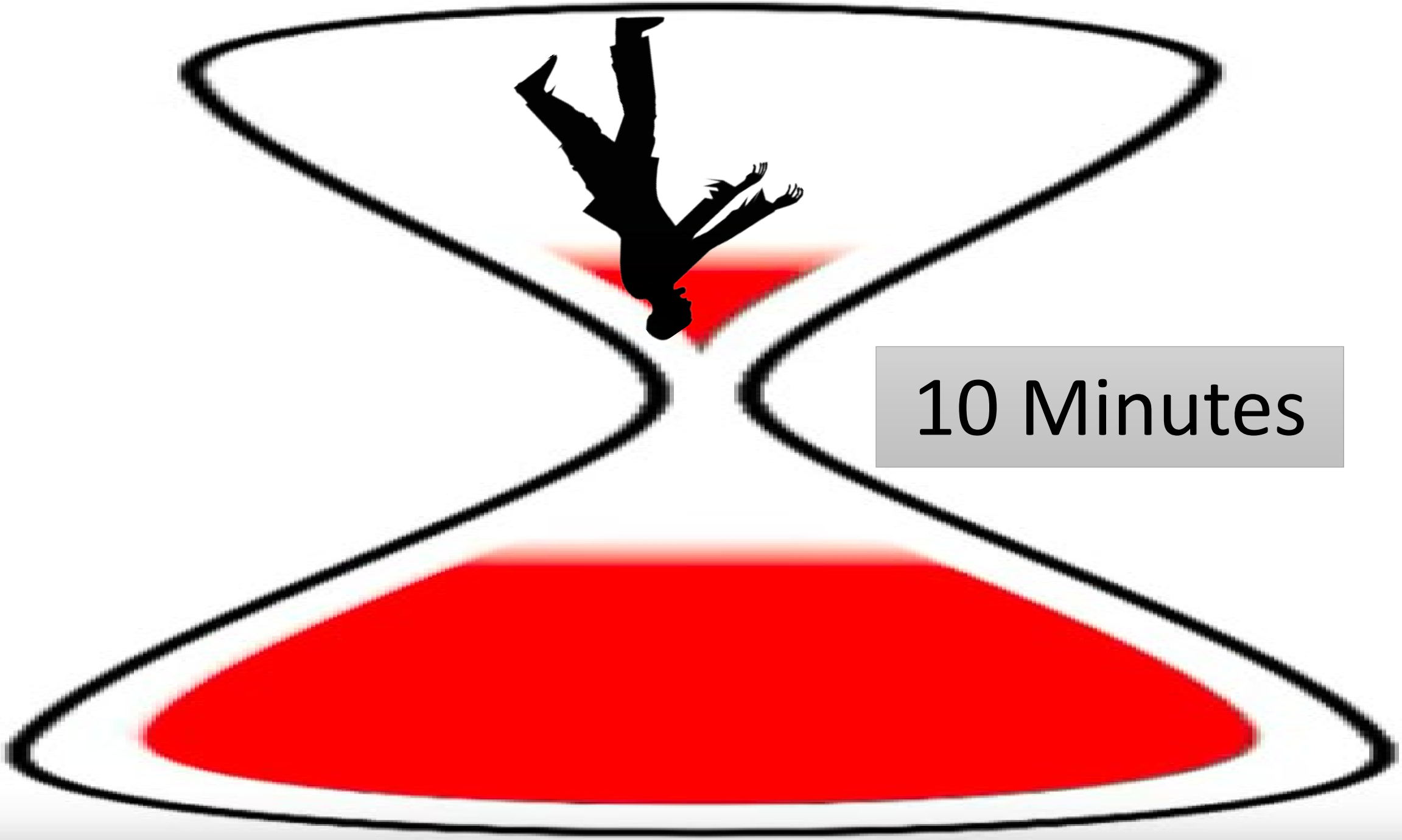
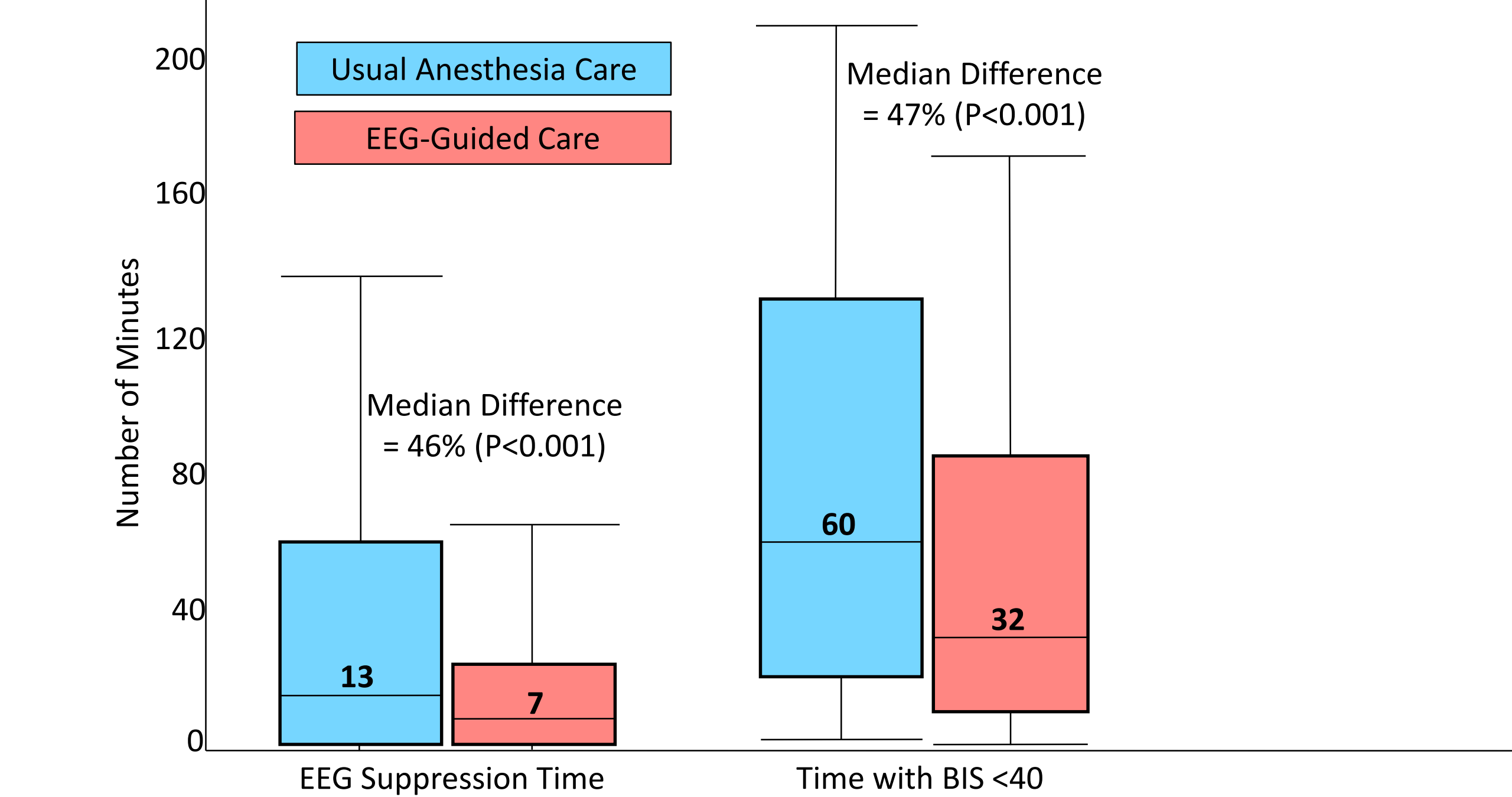
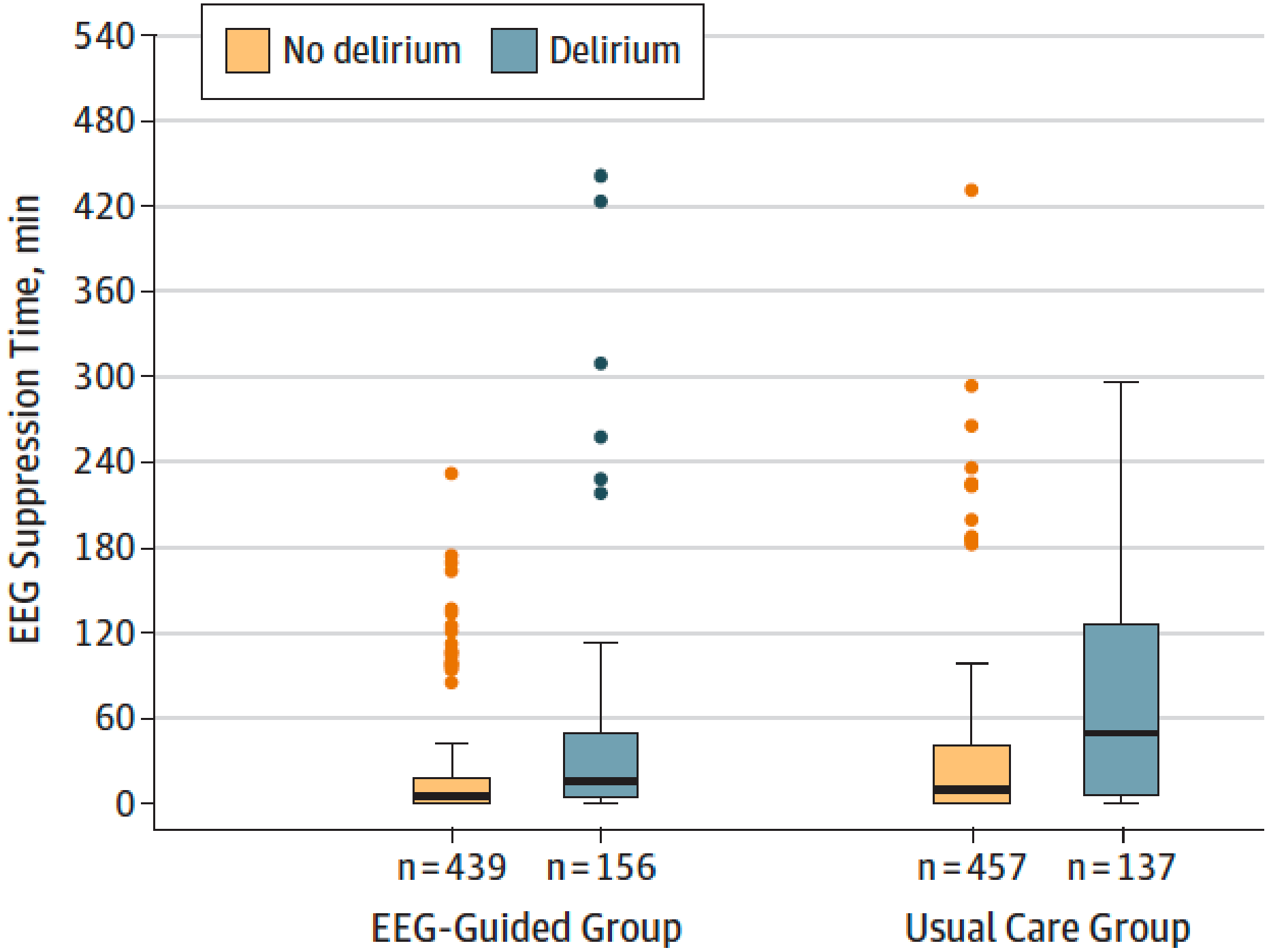

10 Minutes

Table 2. Perioperative Care Measures

Measure	Median (IQR)		Difference (95% CI)[a]
	Guided	Usual Care	
Intraoperative measures			
Duration of anesthesia, min	264.5 (192 to 344)	264.0 (186 to 349)	0.5 (−16.7 to 16.7)
End-tidal volatile agent concentration, MAC[d]	0.69 (0.62 to 0.77)	0.80 (0.71 to 0.86)	−0.11 (−0.13 to −0.10)
Duration of BIS <40, min[e]	32 (9 to 81)	60 (19 to 132)	−28 (−38.0 to −18.0)
Time with SR >1%, min[f]	7 (1 to 23)	13 (2 to 58)	−6 (−9.9 to −2.1)
MAP, mean (SD), mm Hg	81.2 (8.26)	79.6 (7.68)	1.5 (0.63 to 2.42)
Duration of MAP <60 mm Hg, min	7 (2 to 19)	7 (1 to 19)	0 (−1.7 to 1.7)


Usual Anesthesia Care
EEG-Guided Care
Number of Minutes
200
160
120
80
40
0
Median Difference
= 46% (P<0.001)
Median Difference
= 47% (P<0.001)
13
7
60
32
EEG Suppression Time
Time with BIS <40


No delirium
Delirium
EEG Suppression Time, min
540
480
420
360
300
240
180
120
60
0
n = 439
n = 156
n = 457
n = 137
EEG-Guided Group
Usual Care Group

Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES Randomized Clinical Trial

JAMA Network™

QUESTION Does EEG-guided anesthetic administration decrease postoperative delirium incidence in older patients undergoing major surgery?

CONCLUSION This randomized clinical trial of older adults undergoing major surgery found that EEG-guided anesthetic did not reduce the incidence of postoperative delirium.

POPULATION

669 Men
563 Women

Adults aged ≥60 years undergoing major surgery under general anesthesia

Median age: 69 years

LOCATIONS

1
Hospital in St Louis, MO

INTERVENTION

1232 Patients randomized

614
EEG-guided anesthesia
Anesthesiologists and nurse anesthetists viewed display of EEG waveforms of anesthetic depth

618
Usual anesthesia
Anesthesiologists and nurse anesthetists blinded to EEG waveforms of anesthetic depth

PRIMARY OUTCOME

Incidence of delirium during postoperative days 1 to 5 as assessed by validated instruments or through chart review

FINDINGS

Delirium during postoperative days 1 to 5

EEG-guided anesthesia
Delirium occurred in 157 of 604 patients

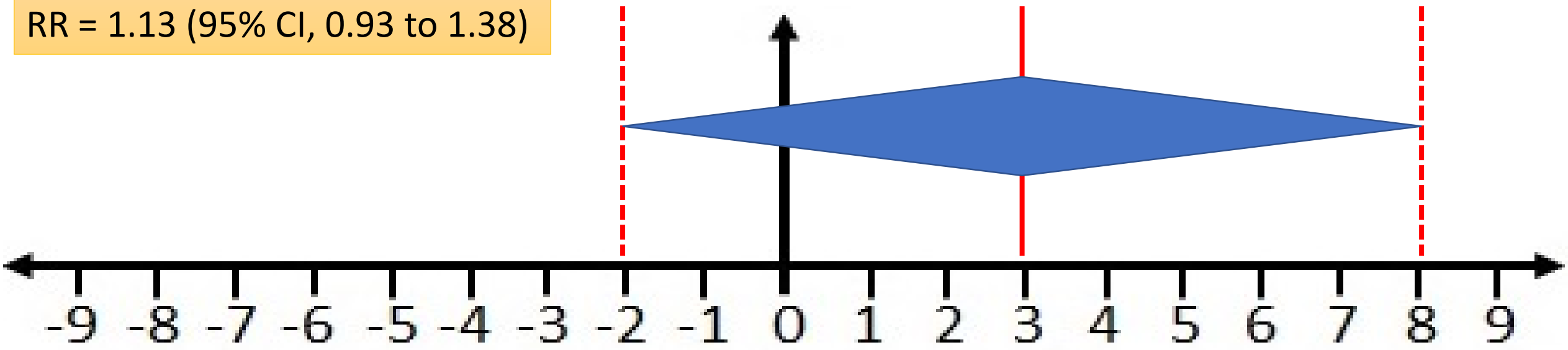
Usual anesthesia
Delirium occurred in 140 of 609 patients

Between-group difference:
3.0% (95% CI, -2.0% to 8.0%)

Wildes TS, Mickle AM, Abdallah AB, et al, for the ENGAGES research group. Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial [published February 5, 2019]. *JAMA*. doi:10.1001/jama.2018.22005

Outcome Category	Usual Care Group	EEG Guided Group	Difference¥ (95% CI)	P value§
Delirium Outcomes				
Delirium incidence* – no. (%)	140/609 (23.0)	157/604 (26.0)	3.0% (-2.0 to 8.0)	0.224

OR = 1.18 (95% CI, 0.91 to 1.53)
RR = 1.13 (95% CI, 0.93 to 1.38)

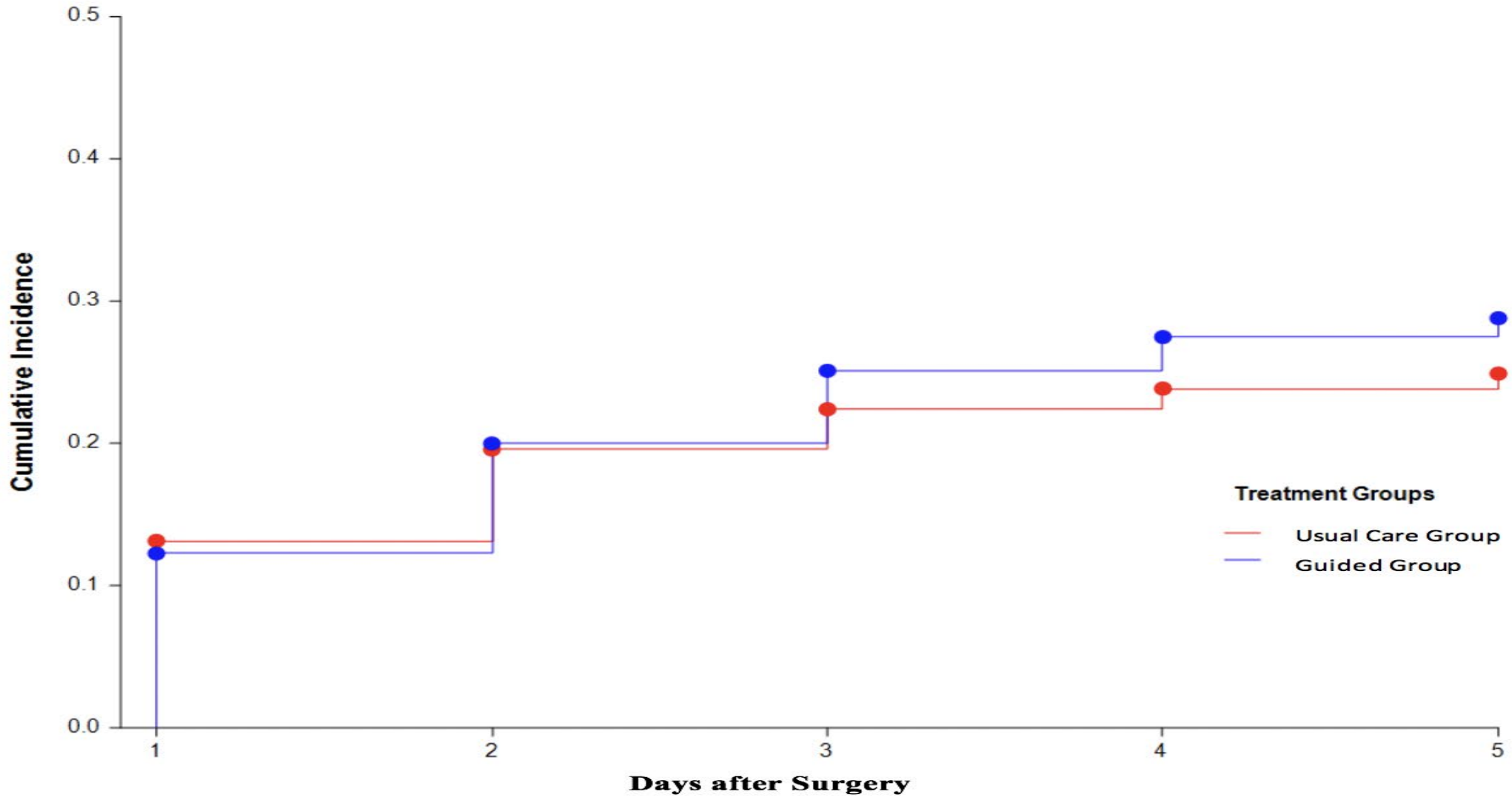


EEG Guidance is Good

EEG Guidance is Bad

eFigure5: Kaplan-Meier Curve: Cumulative Incidence of Delirium

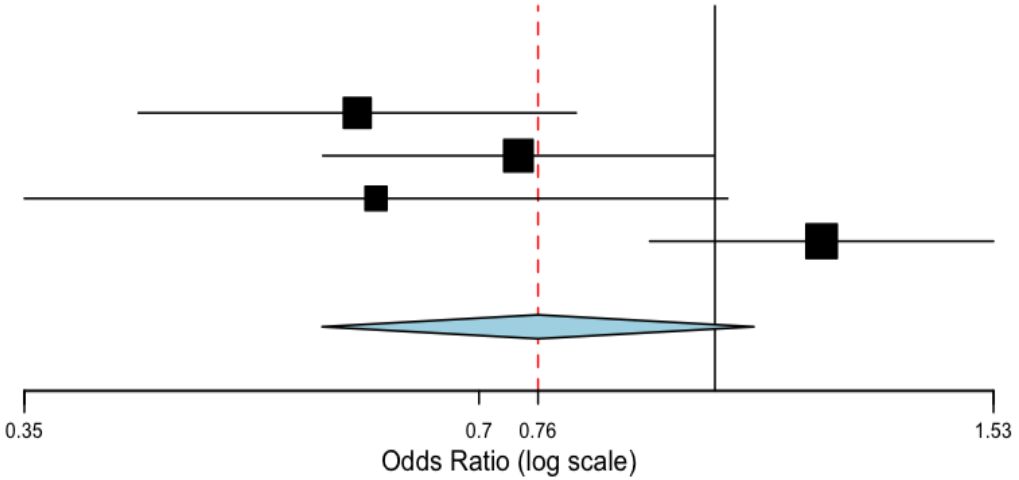
Kaplan-Meier curves showing cumulative incidence of delirium incidence over postoperative days 1 to 5, by treatment groups.



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

Meta-analysis summarizing 4 trials in which the intervention group received EEG-guided anesthesia

Study	Estimate (95% C.I.)	Delirium Guided	Delirium Usual Care
CODA 2013	0.580 (0.415, 0.809)	70/450	109/452
SuDoCo-PP 2013	0.741 (0.550, 0.999)	123/716	96/439
BAG-RECALL 2014	0.597 (0.349, 1.020)	28/149	45/161
ENGAGES 2019	1.177 (0.905, 1.529)	157/604	140/609
Overall (I^2=7351 % , P=0.004)	**0.764 (0.549, 1.061)**	**378/1919**	**390/1661**



This analysis was conducted using OpenMetaAnalyst. It is a binary, random effects, Hartung-Knapp-Sidik-Jonkman model.

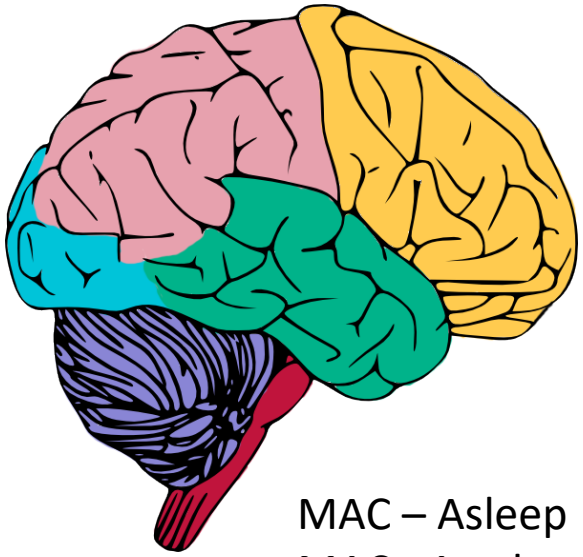
The I^2 = 74%, tau^2 = 0.08, Q(df=3) = 13.234, and heterogeneity *P*-value = 0.004.

The estimated OR for delirium with EEG-guided anesthesia = 0.764 (95% CI, 0.549 to 1.061, *P*=0.108).

Table 3. Primary and Exploratory Outcomes and Adverse Events

Outcome Category	No./Total No. (%)		Difference, % (95% CI)[a]	*P* Value[b]
	Guided	Usual Care		
Adverse events				
Undesirable intraoperative movement	137/614 (22.3)	95/618 (15.4)	6.9 (2.5 to 11.4)	.002
Intraoperative awareness	0/563 (0.0)	0/568 (0.0)	0 (−0.8 to 0.8)	NA
Postoperative nausea and vomiting	48/614 (7.8)	55/617(8.9)	−1.1 (−4.3 to 2.1)	.49
Perioperative serious adverse events[g]	124/614 (20.2)	130/618 (21.0)	−0.8 (−5.5 to 3.8)	.72
Mortality up to 30 days after surgical procedure	4/614 (0.7)	19/618 (3.1)	−2.42 (−4.3 to −0.8)	.004

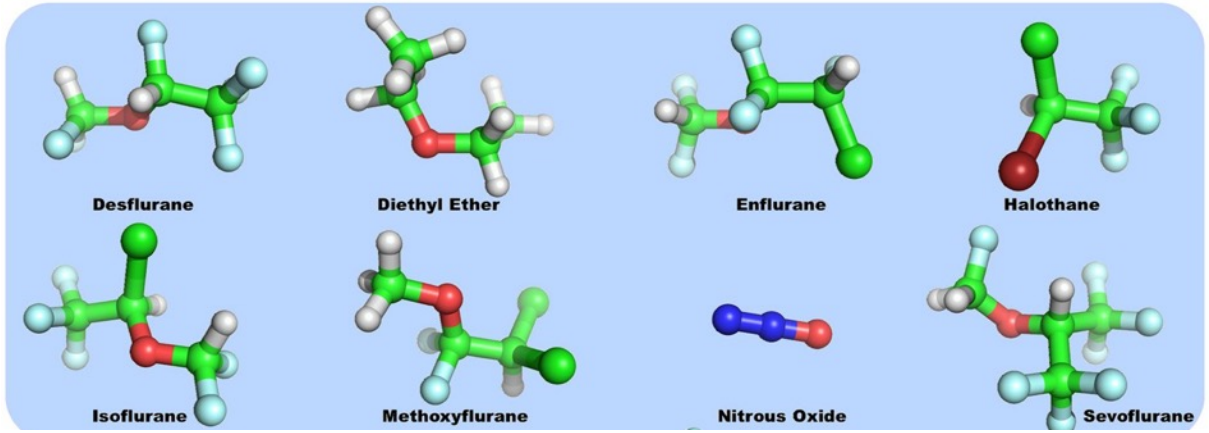
Outcome Category	Usual Care Group	EEG Guided Group	Difference[¥] (95% CI)	P value[§]
Undesirable intraoperative movement – no. (%)	95/618 (15.4)	137/614 (22.3)	6.9% (2.5 to 11.4)	0.002



Awareness

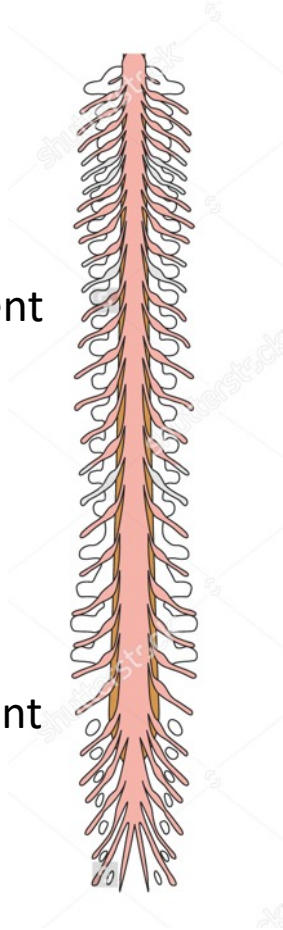
MAC – Asleep

MAC - Awake



Movement

MAC – Movement



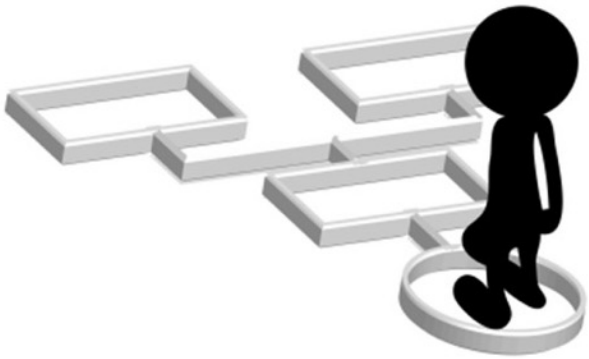
Outcome Category	Usual Care Group	EEG Guided Group	Difference¥ (95% CI)	P value§
Mortality up to 30-days post-surgery – no. (%)	19/618 (3.07)	4/614 (0.65)	2.42% (0.81 to 4.25)	0.004

Deep anesthesia is in the dock

How do you determine culpability?

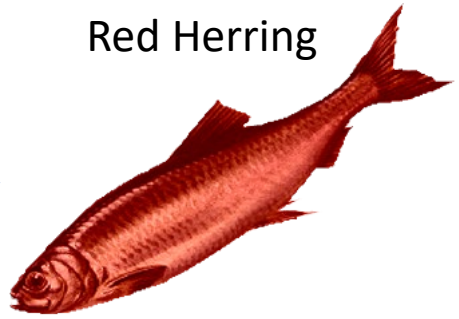
HUGE Difference

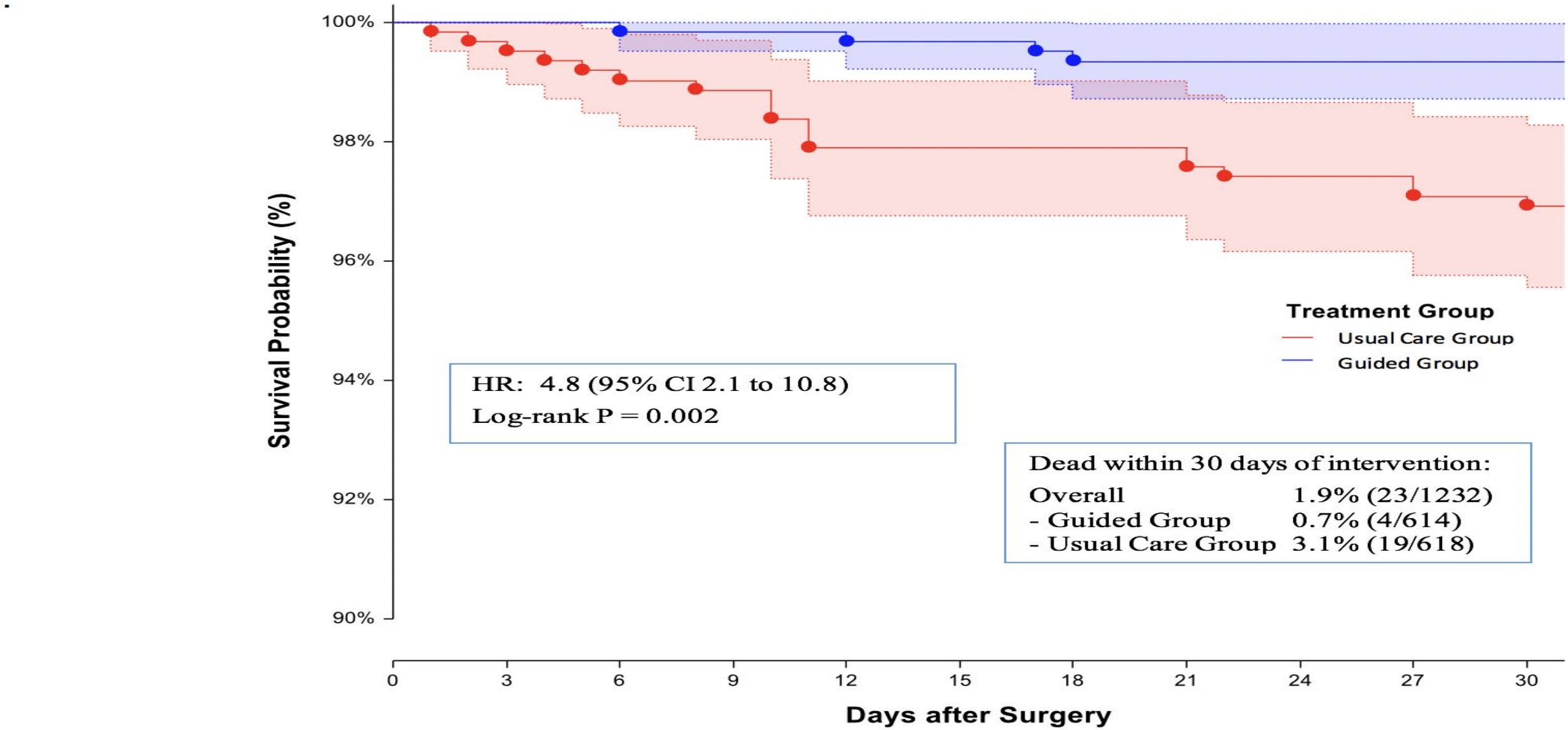
Preponderance of Evidence



Fragility Index = 5

Red Herring





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

ClinCalc.com

Fragility Index Calculator

Calculates the number of patients required to lose statistical significance

RESULTS

Fragility Index

5

A fragility index of 5 indicates that if 5 patients in the experimental group were "converted" from NOT having the primary endpoint to HAVING the primary endpoint, the study would lose statistical significance ($p > 0.05$). The higher the fragility index, the more robust the results of a study are. Learn more about an "acceptable" fragility index.

	Original Study	Fragility Index	"Fragile" Study
Control group with outcome (N)	19		19
Control group without outcome (N)	599		599
Experimental group with outcome (N)	4	+ 5	9
Experimental group without outcome (N)	610	- 5	605
P value	0.002		0.084

Biological Plausibility?

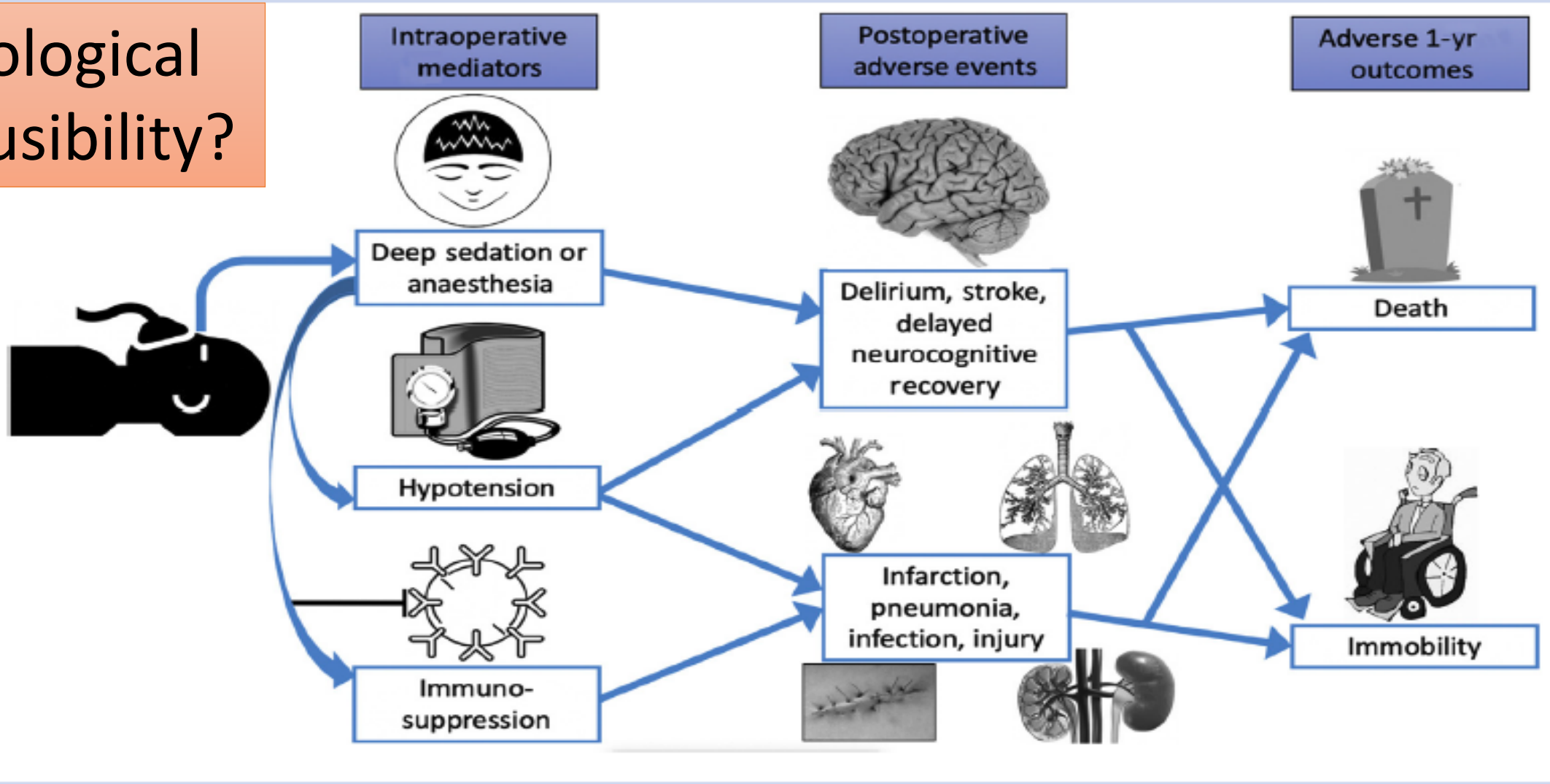


Fig 1. Deep sedation or anaesthesia and poor intermediate-term outcomes. This figure illustrates possible intraoperative mediators and postoperative adverse events associated with 'deeper' hypnosis during sedation or general anaesthesia, which could in turn increase the likelihood of intermediate-term immobility and death.

Br J Anaesth. 2019 Apr;122(4):421-427.

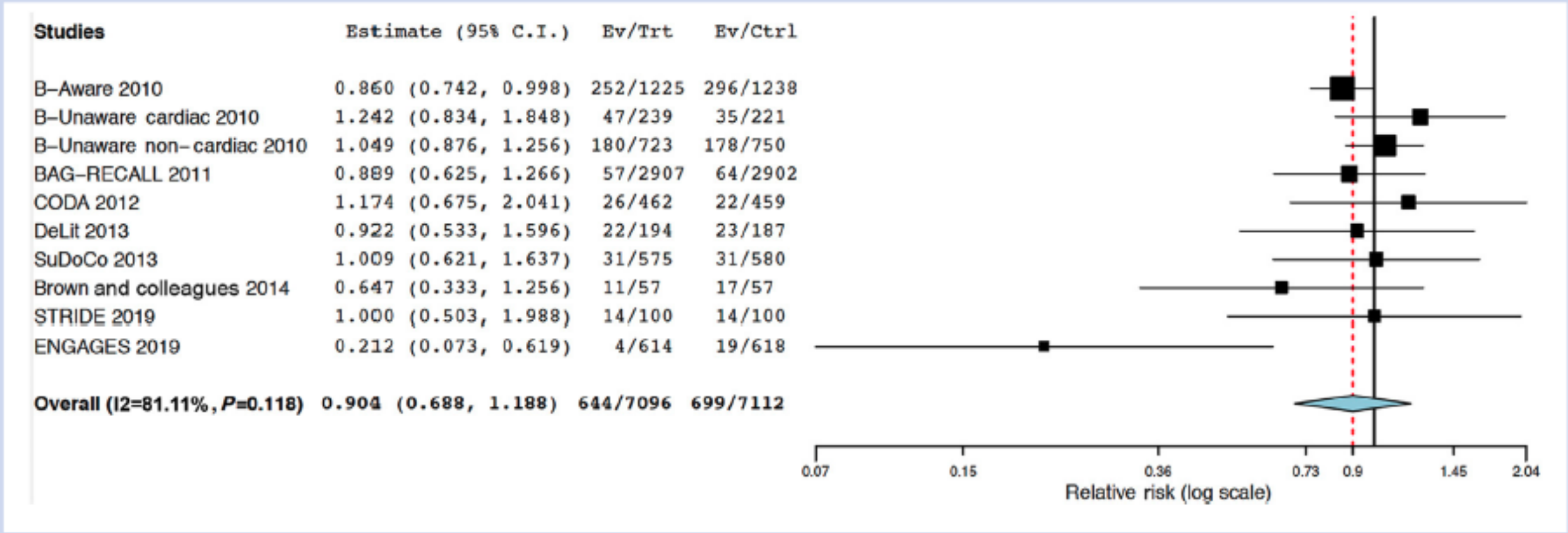


Fig 2. Meta-analysis summarising 10 trials in which the intervention group had received EEG or bispectral index (BIS) guidance, with or without the explicit goal of 'light' anaesthesia or sedation. This analysis was conducted using OpenMetaAnalyst.[22] It is a binary, random effects, Hartung-Knapp-Sidik-Jonkman model.[23,24] The I^2=81%, tau^2=0.131, Q(df=9)=14.135, and heterogeneity P-value=0.118. As shown in the figure, the estimated overall risk ratio for death with the intervention (BIS-guided [reduction in] sedation/anaesthesia)=0.904 (95% confidence interval, 0.688–1.188, P=0.471).

Br J Anaesth. 2019 Apr;122(4):421-427.

WORLD VIEW · 04 DECEMBER 2018

How sure are you of your result? Put a number on it

Any scientist publishing a claim should quantify their confidence in it with a probability, argues Steven N. Goodman.

Steven N. Goodman

Nature. 2018 Dec;564(7734):7.

Based on the evidence **prior to ENGAGES**, what was the probability that avoiding intraoperative burst suppression decreases postoperative delirium?

A. <1%

B. ~5% (big effect)

C. ~50% (small effect)

A. >90%

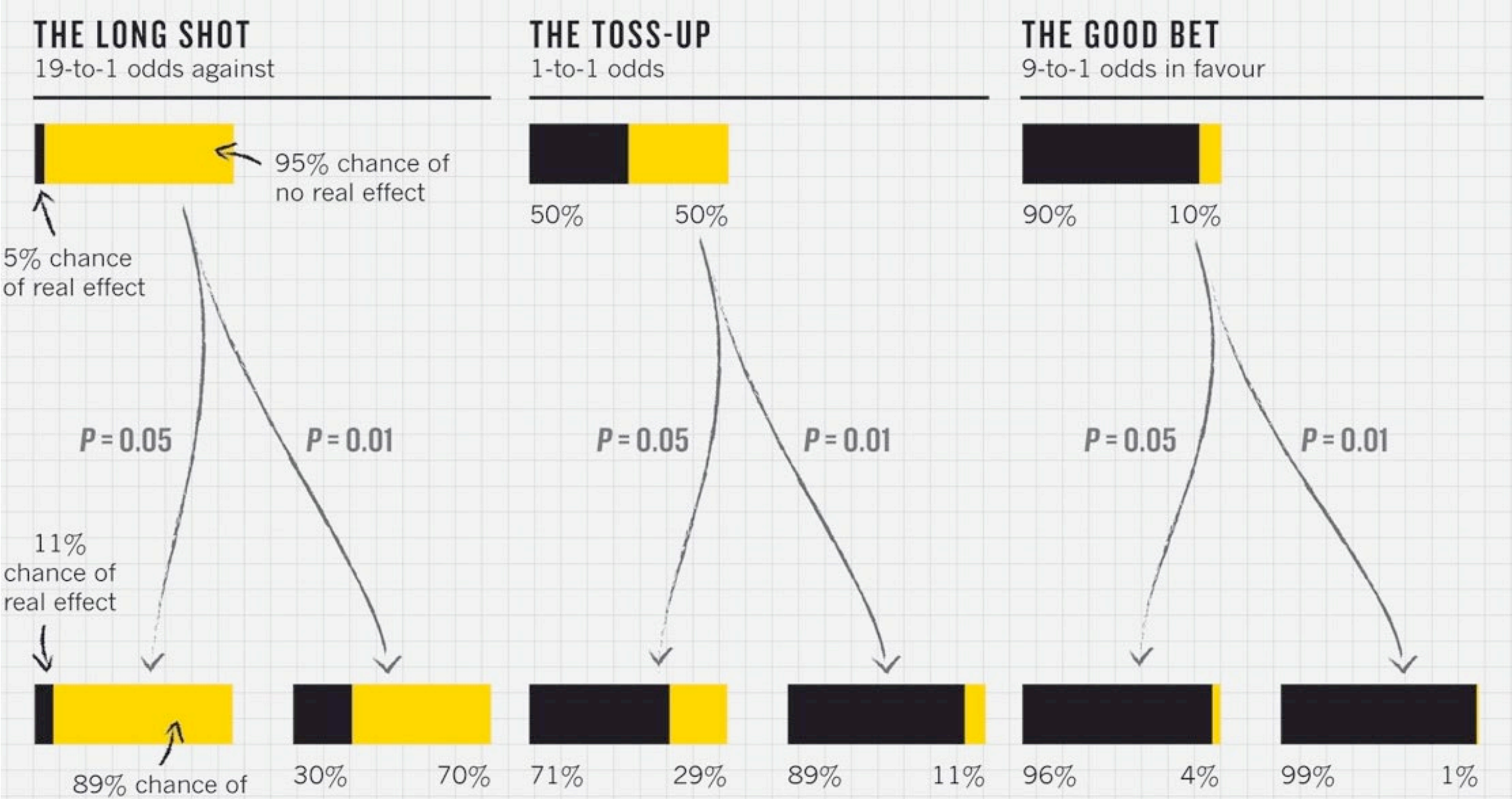
Based on the evidence **prior to ENGAGES**, what was the probability that avoiding intraoperative burst suppression decreases postoperative death?

A. **<1% (any effect)**

B. ~5%

C. ~50%

A. >90%



Nuzzo R. Scientific method: statistical errors. Nature. 2014 13;506(7487):150-2.

One swallow does not a summer make!

Limitations of ENGAGES

- Too small
- Single center
- Insufficient change in practice
- The wrong EEG signal
- Not enough at-risk patients enrolled

ENGAGES - Canada

- Same size (1,200)
- Four centers
- Change in practice?
- The same EEG signal
- Only older cardiac surgery patients enrolled

ClinicalTrials.gov Identifier: NCT02692300

Recapitulate

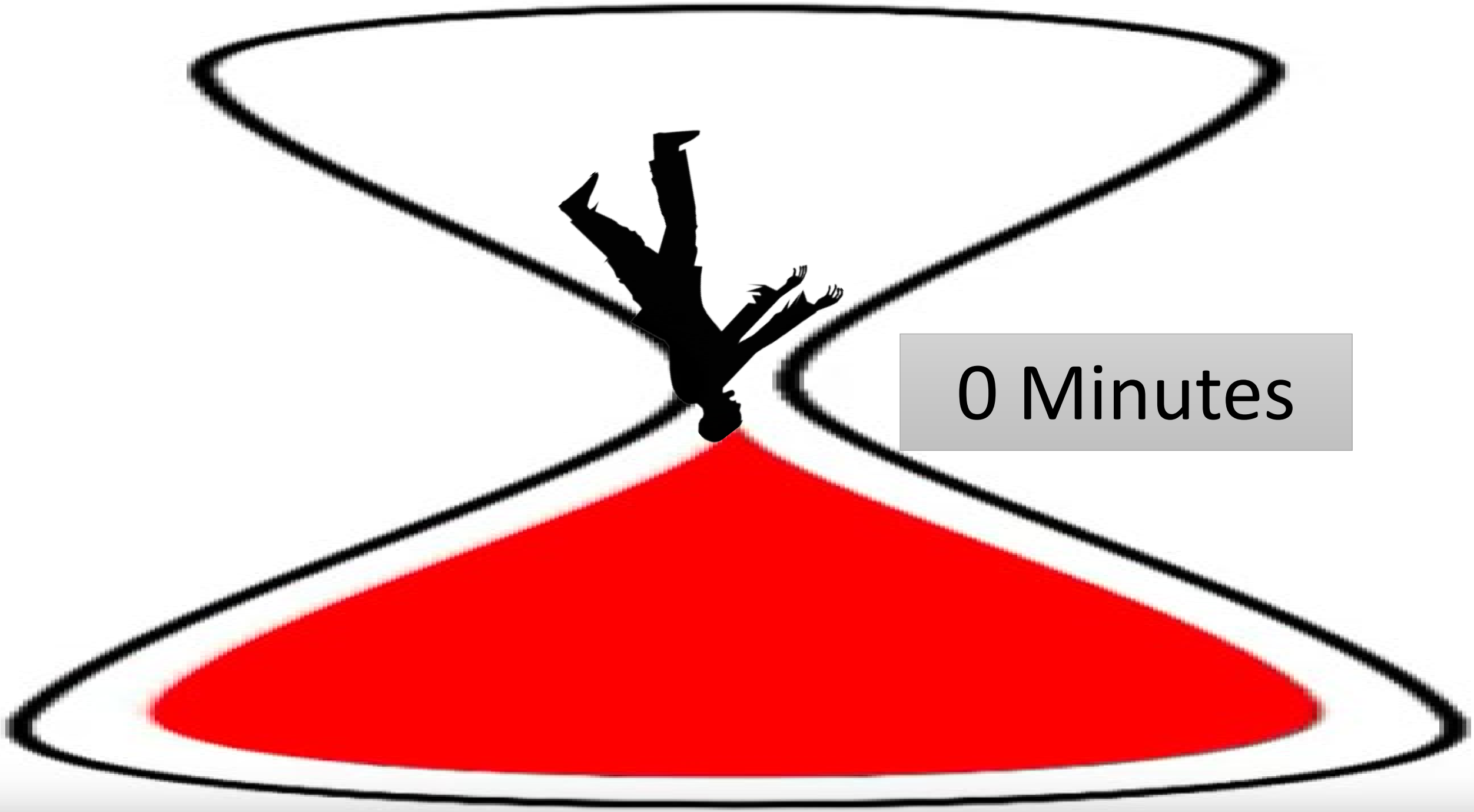
1. Why ENGAGES
2. Patient Centered
3. Efficient
4. Pragmatic
5. Successes
6. Limitations
7. Next Steps

Epilogue

The mind is
its own place,
and in itself
can make
a heaven of hell,
a hell of heaven.

John Milton
Paradiſe Loſt

Image by Gustave Doré, Depiction of Satan c. 1866


0 Minutes