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)
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NIH National Institute on Aging

Washington University in St. Louis
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National Institute on Aging
Grand Rounds: A Shared Forum of the NIH Collaboratory and PCORnet
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’”

INSSENSIBILITY 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.

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

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

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.
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.
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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 |
~25% to 50% of older adults experience delirium after major surgery.

The number is even higher for ICU patients.

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
Delirium

Association

Grim Reaper
Deliriogenicity of Deep Anesthesia
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.
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.

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).
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

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Association between intraoperative electroencephalographic suppression and postoperative mortality

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

NIH
National Institute on Aging

Washington University in St. Louis
School of Medicine
The ENGAGES Clinical Trial

1232 patients consented & enrolled to ENGAGES Study

Randomization

616 to Routine Anesthetic Care

Up to 616

Postoperative Delirium

Targeted Multi-Component Safety Intervention

Quality of Life & Falls

Aim 1

616 to EEG-Guided Anesthetic Care

Up to 616

Postoperative Delirium

Quality of Life & Falls

Aim 2

1232 Control patients matched from participants in SATISFY-SOS Registry

10,000 patients per year enrolled to SATISFY-SOS Study

Quality of Life & Falls

Aim 3
Outcomes patients care about:
  • Delirium
  • Falls
  • Quality of Life

Active patient involvement:
  • Home safety assessment
  • Patient self-assessment
  • FAM-CAM
  • PROs
Efficient
SATISFY

Surgical Outcomes Surveys

Tracking Your Health & Well-Being After Surgery

Barnes-Jewish Hospital

BJC HealthCare

Washington University in St. Louis
School of Medicine

National Leaders in Medicine
Patient Timeline for SATISFY-SOS

-30 0 30 90 ← Day → 365

Preoperative clinic

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

Patient Timeline for SATISFY-SOS

Detailed intraoperative records
Data from EMRs for inpatient care and complications

Patient Timeline for SATISFY-SOS

-30 0 30 90 365

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

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

1. Eligibility
Who is selected to participate in the trial?

2. Recruitment
How are participants recruited?

3. Setting
Where is the trial being done?

4. Organization
What expertise and resources are needed to deliver the intervention?

5. Flexibility: delivery
How should the Intervention be delivered?

6. Flexibility: adherence
What measures are in place to make sure participants adhere to the intervention?

7. Follow-up
How closely are participants followed up?

8. Primary outcome
How relevant is it to participants?

9. Primary analysis
To what extent are all data included?
### ENGAGES Trial Participation Schedule

#### Before Surgery
- **Cognitive tests and health questionnaires**

#### Day of Surgery
- **Actwatch and forehead stickers**

#### Postoperative Day 1
- **Interview**
  - Stickers and watch removed, interview

#### Postoperative Day 2
- **Interview**
  - Postoperative Day 2 interview

#### Postoperative Day 3
- **Interview**
  - Postoperative Day 3 interview

#### Postoperative Day 4
- **Interview**
  - Postoperative Day 4 interview

#### Discharge
- **Possible home safety visits**
  - Discharge possible home safety visits

#### 1 month after surgery
- Two surveys

#### 1 year after surgery
- **Survey**
  - 1 year after surgery survey

---

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>What to expect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Surgery</strong></td>
<td><strong>At least one day before surgery (60-90 min)</strong> An ENGAGES researcher will ask you a series of questions about your health.</td>
</tr>
<tr>
<td><strong>Day of Surgery</strong></td>
<td><strong>Just before surgery</strong> 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.</td>
</tr>
<tr>
<td><strong>Postoperative Days One to Five</strong></td>
<td><strong>Between 4 PM and 8 PM (10 min)</strong> An ENGAGES researcher will visit you in the hospital and ask questions about how you are thinking and your pain.</td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
<td><strong>After you leave the hospital (2 or 3 visits lasting one hour each)</strong> Occupational therapy might visit your home and suggest changes to reduce your risk of falls.</td>
</tr>
<tr>
<td><strong>One month after surgery</strong></td>
<td><strong>Around 30 days after surgery (2 surveys lasting 15 min each)</strong> 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.</td>
</tr>
<tr>
<td><strong>One year after surgery</strong></td>
<td><strong>Around one year after surgery (10 min)</strong> You will receive one SATISFY-SOS survey by phone, mail, or email.</td>
</tr>
</tbody>
</table>
Challenges

• Representative enrollment
• Baseline Assessment
• Altering anesthetic management
• Avoiding trial-related temporal change in practice
• Home safety intervention
www.icetap.org

ICE-TAP

... The cool way to learn about brain monitoring
Teaching Modules on icetap.org

EEG Waveforms and Depth of Anesthesia

Intraoperative EEG Presentation & Answered Questions

Training Module for the ENGAGES Clinical Trial (1UH2AG050312-01 - NCT02241655)

Dr. Michael Avidan, Dr. Troy Wildes, Dr. Tracey Stevens
Rachel Steinhorn and Maxim Wolfson, WUMSIV

Clinical decision making in anesthesia using the EEG

>3,000 Views

>5,000 Views
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.
39,144 Patients assessed for eligibility

36,580 Excluded because they did not meet inclusion criteria or were unable to provide informed consent

2,564 Eligible

1,164 Excluded
107 Met exclusion criteria
978 Declined participation
79 Not approached

1,400 Enrolled

168 Excluded
2 Died
40 Deemed ineligible after enrollment
49 Surgery was canceled
31 Research team missed surgery
37 Withdrawn

1,232 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)

10 Primary outcome not collected
6 Comatose
2 Withdraw from study
2 Early hospital discharge

504 Analyzed for primary outcome of postoperative delirium incidence

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)

9 Primary outcome not collected
1 Died
5 Comatose
1 Withdraw from study
2 Early hospital discharge

608 Analyzed for primary outcome of postoperative delirium incidence
<table>
<thead>
<tr>
<th>Table 1. Preoperative Patient Characteristics</th>
<th>No. (%) Guided (n = 614)</th>
<th>Usual Care (n = 618)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>69.5 (65.0-74.7)</td>
<td>69.4 (64.2-75.8)</td>
</tr>
<tr>
<td>Women</td>
<td>282 (45.9)</td>
<td>281 (45.5)</td>
</tr>
<tr>
<td>Men</td>
<td>232 (54.1)</td>
<td>237 (54.5)</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>29.0 (25-33)</td>
<td>29.0 (25-33)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>555 (90.4)</td>
<td>558 (90.3)</td>
</tr>
<tr>
<td>Black</td>
<td>54 (8.8)</td>
<td>53 (8.6)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (0.8)</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Attended college</td>
<td>198 (36.3)</td>
<td>208 (37.3)</td>
</tr>
<tr>
<td>Lifetime tobacco usea</td>
<td>276 (61.2)</td>
<td>249 (56.8)</td>
</tr>
<tr>
<td>Current weekly alcohol usex</td>
<td>289 (47.1)</td>
<td>297 (48.1)</td>
</tr>
<tr>
<td>Current use of anticonvulsants</td>
<td>94 (15.3)</td>
<td>81 (13.1)</td>
</tr>
<tr>
<td>Regular use of opioids</td>
<td>154 (25.1)</td>
<td>149 (24.1)</td>
</tr>
<tr>
<td>Regular use of benzodiazepines</td>
<td>86 (14.0)</td>
<td>102 (16.5)</td>
</tr>
<tr>
<td>ASA physical classification &gt;3</td>
<td>209 (34.0)</td>
<td>221 (35.8)</td>
</tr>
<tr>
<td>Marginal exercise tolerance (&lt;4 METs)</td>
<td>297 (50.3)</td>
<td>295 (50.4)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>97 (15.8)</td>
<td>95 (15.4)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>90 (14.7)</td>
<td>108 (17.5)</td>
</tr>
<tr>
<td>History of or high risk for obstructive sleep apnea</td>
<td>230 (37.5)</td>
<td>219 (35.4)</td>
</tr>
<tr>
<td>History of delirium</td>
<td>78 (12.8)</td>
<td>79 (12.9)</td>
</tr>
<tr>
<td>No. of comorbidities, median (IQR)</td>
<td>5 (3-6)</td>
<td>5 (3-6)</td>
</tr>
<tr>
<td>History of depression</td>
<td>85 (13.8)</td>
<td>82 (13.4)</td>
</tr>
<tr>
<td>PHQ8, median (IQR)x</td>
<td>3 (1-6)</td>
<td>3 (0-6)</td>
</tr>
<tr>
<td>Short Blessed Test for cognition score, median (IQR)x</td>
<td>2 (0-4)</td>
<td>2 (0-4)</td>
</tr>
<tr>
<td>8-item Interview to Differentiate Aging and Dementia, median (IQR)x</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Barthel Activities of Daily Living index, median (IQR)</td>
<td>15 (15-15)</td>
<td>15 (15-15)</td>
</tr>
<tr>
<td>Handgrip strength score, mean (SD), kg</td>
<td>26.4 (11.0)</td>
<td>25.7 (10.7)</td>
</tr>
<tr>
<td>Timed up-and-go score, median (IQR), s</td>
<td>10.5 (9.2-13.1)</td>
<td>11.0 (9.4-13.4)</td>
</tr>
<tr>
<td>Lawton Instrumental Activities of Daily Living, median (IQR)x</td>
<td>8 (7-8)</td>
<td>8 (8-8)</td>
</tr>
<tr>
<td>VR: 12 Component Score, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>38.1 (11.9)</td>
<td>38.2 (11.8)</td>
</tr>
<tr>
<td>Mental</td>
<td>53.6 (10.6)</td>
<td>53.6 (11.0)</td>
</tr>
<tr>
<td>Measure</td>
<td>Median (IQR) Guided</td>
<td>Median (IQR) Usual Care</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Intraoperative measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of anesthesia, min</td>
<td>264.5 (192 to 344)</td>
<td>264.0 (186 to 349)</td>
</tr>
<tr>
<td>End-tidal volatile agent concentration, MAC&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.69 (0.62 to 0.77)</td>
<td>0.80 (0.71 to 0.86)</td>
</tr>
<tr>
<td>Duration of BIS &lt;40, min&lt;sup&gt;e&lt;/sup&gt;</td>
<td>32 (9 to 81)</td>
<td>60 (19 to 132)</td>
</tr>
<tr>
<td>Time with SR &gt;1%, min&lt;sup&gt;f&lt;/sup&gt;</td>
<td>7 (1 to 23)</td>
<td>13 (2 to 58)</td>
</tr>
<tr>
<td>MAP, mean (SD), mm Hg</td>
<td>81.2 (8.26)</td>
<td>79.6 (7.68)</td>
</tr>
<tr>
<td>Duration of MAP &lt;60 mm Hg, min</td>
<td>7 (2 to 19)</td>
<td>7 (1 to 19)</td>
</tr>
</tbody>
</table>
Number of Minutes

**EEG Suppression Time**

- Usual Anesthesia Care: 13 minutes
- EEG-Guided Care: 7 minutes

Median Difference: 46% (P<0.001)

**Time with BIS <40**

- Usual Anesthesia Care: 60 minutes
- EEG-Guided Care: 32 minutes

Median Difference: 47% (P<0.001)
Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES Randomized Clinical Trial

**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

**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

**FINDINGS**
- Delirium during postoperative days 1 to 5
  - EEG-guided anesthesia: Delirium occurred in 157 of 604 patients (26%)
  - Usual anesthesia: Delirium occurred in 140 of 609 patients (23%)

**LOCATIONS**
- 1 Hospital in St Louis, MO

**PRIMARY OUTCOME**
- Incidence of delirium during postoperative days 1 to 5 as assessed by validated instruments or through chart review
- Between-group difference: 3.0% (95% CI, -2.0% to 8.0%)

### Delirium Outcomes

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Usual Care Group</th>
<th>EEG Guided Group</th>
<th>Difference* (95% CI)</th>
<th>P value$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium incidence* – no. (%)</td>
<td>140/609 (23.0)</td>
<td>157/604 (26.0)</td>
<td>3.0% (-2.0 to 8.0)</td>
<td>0.224</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Days after Surgery</th>
<th>Guided Number At Risk</th>
<th>Usual Care Number At Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/592</td>
<td>80/602</td>
</tr>
<tr>
<td>2</td>
<td>41/573</td>
<td>34/584</td>
</tr>
<tr>
<td>3</td>
<td>25/537</td>
<td>14/524</td>
</tr>
<tr>
<td>4</td>
<td>11/451</td>
<td>7/444</td>
</tr>
<tr>
<td>5</td>
<td>6/373</td>
<td>5/383</td>
</tr>
</tbody>
</table>
Meta-analysis summarizing 4 trials in which the intervention group received EEG-guided anesthesia

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% C.I.)</th>
<th>Delirium Guided</th>
<th>Delirium Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>CODA 2013</td>
<td>0.580 (0.415, 0.809)</td>
<td>70/450</td>
<td>109/452</td>
</tr>
<tr>
<td>SuDoCo-PP 2013</td>
<td>0.741 (0.550, 0.999)</td>
<td>123/716</td>
<td>96/439</td>
</tr>
<tr>
<td>BAG-RECALL 2014</td>
<td>0.597 (0.349, 1.020)</td>
<td>28/149</td>
<td>45/161</td>
</tr>
<tr>
<td>ENGAGES 2019</td>
<td>1.177 (0.905, 1.529)</td>
<td>157/604</td>
<td>140/609</td>
</tr>
<tr>
<td>Overall (I^2=73.51 %, P=0.004)</td>
<td>0.764 (0.549, 1.061)</td>
<td>378/1919</td>
<td>390/1661</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Outcome Category</th>
<th>Guided</th>
<th>Usual Care</th>
<th>Difference, % (95% CI) (^a)</th>
<th>P Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undesirable intraoperative movement</td>
<td>137/614 (22.3)</td>
<td>95/618 (15.4)</td>
<td>6.9 (2.5 to 11.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Intraoperative awareness</td>
<td>0/563 (0.0)</td>
<td>0/568 (0.0)</td>
<td>0 (−0.8 to 0.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>48/614 (7.8)</td>
<td>55/617 (8.9)</td>
<td>−1.1 (−4.3 to 2.1)</td>
<td>.49</td>
</tr>
<tr>
<td>Perioperative serious adverse events(^9)</td>
<td>124/614 (20.2)</td>
<td>130/618 (21.0)</td>
<td>−0.8 (−5.5 to 3.8)</td>
<td>.72</td>
</tr>
<tr>
<td>Mortality up to 30 days after surgical procedure</td>
<td>4/614 (0.7)</td>
<td>19/618 (3.1)</td>
<td>−2.42 (−4.3 to −0.8)</td>
<td>.004</td>
</tr>
<tr>
<td>Outcome Category</td>
<td>Usual Care Group</td>
<td>EEG Guided Group</td>
<td>Difference* (95% CI)</td>
<td>P value$</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Undesirable intraoperative movement – no. (%)</td>
<td>95/618 (15.4)</td>
<td>137/614 (22.3)</td>
<td>6.9% (2.5 to 11.4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Difference in percent of patients experiencing undesirable intraoperative movement.

\$P value from statistical significance test.
### Table: Outcomes

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Usual Care Group</th>
<th>EEG Guided Group</th>
<th>Difference* (95% CI)</th>
<th>P value$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality up to 30-days post-surgery – no. (%)</td>
<td>19/618 (3.07)</td>
<td>4/614 (0.65)</td>
<td>2.42% (0.81 to 4.25)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

### Diagram: Anesthesia in the Dock

**Deep anesthesia is in the dock**

**Preponderance of Evidence**

**HUGE Difference**

**How do you determine culpability?**

**Fragility Index = 5**

**Red Herring**
**Survival Probability (%)**

- **Treatment Group**
  - **Usual Care Group**
  - **Guided Group**

**HR:** 4.8 (95% CI 2.1 to 10.8)  
Log-rank $P = 0.002$

**Dead within 30 days of intervention:**
- Overall: 1.9% (23/1232)  
- Guided Group: 0.7% (4/614)  
- Usual Care Group: 3.1% (19/618)

**Number at Risk**
- **Guided Group:** 614 614 613 613 612 612 610 610 610 610 610 610
- **Usual Care Group:** 618 614 610 607 604 604 604 602 602 600 599
Fragility Index Calculator

Calculates the number of patients required to lose statistical significance

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.

<table>
<thead>
<tr>
<th></th>
<th>Original Study</th>
<th>Fragility Index</th>
<th>&quot;Fragile&quot; Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group with outcome (N)</td>
<td>19</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Control group without outcome (N)</td>
<td>599</td>
<td>599</td>
<td></td>
</tr>
<tr>
<td>Experimental group with outcome (N)</td>
<td>4</td>
<td>+ 5</td>
<td>9</td>
</tr>
<tr>
<td>Experimental group without outcome (N)</td>
<td>610</td>
<td>- 5</td>
<td>605</td>
</tr>
<tr>
<td>P value</td>
<td>0.002</td>
<td>0.084</td>
<td></td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Ev/Ttr</th>
<th>Ev/Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Aware 2010</td>
<td>0.860 (0.742, 0.998)</td>
<td>252/1225</td>
<td>296/1238</td>
</tr>
<tr>
<td>B-Unaware cardiac 2010</td>
<td>1.242 (0.834, 1.848)</td>
<td>47/239</td>
<td>35/221</td>
</tr>
<tr>
<td>B-Unaware non-cardiac 2010</td>
<td>1.049 (0.876, 1.256)</td>
<td>180/723</td>
<td>178/750</td>
</tr>
<tr>
<td>BAG-RECALL 2011</td>
<td>0.889 (0.625, 1.266)</td>
<td>57/2907</td>
<td>64/2902</td>
</tr>
<tr>
<td>CODA 2012</td>
<td>1.174 (0.675, 2.041)</td>
<td>26/462</td>
<td>22/459</td>
</tr>
<tr>
<td>DeLit 2013</td>
<td>0.922 (0.533, 1.596)</td>
<td>22/194</td>
<td>23/187</td>
</tr>
<tr>
<td>SuDoCo 2013</td>
<td>1.009 (0.621, 1.637)</td>
<td>31/575</td>
<td>31/580</td>
</tr>
<tr>
<td>Brown and colleagues 2014</td>
<td>0.647 (0.333, 1.256)</td>
<td>11/57</td>
<td>17/57</td>
</tr>
<tr>
<td>STRIDE 2019</td>
<td>1.000 (0.503, 1.988)</td>
<td>14/100</td>
<td>14/100</td>
</tr>
<tr>
<td>ENGAGES 2019</td>
<td>0.212 (0.073, 0.619)</td>
<td>4/614</td>
<td>19/618</td>
</tr>
</tbody>
</table>

**Overall (I²=81.11%, P=0.118)**

0.904 (0.688, 1.188) | 644/7096 | 699/7112

**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. It is a binary, random effects, Hartung-Knapp-Sidik-Jonkman model. The I²=81%, τ²=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).
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.
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%
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