Michael S. Avidan – 17th June 2018

Dr. Seymour and Rose T. Brown Professor of Anesthesiology

The Role of Ketamine in Preventing Postoperative Delirium and Pain

Acknowledgements

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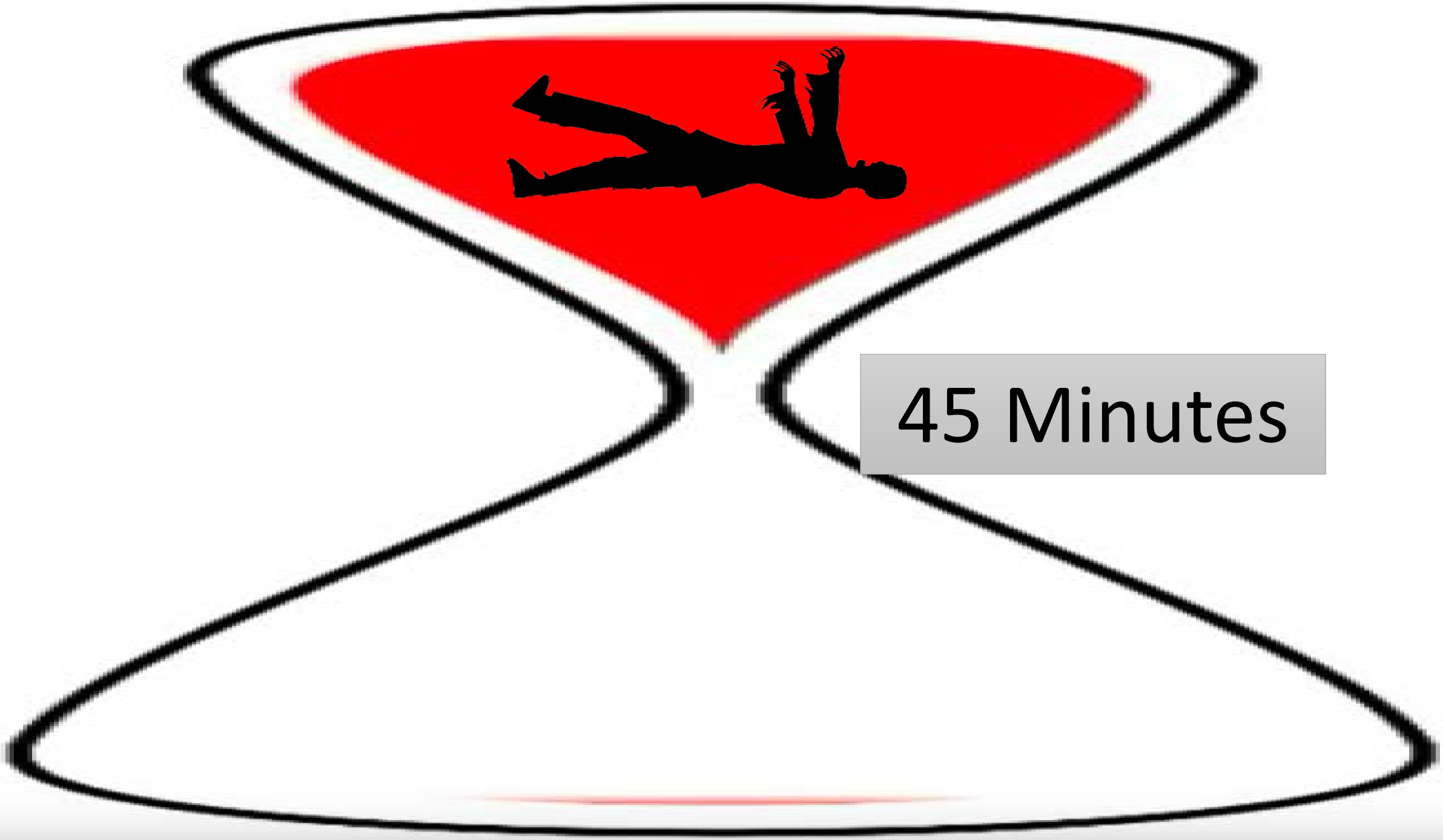
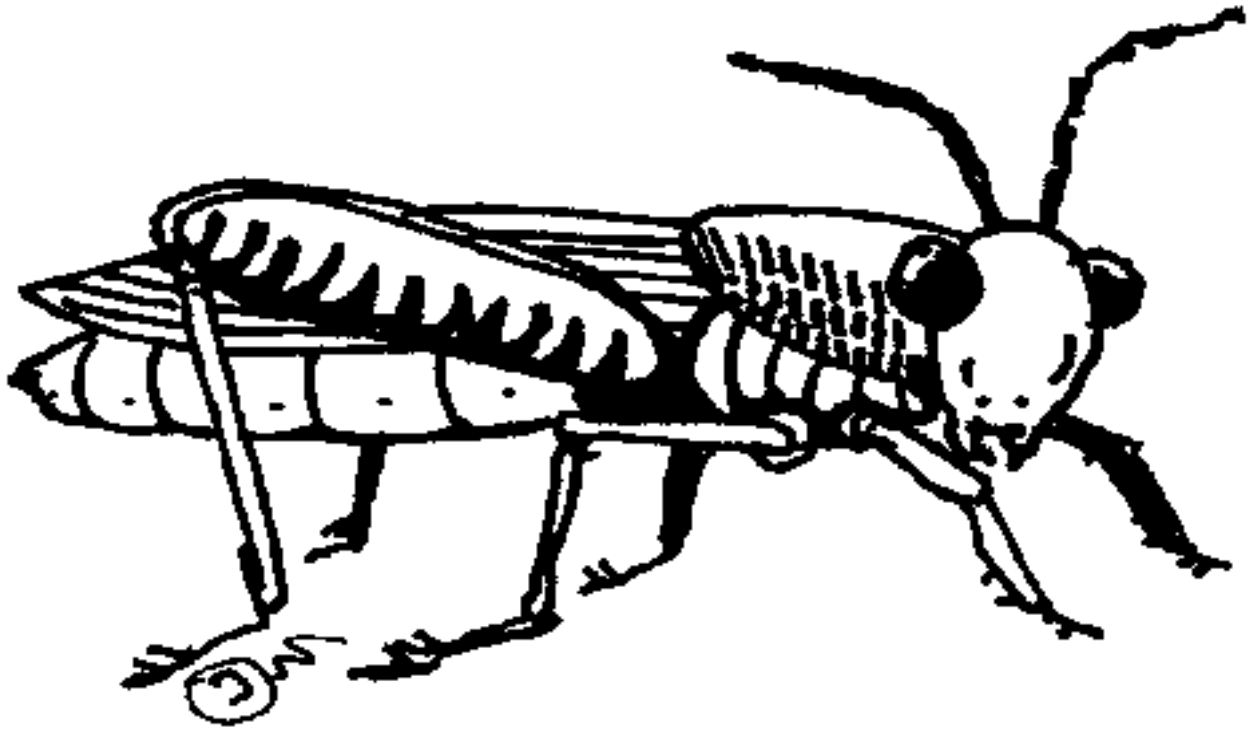
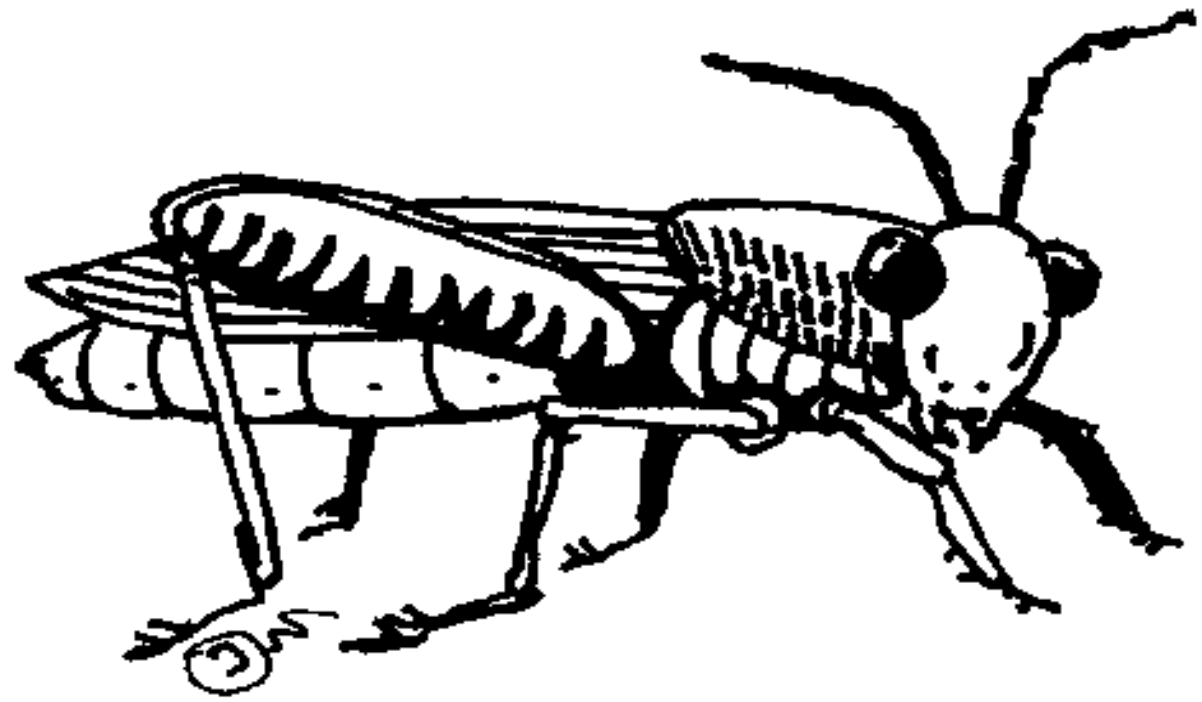
Special Thanks

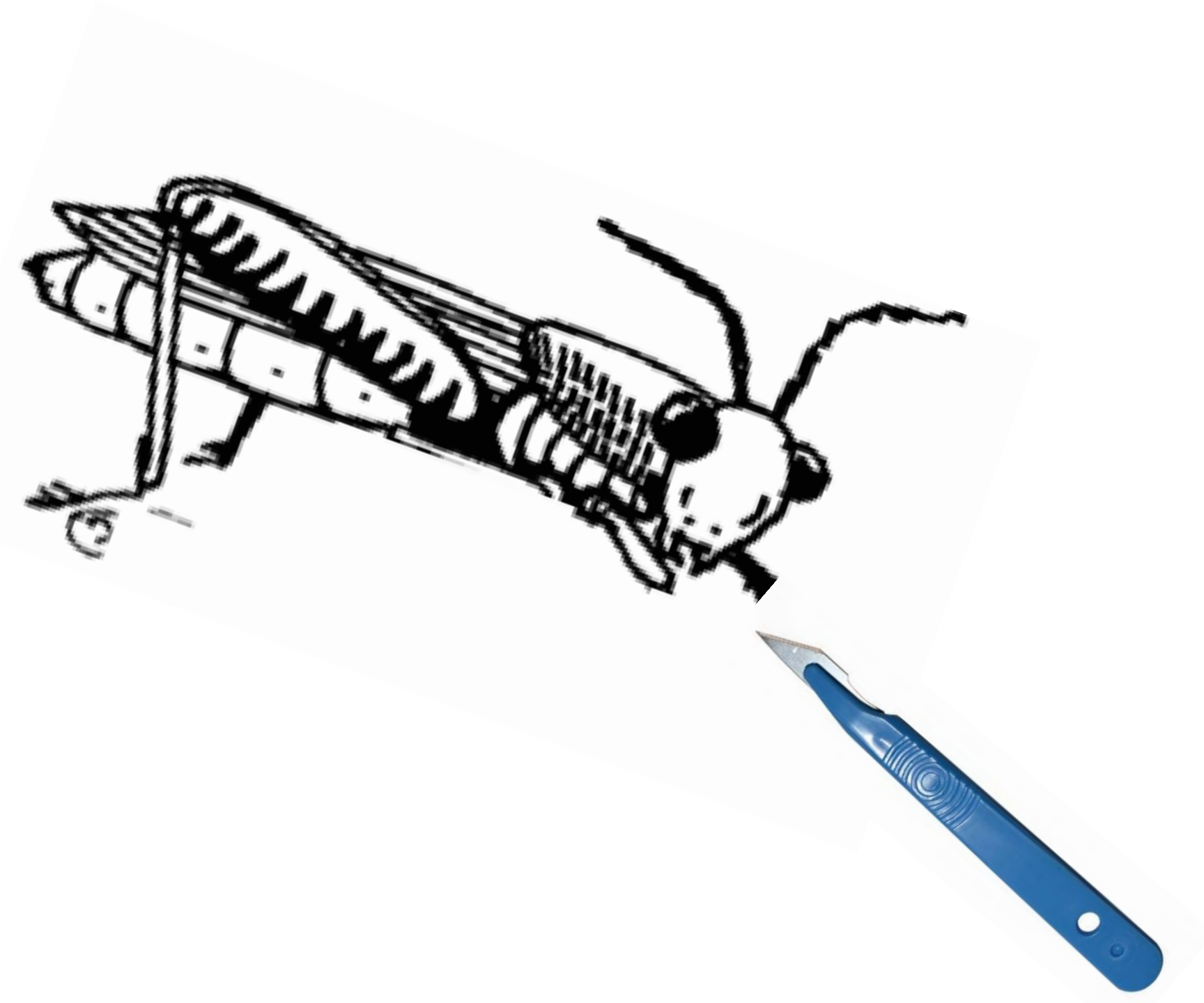

45 Minutes

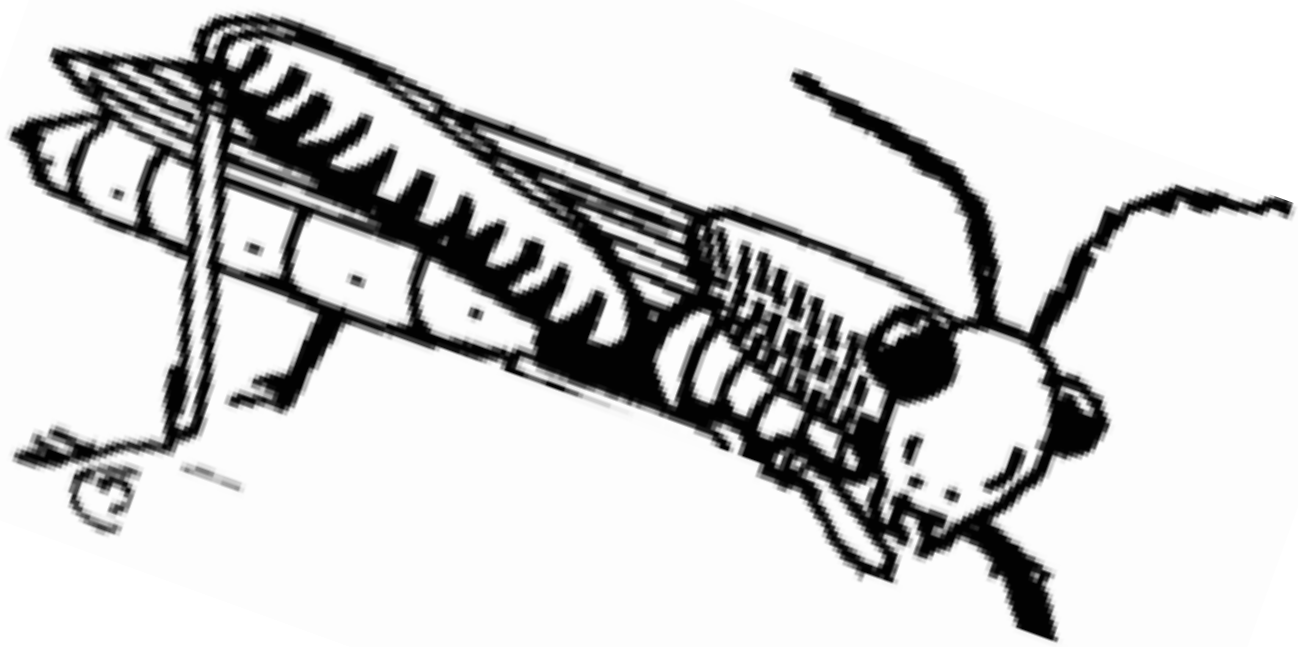
Objectives

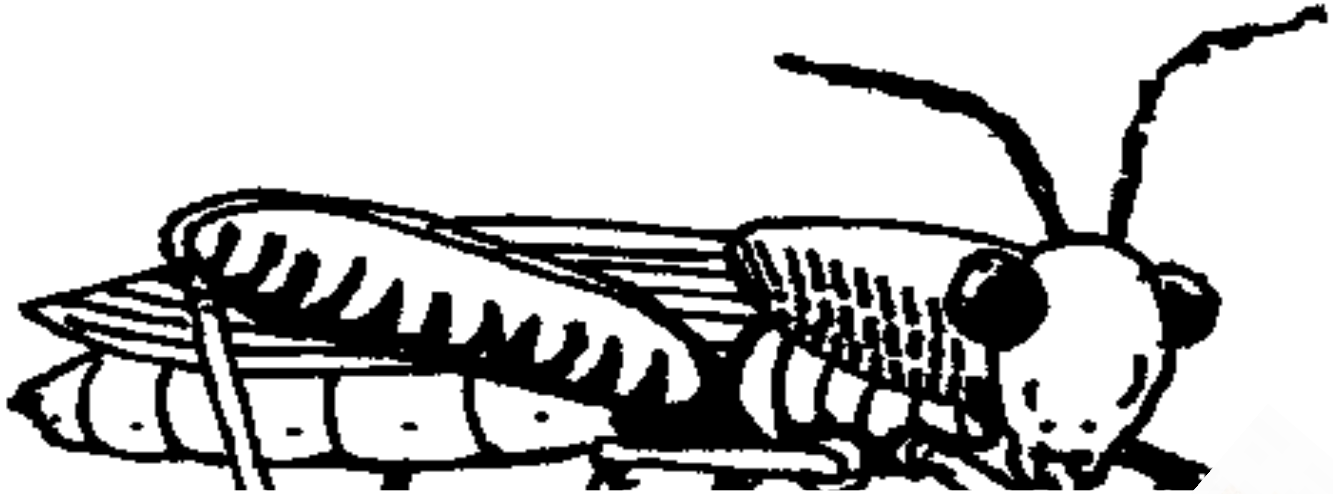
- Gain insight into the current reproducibility crisis in science;
- Learn about the three pillars of reproducibility;
- Understand some of the solutions to the crisis;
- Acquire ability to discern whether results of a study are likely to be true.

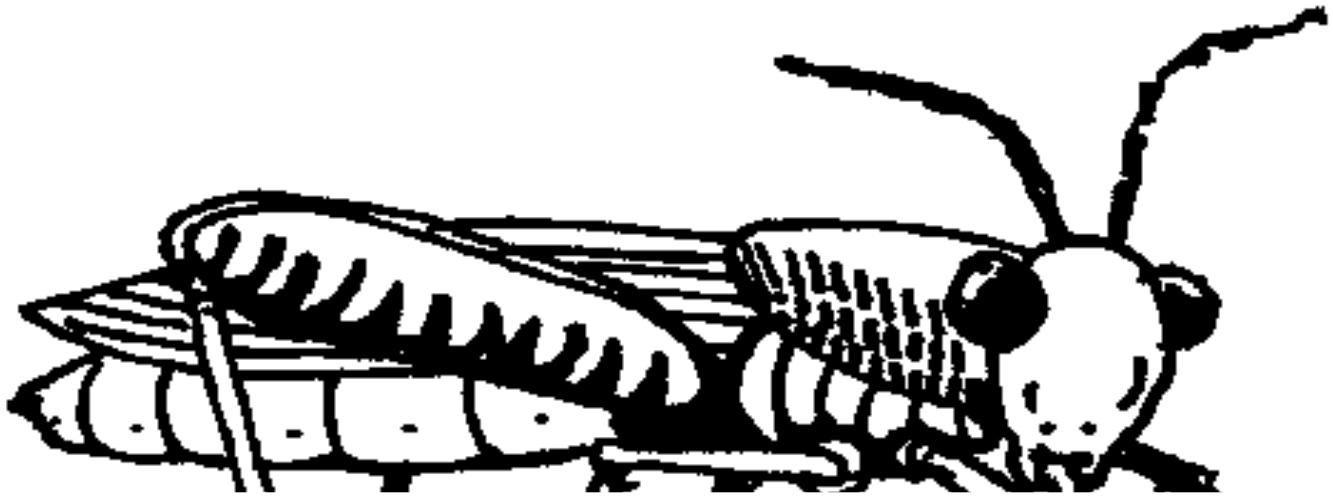












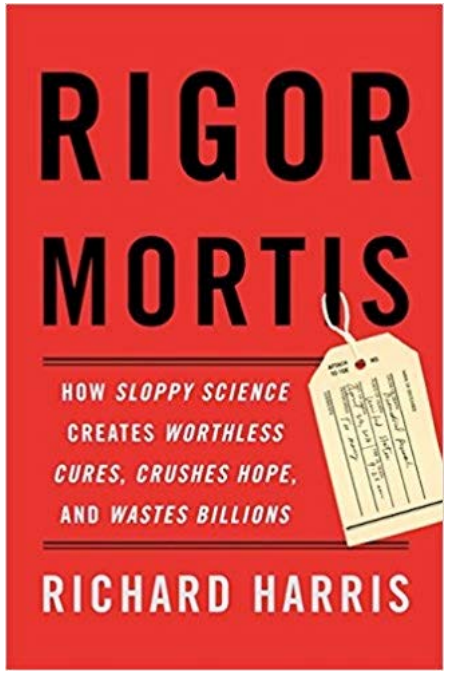
A cricket with no legs can’t hear.

One Profound Question

At what point should clinical practice be changed based on the scientific evidence?

Incentives are malaligned

"Scientists often face a stark choice: they can do what's best for medical advancement by adhering to the rigorous standards of science, or they can do what they perceive is necessary to maintain a career in the hypercompetitive environment of academic research."



You conduct an RCT and expose 58 people to Rx or placebo. The next day, 31% of those exposed to Rx have fever compared with 3% of controls ($p<0.01$).

A. There is a probability of >90% that Rx causes fever.

B. There is a probability of >50% that Rx causes fever.

C. Replication attempts will achieve ~50% success.

D. It is probable that more fever will be found with Rx than placebo in the majority of replication attempts.

Redefine statistical significance

"we believe that a leading cause of non-reproducibility has not yet been adequately addressed: statistical standards of evidence for claiming new discoveries in many fields of science are simply too low. Associating statistically significant findings with $P < 0.05$ results in a high rate of false positives even in the absence of other experimental, procedural and reporting problems."

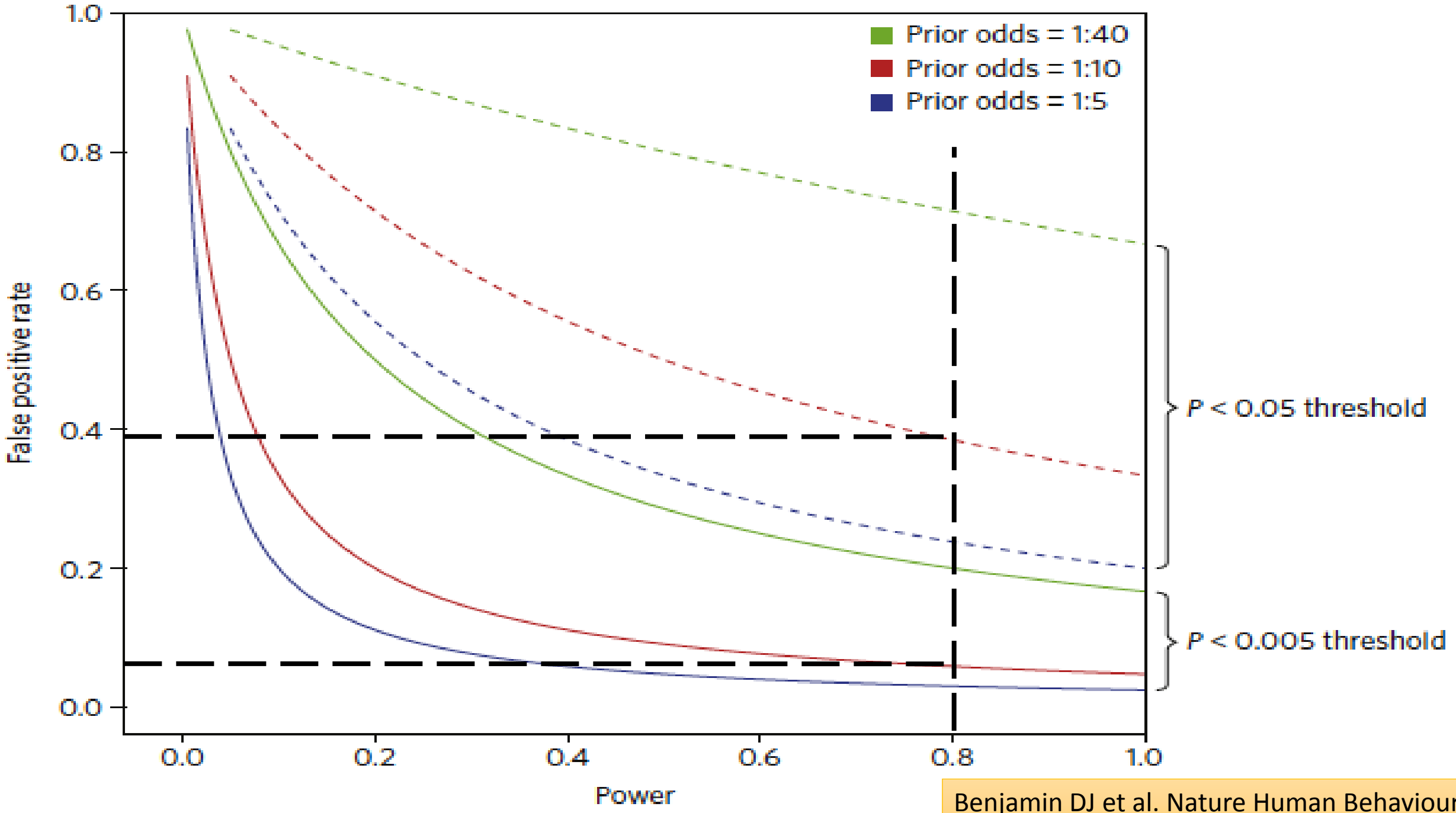
"We propose **to change the default P-value threshold for statistical significance from 0.05 to 0.005** for claims of new discoveries."

Benjamin DJ et al. Nature Human Behaviour 2017

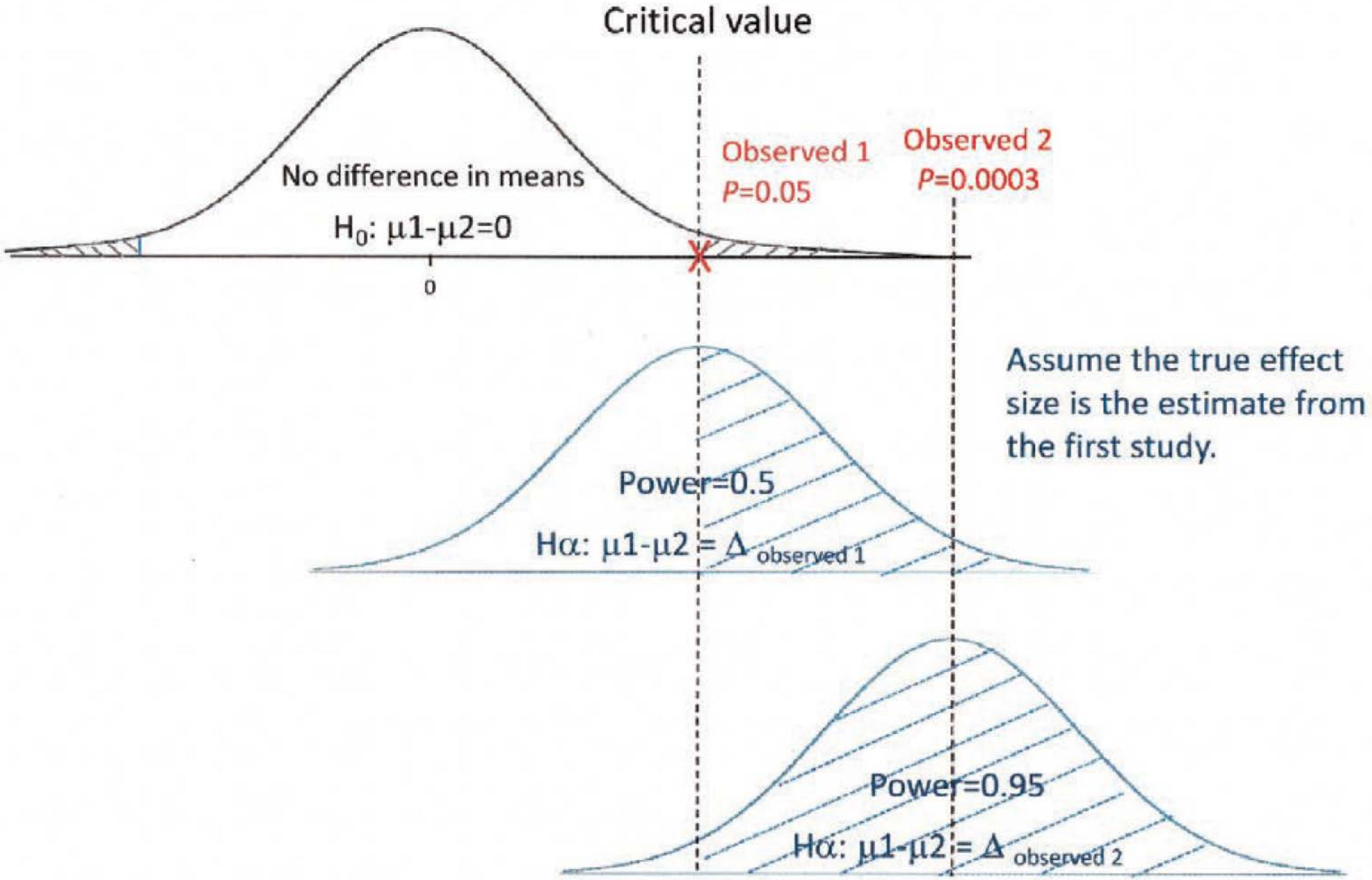
What would this require?

"For a wide range of common statistical tests, transitioning from a P value threshold of $\alpha = 0.05$ to $\alpha = 0.005$ while maintaining 80% power would require an increase in sample sizes of about 70%."

Benjamin DJ et al. Nature Human Behaviour



Benjamin DJ et al. Nature Human Behaviour



Sessler D. Anesthesiology 2017; 126:995-1004

The Real Solution

"Changing the significance threshold is a distraction from the real solution, which is to replace null hypothesis significance testing (and bright-line thresholds) with more focus on effect sizes and confidence intervals, treating the P value as a continuous measure, and/or a Bayesian method."

Benjamin DJ et al. Nature Human Behaviour

Should not impact publication…

"This proposal should not be used to reject publications of novel findings with $0.005 < P < 0.05$ properly labelled as suggestive evidence."

Benjamin DJ et al. Nature Human Behaviour

We don’t appreciate the difference between statistical significance and probability

What question does the p value address?

P values **do not address the question**: how likely is the hypothesis, given the data?

P values **address only one question**: how likely are the data, assuming a true null hypothesis?

i.e., They should not be used to test hypotheses

MÉMOIRE
SUR LA DÉCOUVERTE
DU
MAGNÉTISME
ANIMAL;

Par M. MESMER, *Docteur en Médecine de la Faculté de Vienne.*

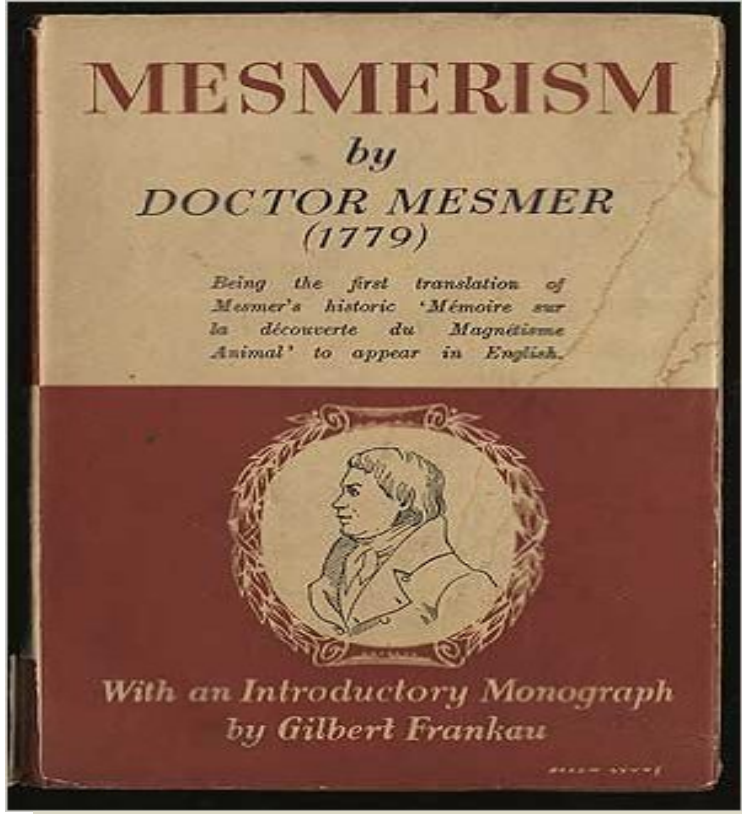
A GENEVE;

Et se trouve

A PARIS,

Chez P. Fr. Didot le jeune, Libraire-Imprimeur de MONSIEUR, quai des Augustins.

M. DCC. LXXIX.



Mesmeric Pass

The modern era of hypnosis and hypnotherapy really begins with Franz Anton Mesmer (1734-1815), the Viennese physician who left the word “mesmerism” to posterity.

Ambassador Franklin and Dr. Mesmer

- Dr. Mesmer “magnetizes” a coin with his mind, flips it 6 times, and each time it lands on tails.

- Franklin blindfolds Mesmer, who again flips the coin 6 times; it now lands twice on tails.

Who thinks Mesmer is a Charlatan?

Lopez CA. Franklin and Mesmer: an encounter. Yale J Biol Med. 1993 Jul-Aug;66(4):325-31.
Kaptchuk TJ. Placebo controls, exorcisms, and the devil.Lancet. 2009 Oct 10;374(9697):1234-5.

Magnetism Revealed (1784)

“Mesmeric” effect exposed

Three major discoveries:
-Control
-Blinding
-Placebo

Franklin routs the mesmerists. “Le magnétisme dévoilé.”
BIBLIOTHÈQUE NATIONALE DE FRANCE.

P value doesn’t take prior knowledge into account

Mr. Fisher is blindfolded. He flips a coin six times and get 6 tails in a row.

P=0.03

Who thinks the coin is biased towards tails?

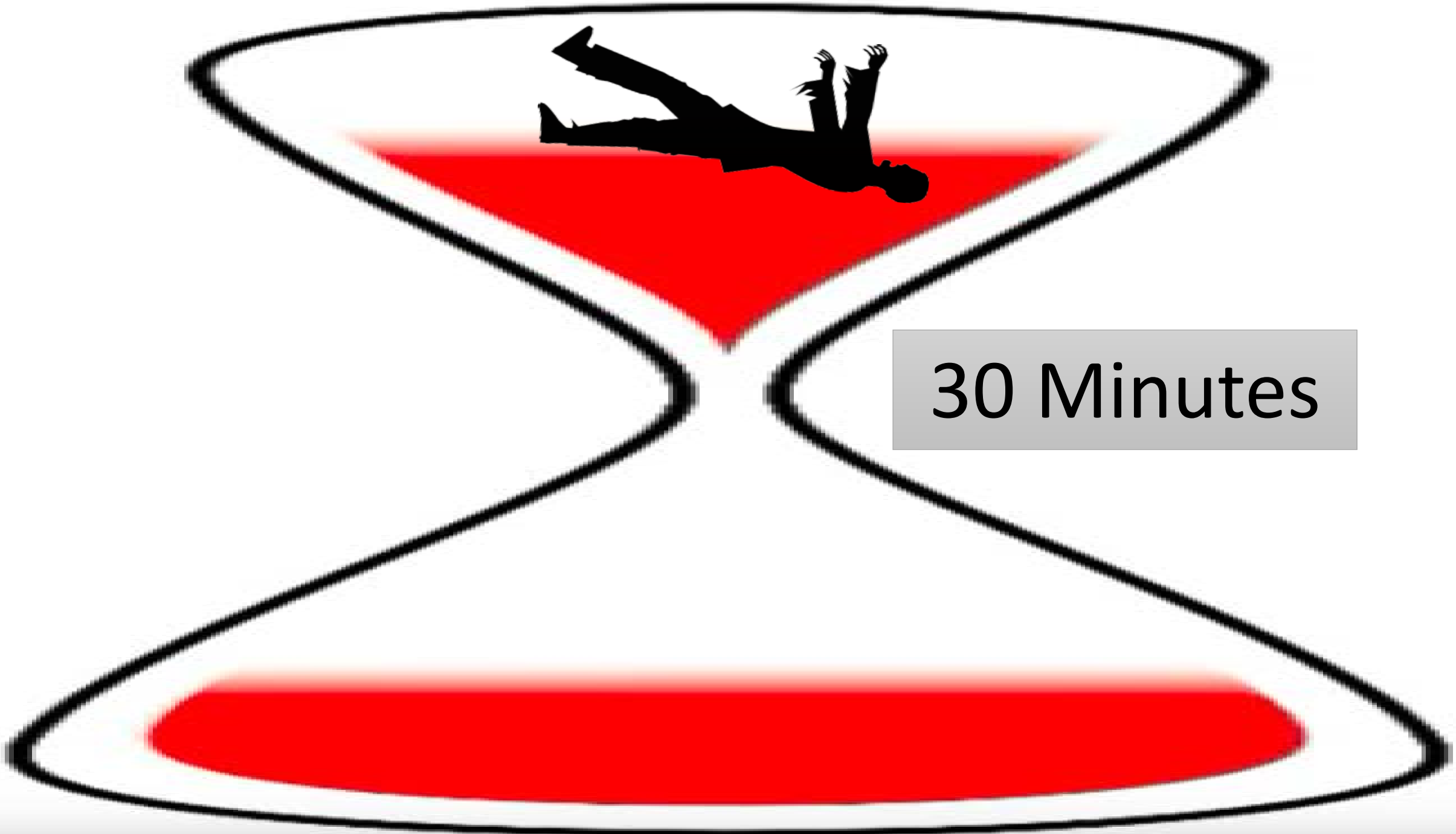
We are naturally Bayesian

Yesterday, a coin was flipped 1,000 times and lands 50 times on heads and **950 on tails**.

Today, a blindfolded Mr. Savage flips the same coin six more times and get **6 tails in a row**.

P=0.03

Now who thinks the coin is biased towards tails?


30 Minutes

Most published research findings are false

"Scientific investigation is the noblest pursuit. I think we can improve the respect of the public for researchers by showing how difficult success is. **Confidence in the research enterprise is probably undermined primarily when we claim that discoveries are more certain than they really are**, and then the public, scientists, and patients suffer the painful refutations."

1: Ioannidis JP. PLoS Med. 2014 Oct 21;11(10):e1001747
2: Ioannidis JP. PLoS Med. 2005 Aug;2(8):e124.
3: Ioannidis JP. PLoS Med. 2007 Jun;4(6):e215
4: Goodman S, Greenland S. PLoS Med. 2007 Apr;4(4):e168.

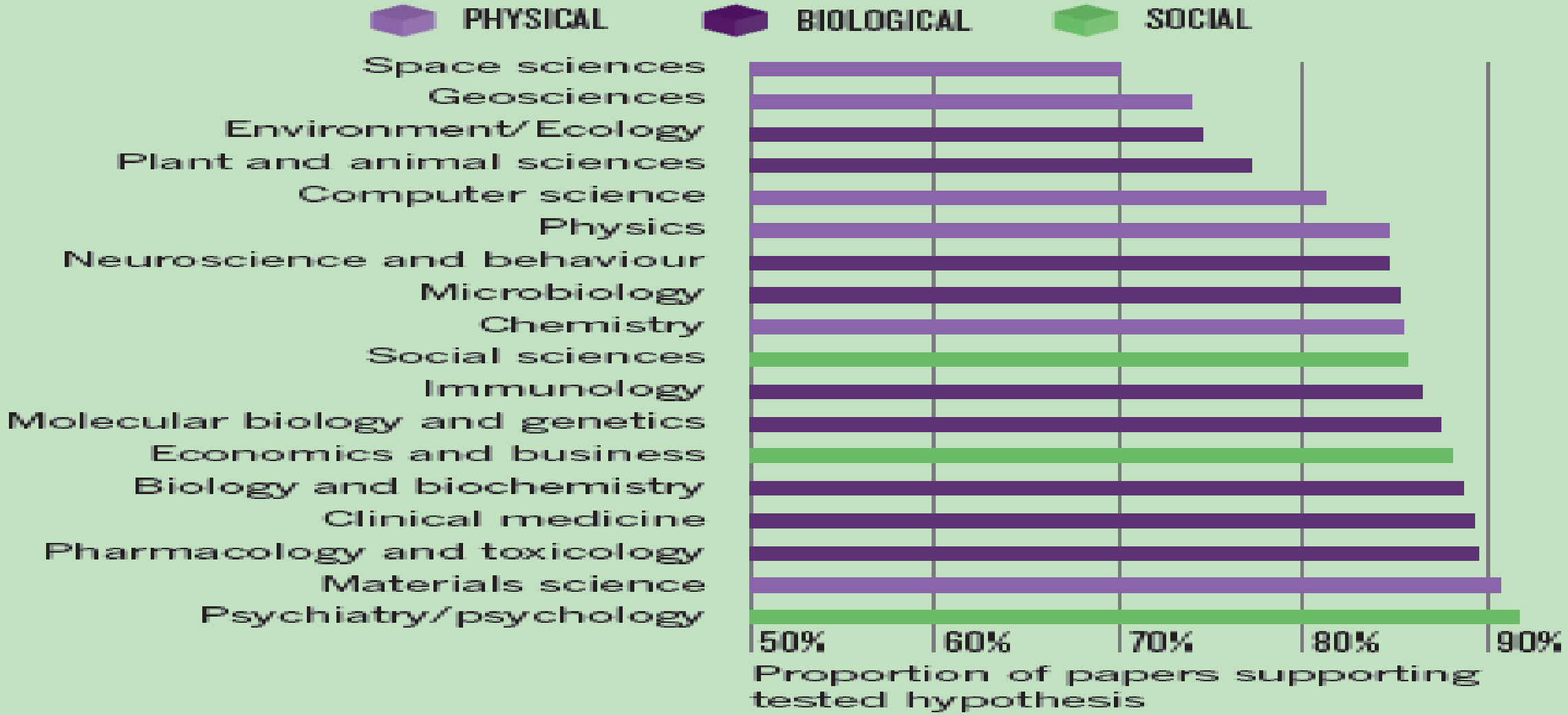
Hypotheses are hard to disprove

“Positive results can behave like rumors: easy to release but hard to dispel. They dominate most journals, which strive to present new, exciting research. Meanwhile, attempts to replicate those studies, especially when the findings are negative, go unpublished, languishing in personal file drawers or circulating in conversations around the water cooler.”

Yong E. Replication studies: Bad copy. Nature. 2012 May 16;485(7398):298-300.

ACCENTUATE THE POSITIVE

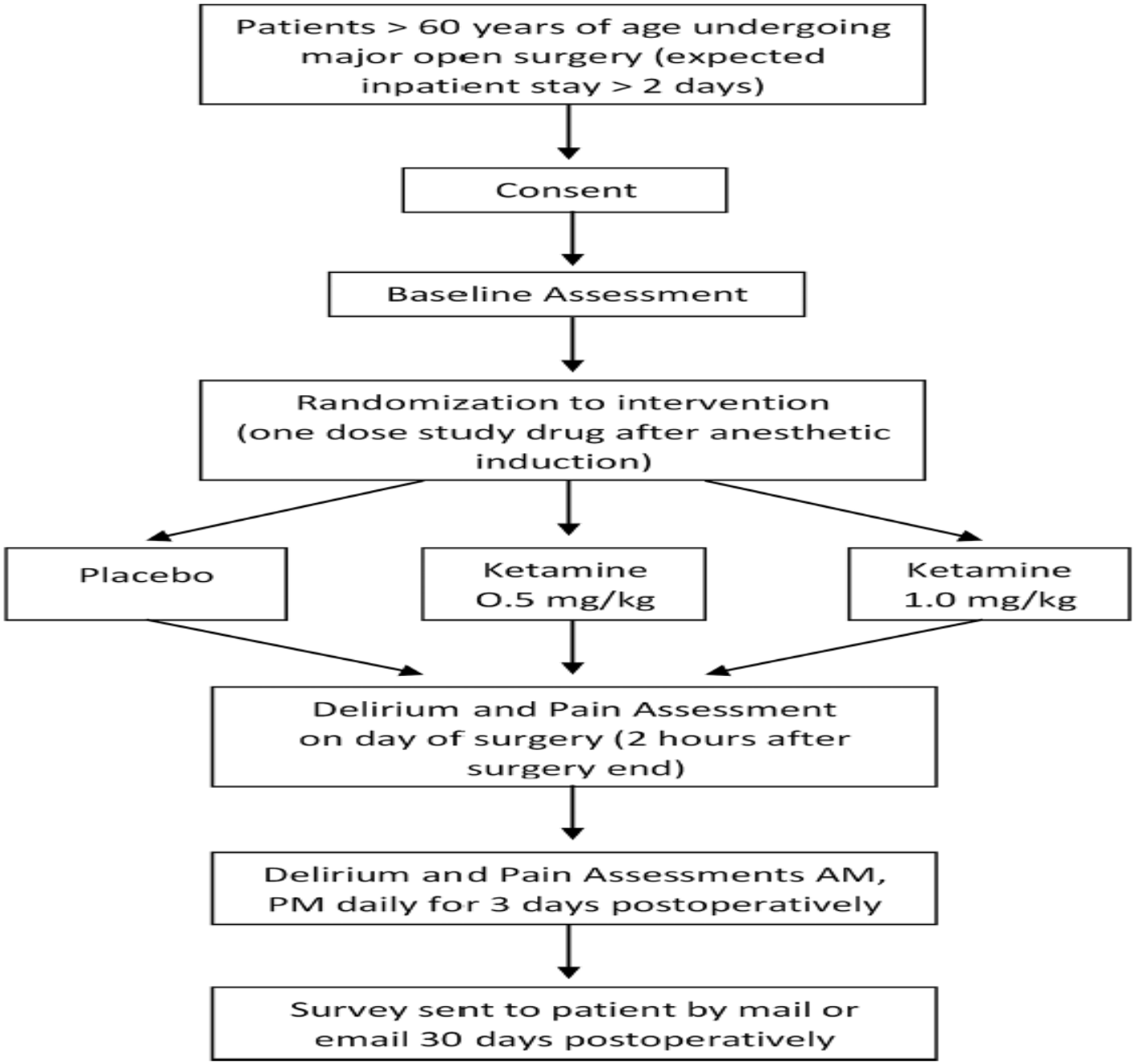
A literature analysis across disciplines reveals a tendency to publish only 'positive' studies — those that support the tested hypothesis. Psychiatry and psychology are the worst offenders.



Yong E. Replication studies: Bad copy. Nature. 2012 May 16;485(7398):298-300.

	Original Study	Fragility Index	"Fragile" Study
Control group with outcome (N)	9		9
Control group without outcome (N)	20		20
Experimental group with outcome (N)	1	+ 2	3
Experimental group without outcome (N)	28	- 2	26
P value	0.012		0.103

Hudetz JA et al. J Cardiothorac Vasc Anesth. 2009 Oct; 23(5):651-7.



Avidan MS et al BMJ Open. 2014 Sep 17;4(9):e005651

What **would** this mean in relation to ketamine and postoperative delirium?

NONE of these is correct. The p value is the probability of finding the experimental result **assuming that the null hypothesis is true**.

This same p Value cannot **also** be used for hypothesis testing or probability generation.

Goodman S. A dirty dozen: twelve p-value misconceptions. Semin Hematol. 2008 Jul;45(3):135-40

Based on current evidence, what is the probability that intraoperative ketamine decreases postoperative delirium?

A. ~1%

B. ~5%

C. ~50%

A. ~90%

Biological Plausibility

- Ketamine - diverse therapeutic effects
- Ketamine reduces postoperative markers of inflammation
- Ketamine decreases postoperative pain and opioid consumption
- Pain and delirium are overlapping syndromes
- Ketamine is a rapidly acting anti-depressant with long-lasting action

BUT - ketamine is a psychoactive drug with known hallucinogenic properties

Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

What did the evidence show - delirium?

We identified six studies with a total of 357 patients. Of the six trials, two showed a decrease in delirium with ketamine, one showed an increase in delirium, one had equivocal results, and in two trials there were no patients with delirium.

Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

What did the evidence show - pain?

A systematic review of 70 of these trials involving 4701 patients published in 2011 showed that a subanaesthetic dose of ketamine decreased pain for up to 48 h and decreased requirement for opioids after surgery. Twenty eight additional studies with a total of 2159 patients were identified. 15 trials showed no decrease in pain with ketamine, 11 found a decrease in pain with ketamine, and two trials had ambiguous findings.

Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

Next Steps

Before recommending widespread administration of an intraoperative bolus of subanaesthetic ketamine, demonstrating that ketamine decreases either delirium or pain, or both, without incurring adverse effects in a large, pragmatic trial was warranted.

Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial

*Michael S Avidan, Hannah R Maybrier, Arbi Ben Abdallah, Eric Jacobsohn, Phillip E Vlisides, Kane O Pryor, Robert A Veselis, Hilary P Grocott, Daniel A Emmert, Emma M Rogers, Robert J Downey, Heidi Yulico, Gyu-Jeong Noh, Yonghun H Lee, Christine M Waszynski, Virendra K Arya, Paul S Pagel, Judith A Hudetz, Maxwell R Muench, Bradley A Fritz, Witold Waberski, Sharon K Inouye, George A Mashour, on behalf of the PODCAST Research Group**

THE LANCET

Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

Primary Finding of PODCAST

There was no difference in delirium incidence between patients in the combined ketamine groups and the placebo group (19·45% vs 19·82%, respectively; absolute difference 0·36%, 95% CI –6·07 to 7·38, p=0·92).

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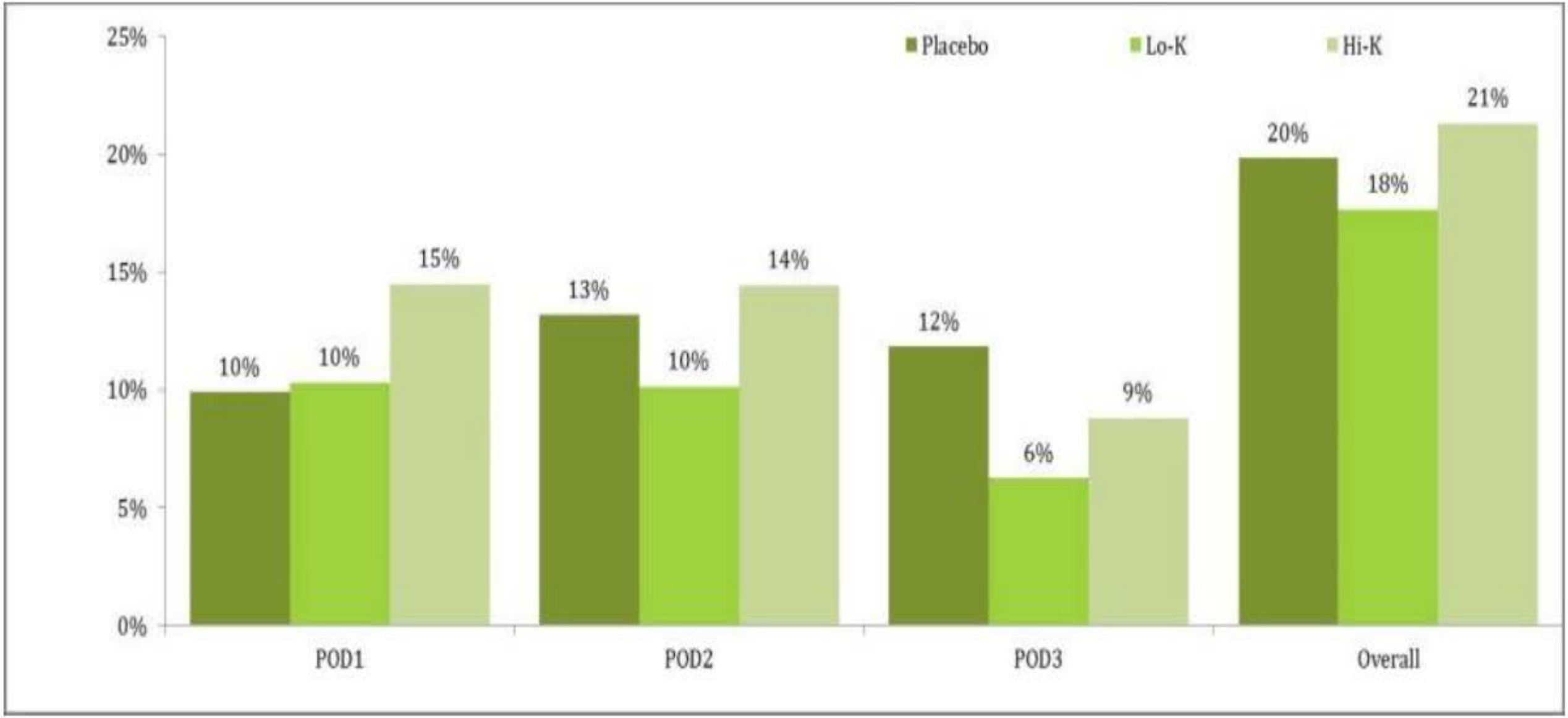
Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

Figure 1s: Daily Delirium Incidence



Delirium incidence on each postoperative day. POD, postoperative day. Lo-K, low dose (0.5 mg/kg) ketamine group.
Hi-K, high dose ketamine group (1 mg/kg).

Delirium Severity

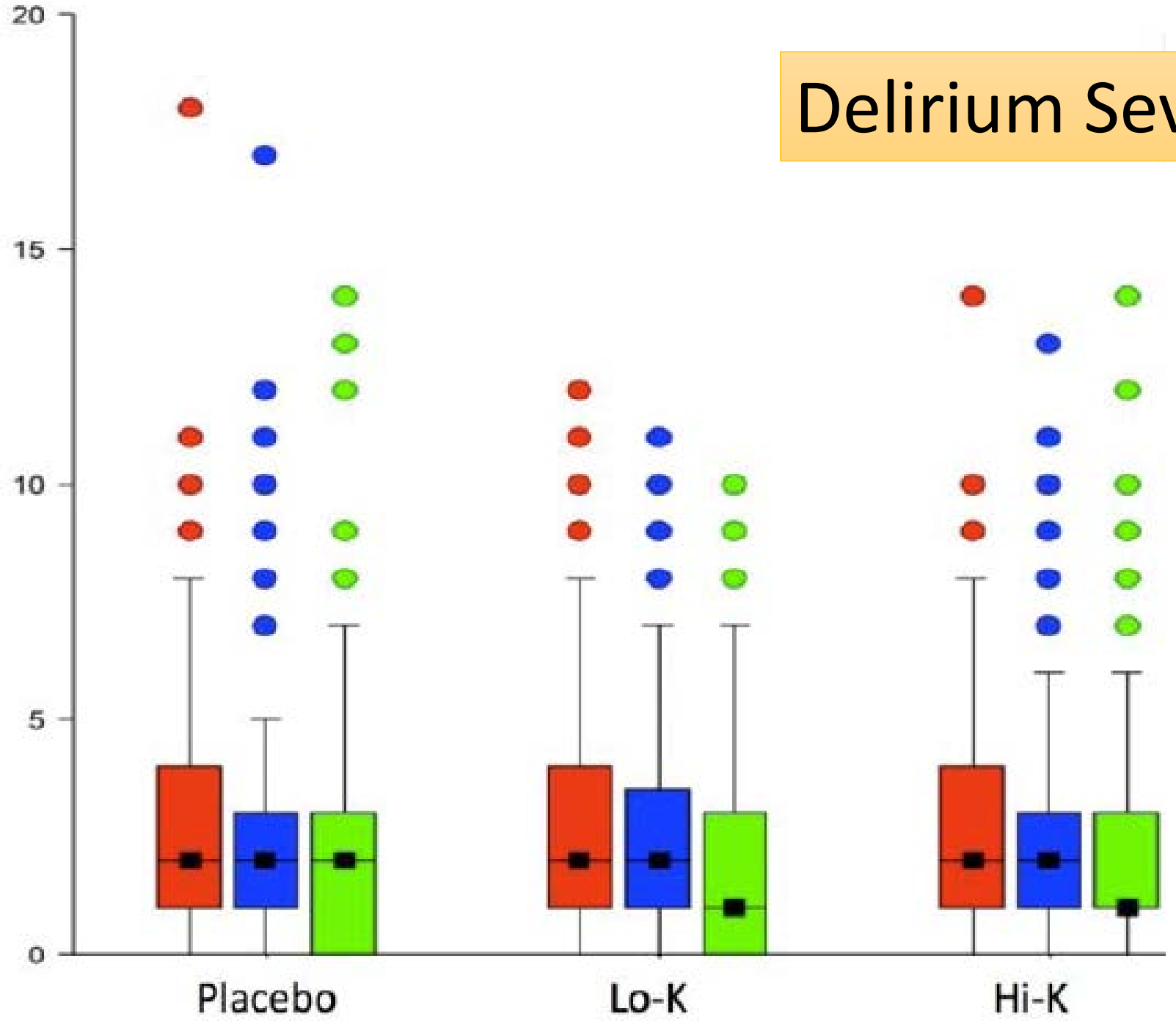
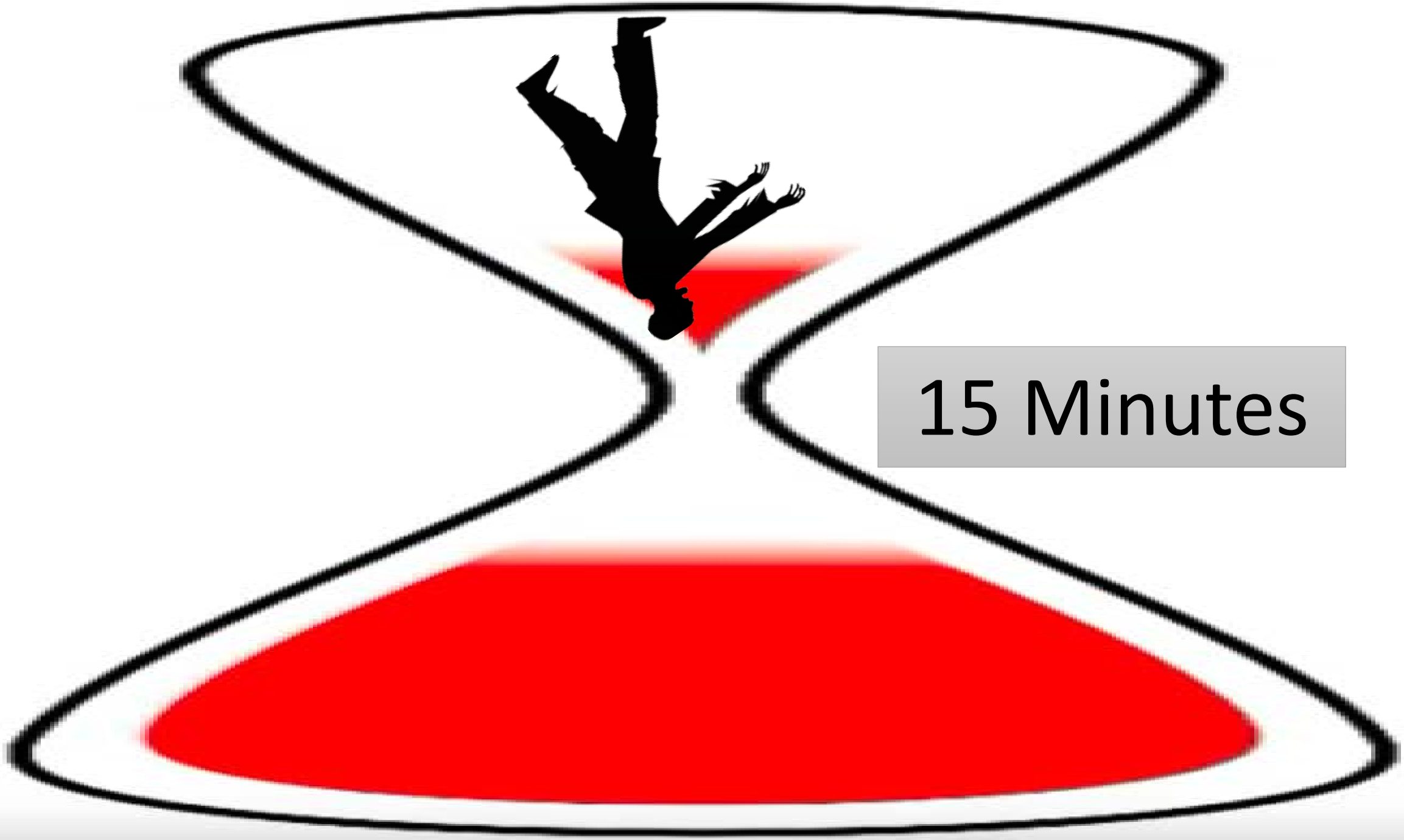


Table 10s: Cox regression for time to delirium onset with post hoc sensitivity analysis assuming missing delirium assessments to be positive

	Maximum Likelihood Parameter Estimates									
	Actual incidence rates†					Post hoc sensitivity analysis‡				
Any Positive CAM During POD 1 - 3	Coef.	Chi2	P> Chi2	95% Conf. Interval		Coef.	Chi2	P> Chi2	95% Conf. Interval	
Study Arms										
Lo-K Study Arm	0.049	0.05	0.818	-0.365	0.461	0.017	0.01	0.935	-0.399	0.434
Hi-K Study Arm	-0.013	0.00	0.951	-0.412	0.386	-0.045	0.05	0.827	-0.450	0.360
Canadian Sites	0.017	0.01	0.943	-0.456	0.490	0.096	0.15	0.698	-0.389	0.581
Female	-0.135	0.55	0.459	-0.492	0.222	-0.154	0.70	0.403	-0.515	0.207
Age	-0.057	20.77	<.0001	-0.081	-0.032	-0.052	17.76	<.0001	-0.076	-0.028
Charlson Comorbidity Index	-0.063	3.08	0.080	-0.134	0.007	-0.058	2.53	0.112	-0.131	0.014
Falls (Within past six months)	-0.049	0.05	0.826	-0.486	0.388	-0.117	0.28	0.594	-0.547	0.313
History of OSA	-0.421	3.90	0.048	-0.839	-0.003	-0.433	4.18	0.041	-0.849	-0.018
History of Depression	-0.655	8.02	0.005	-1.108	-0.202	-0.694	9.02	0.003	-1.146	-0.241
Alcohol Use (Weekly)	0.271	2.16	0.142	-0.091	0.632	0.257	1.91	0.167	-0.107	0.620
Intraop. Midazolam Administered	-0.010	0.05	0.815	-0.095	0.074	-0.024	0.34	0.561	-0.105	0.057
Intraop. Opiates Administered	0.000	0.26	0.608	-0.001	0.001	0.000	0.57	0.449	-0.001	0.001
Surgery Type (Cardiac vs. the rest)	-0.845	15.26	<.0001	-1.268	-0.421	-0.873	16.23	<.0001	-1.298	-0.448
Intercept	7.846	59.16	<.0001	5.846	9.845	7.557	57.26	<.0001	5.599	9.514
Scale	0.936	--	--	0.792	1.105	0.991	--	--	0.847	1.160
Weilbull Shape	1.069	--	--	0.905	1.262	1.009	--	--	0.862	1.181
Number of observations read	672					672				
Number of observations used	628					641				

Table 11s: Recurrent event regression model for sequentially repeated delirium assessments

	Counting Process Model*										
	With:	Model-Based Variance Estimate†				Sandwich Variance Estimate‡					
Repeated Delirium Count	Coef.	SE	Chi2	P> Chi2	H.R.	Coef.	SE	SE Ratio	Chi2	P> Chi2	H.R.
Study Arms											
Lo-K Study Arm	-0.285	0.159	3.217	0.073	0.752	-0.285	0.233	1.467	1.496	0.221	0.752
Hi-K Study Arm	-0.002	0.144	0.000	0.987	0.998	-0.002	0.225	1.565	0.000	0.992	0.998
Canadian Sites	-0.050	0.185	0.073	0.787	0.951	-0.050	0.302	1.634	0.027	0.869	0.951
Female	0.044	0.134	0.107	0.743	1.045	0.044	0.204	1.519	0.047	0.829	1.045
Age	0.060	0.008	52.529	<0.0001	1.062	0.060	0.011	1.375	27.769	<.0001	1.062
Charlson Comorbidity Index	0.058	0.026	4.931	0.026	1.060	0.058	0.038	1.455	2.331	0.127	1.060
Falls (Within past six months)	0.195	0.154	1.590	0.207	1.215	0.195	0.252	1.631	0.598	0.439	1.215
History of OSA	0.558	0.147	14.426	0.0001	1.747	0.558	0.230	1.564	5.895	0.015	1.747
History of Depression	0.349	0.174	4.011	0.045	1.417	0.349	0.255	1.465	1.869	0.172	1.417
Alcohol Use (Weekly)	-0.324	0.134	5.847	0.016	0.723	-0.324	0.199	1.481	2.664	0.103	0.723
Intraop. Midazolam Administered	0.000	0.031	0.000	0.996	1.000	0.000	0.046	1.476	0.000	0.997	1.000
Intraop. Opiates Administered	0.0001	0.0003	0.117	0.733	1.000	0.0001	0.0004	1.113	0.094	0.759	1.000
Surgery Type (Cardiac vs. the rest)	0.883	0.152	33.588	<0.0001	2.419	0.883	0.244	1.601	13.110	0.0003	2.419
Number of observations read			4,032						4,032		
Number of observations used			3,136						3,768		
Number of delirium events			268						268		


15 Minutes

	All groups (n=672)	Placebo (n=222)	0·5 mg/kg ketamine (n=227)	1·0 mg/kg ketamine (n=223)
Postoperative day 1				
am				
Pain level at rest (n=492)	22 (5–47)	24 (10–46)	22 (5–45)	20 (5–50)
Pain level when taking a deep breath (n=490)	40 (13–70)	43 (18–67)	35 (9–67)	46 (13–73)
Pain level when moving (n=485)	49 (22–76)	46 (27–75)	48 (19–77)	50 (20–76)
pm				
Pain level at rest (n=532)	19 (4–44)	20 (6–39)	17 (4–46)	16 (4–45)
Pain level when taking a deep breath (n=529)	36 (10–67)	38 (16–63)	35 (10–69)	36 (10–70)
Pain level when moving (n=527)	45 (21–74)	45 (27–70)	45 (21–75)	45 (18–74)

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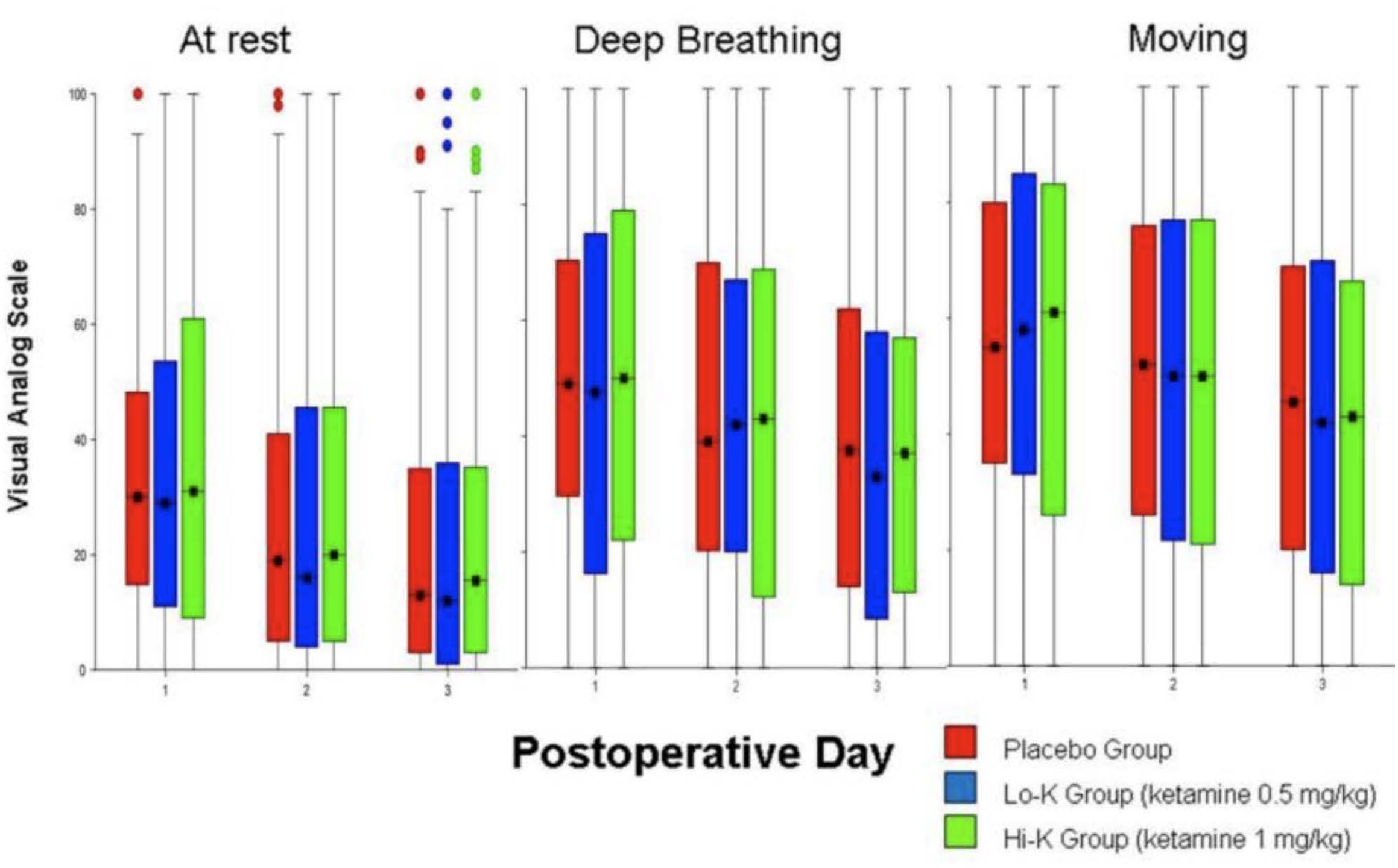
At rest
Deep Breathing
Moving
Visual Analog Scale
100
80
60
40
20
0
1
2
3
Postoperative Day
Placebo Group
Lo-K Group (ketamine 0.5 mg/kg)
Hi-K Group (ketamine 1 mg/kg)

	All groups (n=672)	Placebo (n=222)	0·5 mg/kg ketamine (n=227)	1·0 mg/kg ketamine (n=223)
Morphine equivalents POD0 (n=598)	18 (8–48)	17 (8–49)	17 (8–50)	18 (8–42)
Morphine equivalents POD1 (n=605)	32 (17–68)	33 (17–78)	32 (18–63)	30 (16–59)
Morphine equivalents POD2 (n=559)	24 (12–48)	25 (12–52)	24 (12–44)	22 (12–49)
Morphine equivalents POD3 (n=450)	19 (8–40)	22 (10–42)	17 (8–39)	16 (8–38)

Data are median (IQR). Numbers are rounded to the nearest mg. The conversion table that was used to convert opioids to morphine equivalents in mg is provided in the appendix. Data were not available after hospital discharge.
POD=postoperative day.

***Table 4*: Postoperative opioids in morphine equivalents**

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	Overall	Placebo	Lo-K	Hi-K
	672	222(33%)	227(34%)	223(33%)
	Median(IQR)	Median(IQR)	Median(IQR)	Median(IQR)
Post-Operative Day 1				
AM (n =559)	3(3 - 4)	3(3 - 4)	3(3 - 4)	3(3 - 4)
PM (n =574)	3(3 - 4)	3(3 - 4)	3(3 - 4)	3(3 - 4)
Maximum Daily Score (n =622)	4(3 - 5)	4(3 - 4)	4(3 - 5)	4(3 - 5)
Post-Operative Day 2				
AM (n =557)	3(3 - 4)	3(3 - 4)	3(3 - 4)	3(3 - 4)
PM (n =544)	3(3 - 4)	3(3 - 4)	3(3 - 4)	3(3 - 4)
Maximum Daily Score (n =612)	3(3 - 4)	3(3 - 4)	4(3 - 4)	3(3 - 4)
Post-Operative Day 3				
AM (n =514)	3(3 - 4)	3(3 - 4)	3(3 - 4)	3(3 - 4)
PM (n =478)	3(3 - 4)	3(3 - 4)	3(3 - 3)	3(3 - 4)
Maximum Daily Score (n =571)	3(3 - 4)	3(3 - 4)	3(3 - 4)	3(3 - 4)

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Unintended Consequences

There were more postoperative hallucinations (p=0·01) and nightmares (p=0·03) with increasing ketamine doses compared with placebo.

A single subanaesthetic dose of ketamine did not decrease delirium (or pain) in older adults after major surgery, and might cause harm by inducing negative experiences.

THE LANCET

Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

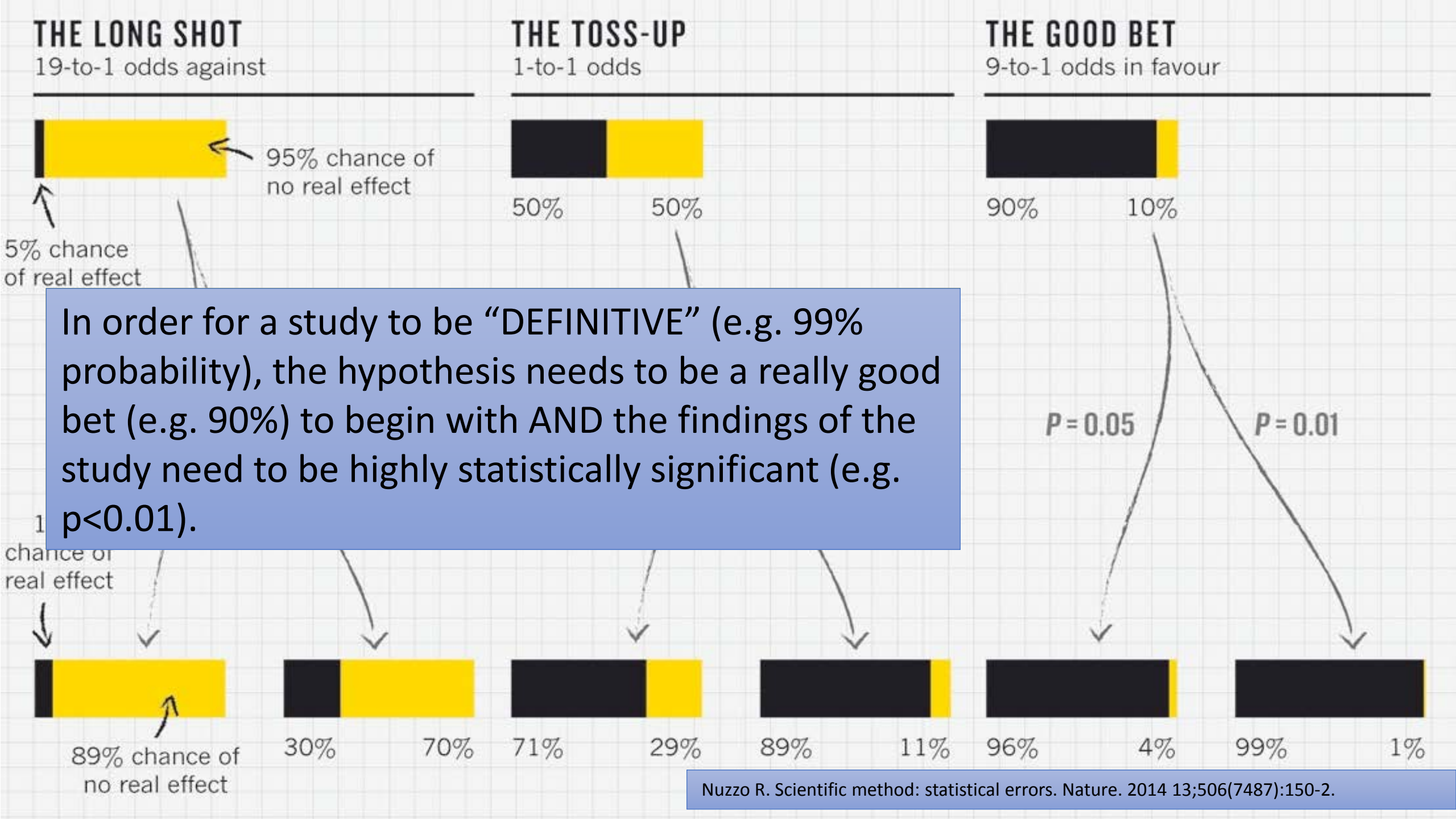
Conclusion

Taking all the evidence into account, the increasingly common clinical practice of administering a single subanaesthetic intraoperative bolus of ketamine should be reconsidered. The likelihood that ketamine prevents postoperative delirium is low. Considering the importance of finding safe analgesic alternatives to opioids, promising previous evidence regarding the analgesic efficacy of subanaesthetic ketamine, and that pain was a secondary outcome of the PODCAST trial, subsequent research should be done to confirm or refute the observed absence of meaningful postoperative analgesia with intraoperative ketamine.

THE LANCET

Avidan MS et al. Lancet Volume 390, No. 10091, p267–275, 15 July 2017

Estimating Probabilities from P Values…



In order for a study to be "DEFINITIVE" (e.g. 99% probability), the hypothesis needs to be a really good bet (e.g. 90%) to begin with AND the findings of the study need to be highly statistically significant (e.g. p<0.01).

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

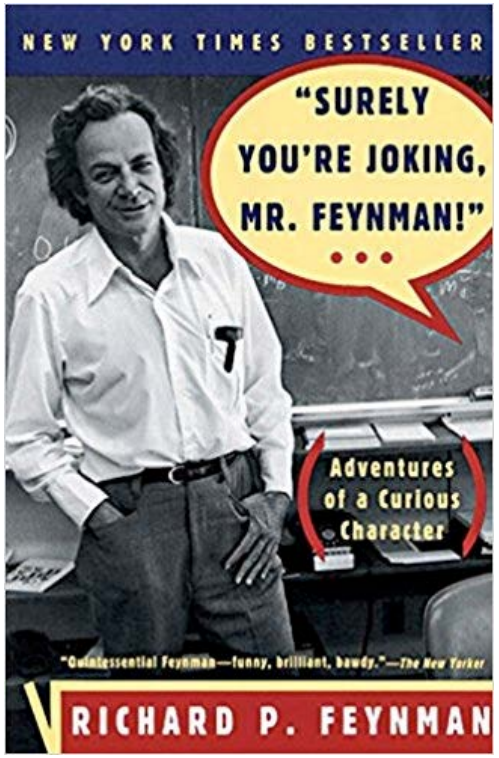
We all suffer from cognitive bias

We like the results of studies with which we agree.

"Ever since I first learned about confirmation bias I've been seeing it everywhere."

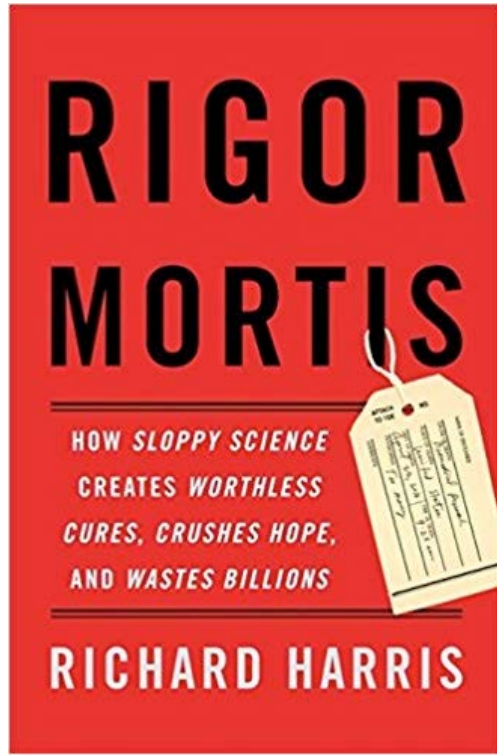
Jon Ronson in *So You've Been Publicly Shamed* (Picador, 2015)

Surely You're Joking, Mr. Feynman!



"The first principle is that you must not fool yourself and you are the easiest person to fool."

"Good methods not only test ideas; they help scientists avoid fooling themselves."



HOW SCIENTISTS FOOL THEMSELVES — AND HOW THEY CAN STOP

Humans are remarkably good at self-deception. But growing concern about reproducibility is driving many researchers to seek ways to fight their own worst instincts.

Nature 526, 182–185 (08 October 2015)

Something we see all the time…

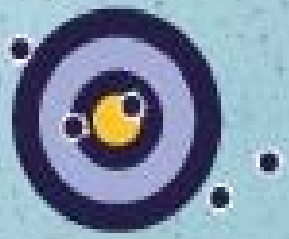
HARKing, or hypothesizing after results are known.

Nature 526, 182–185 (08 October 2015)

COGNITIVE FALLACIES IN RESEARCH

HYPOTHESIS MYOPIA

Collecting evidence to support a hypothesis, not looking for evidence against it, and ignoring other explanations.

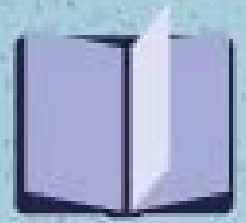


TEXAS SHARPSHOOTER

Seizing on random patterns in the data and mistaking them for interesting findings.

ASYMMETRIC ATTENTION

Rigorously checking unexpected results, but giving expected ones a free pass.



JUST-SO STORYTELLING

Finding stories after the fact to rationalize whatever the results turn out to be.

Nature 526, 182–185 (08 October 2015)

HYPOTHESIS MYOPIA	TEXAS SHARPSHOOTER	ASYMMETRIC ATTENTION	JUST-SO STORYTELLING
			
DEVIL'S ADVOCACY	**PRE-COMMITMENT**	**TEAM OF RIVALS**	**BLIND DATA ANALYSIS**
Explicitly consider alternative hypotheses — then test them out head-to-head.	Publicly declare a data collection and analysis plan before starting the study.	Invite your academic adversaries to collaborate with you on a study.	Analyse data that look real but are not exactly what you collected — and then lift the blind.

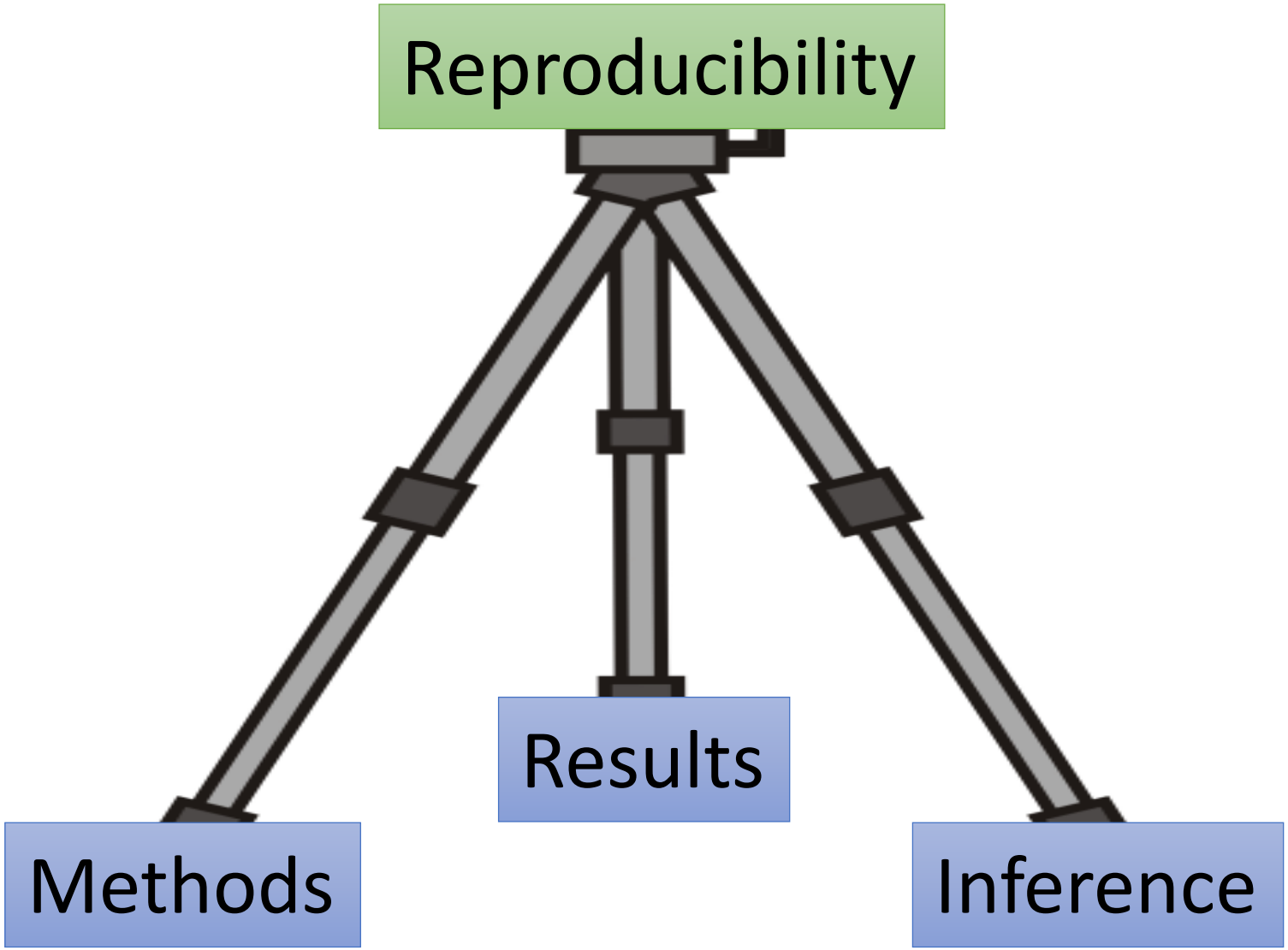
go.nature.com/nqyohl

Nature 526, 182–185 (08 October 2015)

Open Science…

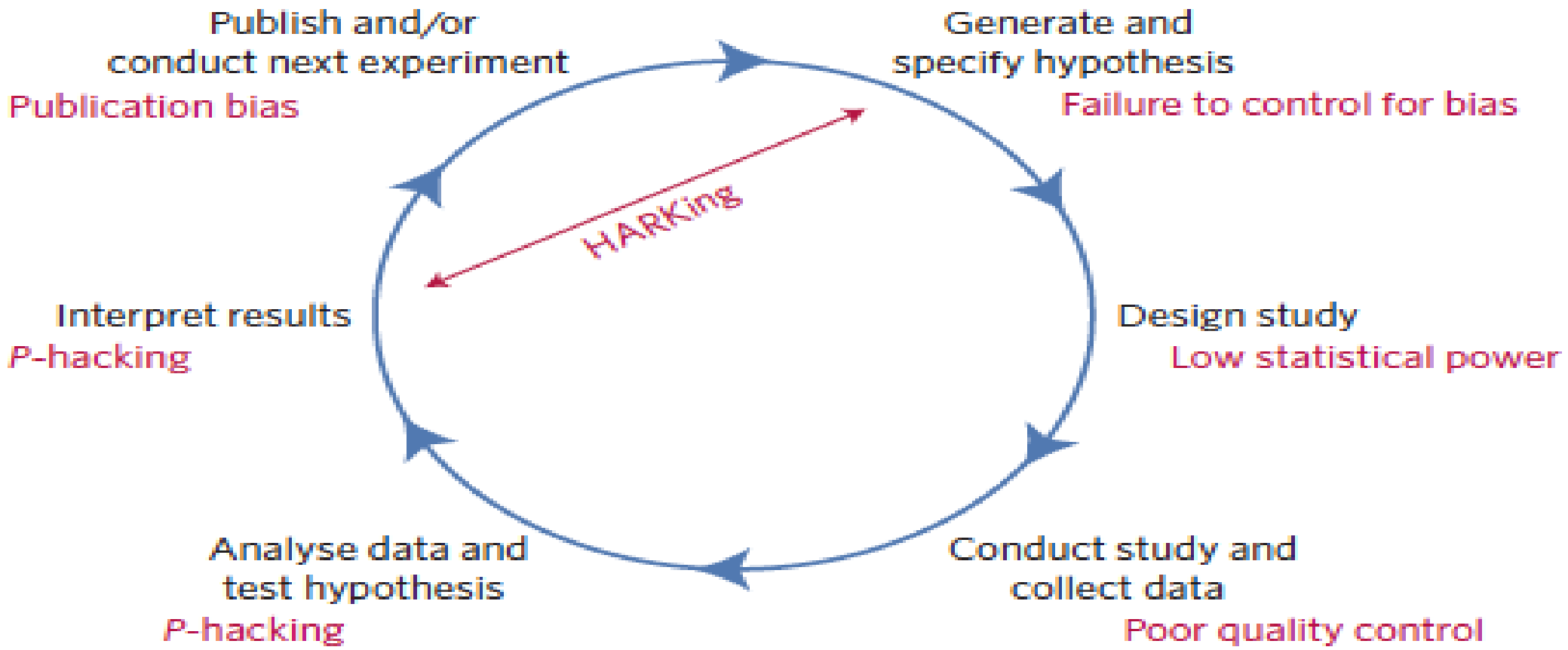
- You like our approach, you “guarantee” that you will publish our results, regardless what they show.

Nature 526, 182–185 (08 October 2015)



Goodman SN, Fanelli D, Ioannidis JP. What does research reproducibility mean? Sci Transl Med. 2016 Jun 1;8(341):341ps12.

Threats to Reproducibility



nature human behaviour
PERSPECTIVE
PUBLISHED: 10 JANUARY 2017 | VOLUME: 1 | ARTICLE NUMBER: 0021

Take-home message

“We have learnt that to understand how life works, describing how the research was done is as important as describing what was observed.”

Validation by the SCIENCE EXCHANGE network

About Projects Press Contact Return to ScienceExchange.com

Validating key experimental results via independent replication

Learn more »

As seen in

Science BBC nature The Economist nature biotechnology REUTERS

Major projects

Reproducibility Initiative

Helping scientists validate their work by facilitating replication through the Science Exchange network

View details »

Reproducibility Project: Cancer Biology

Investigating the replicability of the 50 most impactful cancer biology studies from 2010-2012

View details »

Independent Validation Service

Helping VCs, funding agencies, and others validate findings to promote high-quality research

View details »

MF/PCF Reproducibility Initiative

Assessing the reproducibility of research findings with implications for prostate cancer patients

View details »

http://validation.scienceexchange.com/#/home

Recommended Reading List

1: Goodman S. A dirty dozen: twelve p-value misconceptions. Semin Hematol. 2008 Jul;45(3):135-40. Erratum in: Semin Hematol. 2011;48(4):302.

2: Ioannidis JP. Why most published research findings are false. PLoS Med. 2005;2(8):e124.

3: Halsey LG, Curran-Everett D, Vowler SL, Drummond GB. The fickle P value generates irreproducible results. Nat Methods. 2015 Mar;12(3):179-85.

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

5: Goodman SN, Fanelli D, Ioannidis JP. What does research reproducibility mean? Sci Transl Med. 2016 Jun 1;8(341):341ps12.

What makes Science true?

- https://metrics.stanford.edu/
- https://www.youtube.com/watch?v=NGFO0kdbZmk
- http://www.pbs.org/wgbh/nova/body/reproduce-science.html

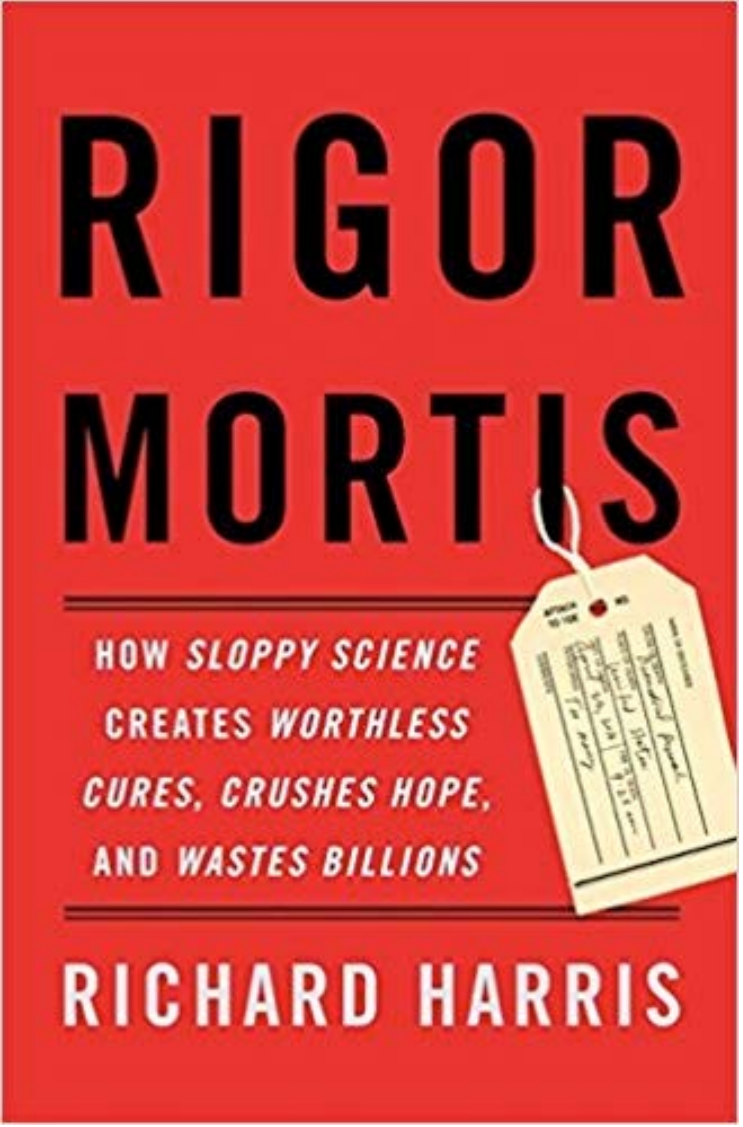

Biology is often more complicated than it seems.
Ear

Objectives

- Gain insight into the current reproducibility crisis in science;
  - Rigor begets reproducibility.
- Learn about the three pillars of reproducibility;
  - Methods, Results, Inference
- Understand some of the solutions to the crisis;
  - Debiasing techniques
- Acquire ability to discern whether results of a study are likely to be true.
  - Negative results, results that make a lot of sense (to skeptics), and results with very low p values are often true.

One Profound Question

At what point should clinical practice be changed based on the scientific evidence?

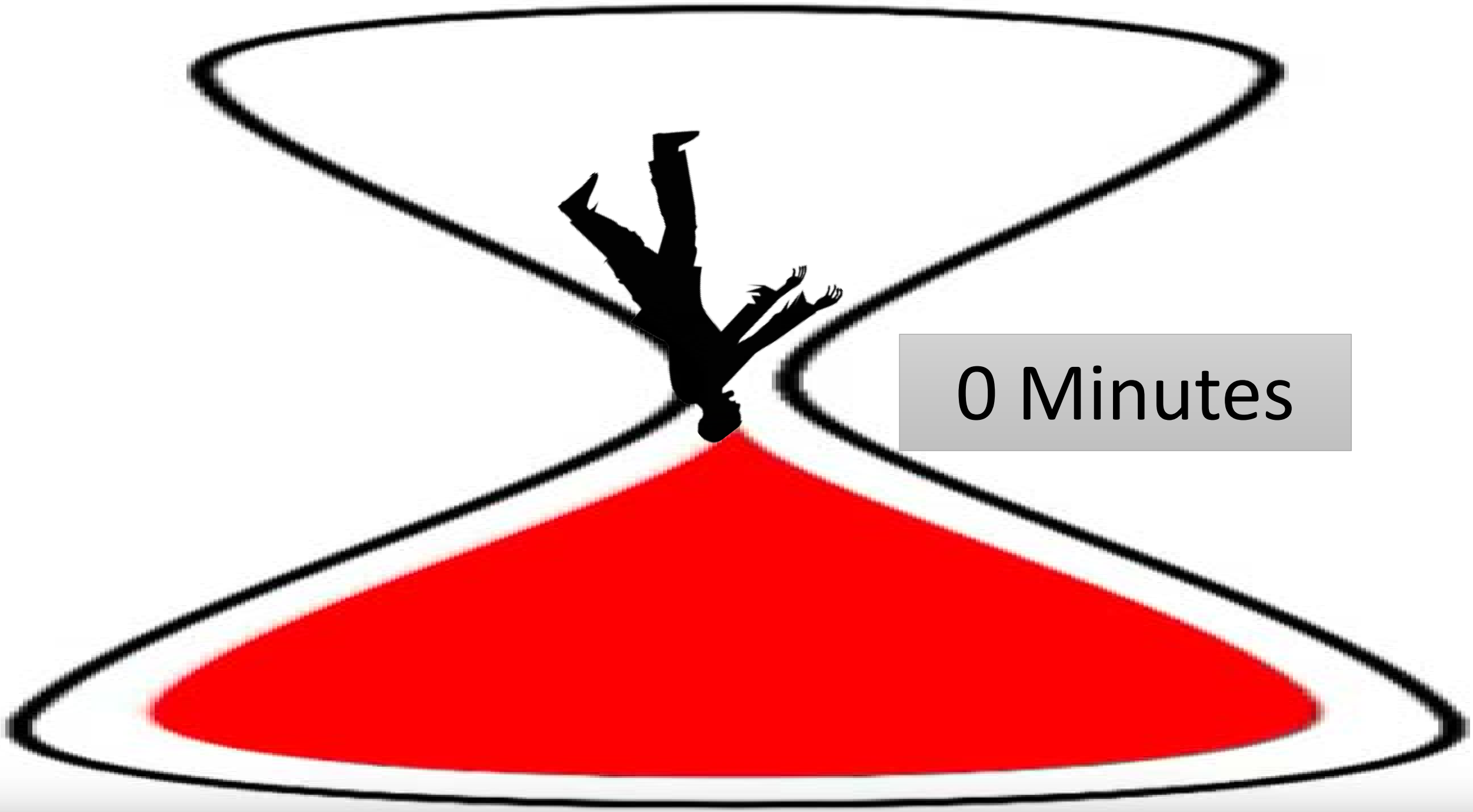


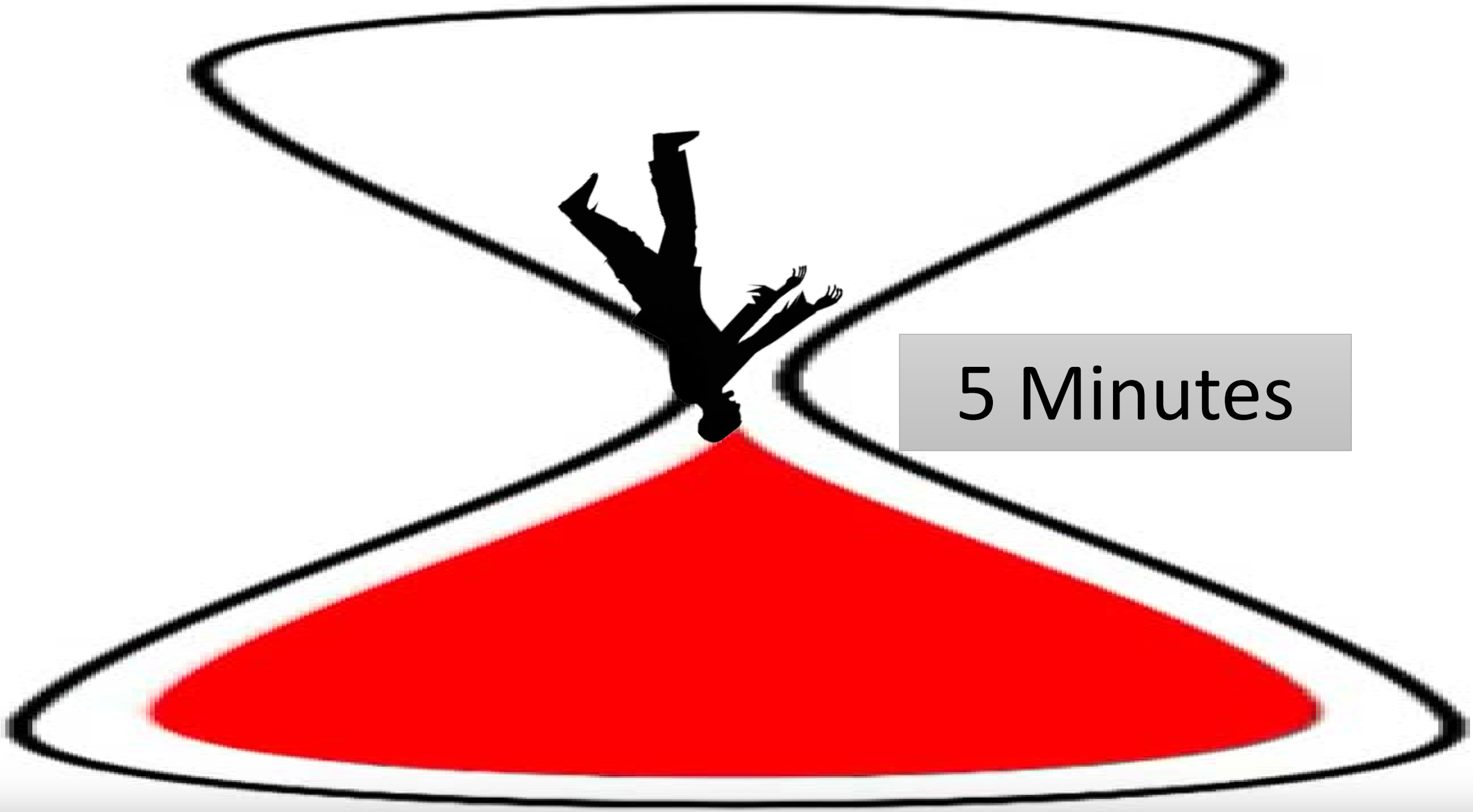
META·RESEARCH INNOVATION CENTER AT STANFORD

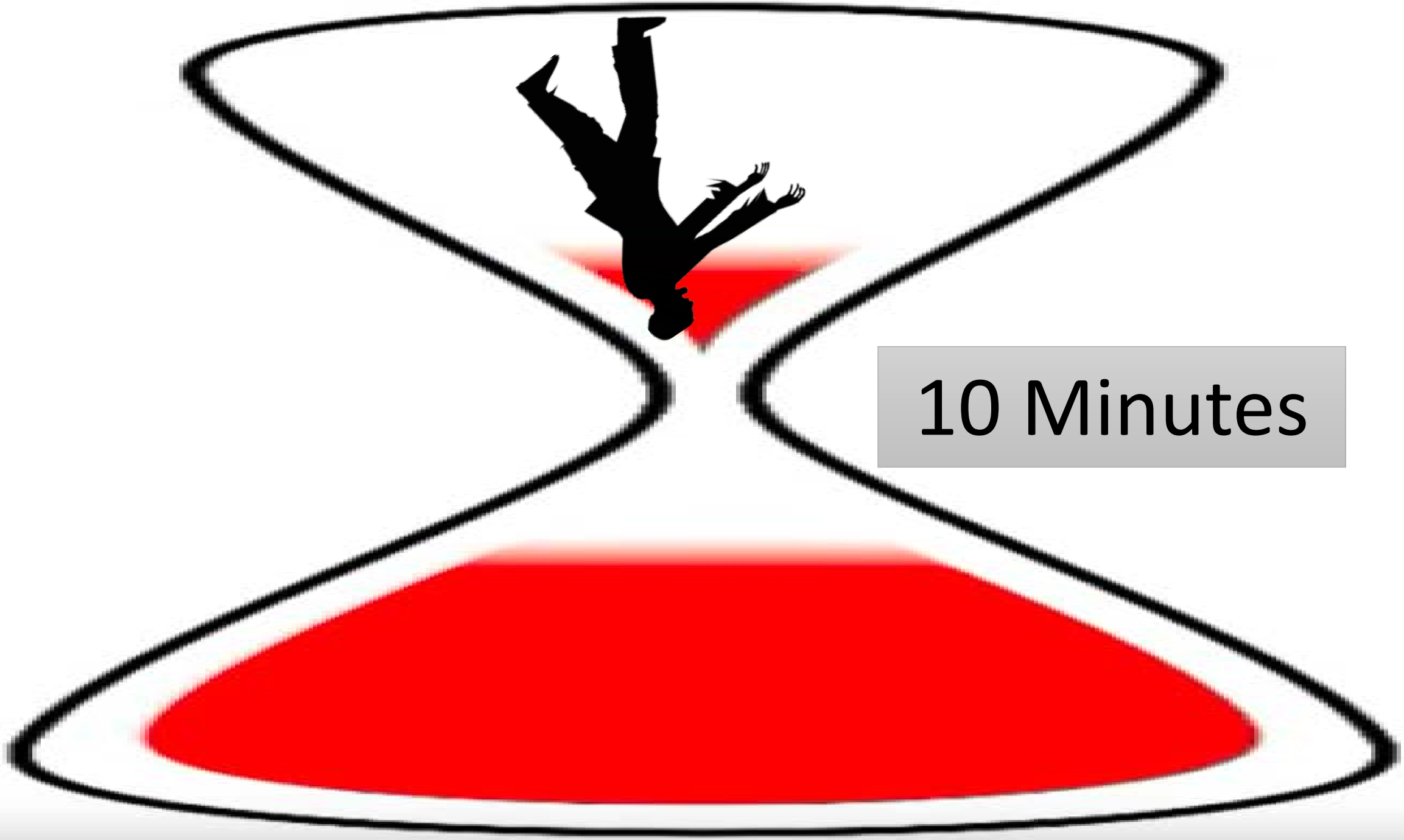
METRICS

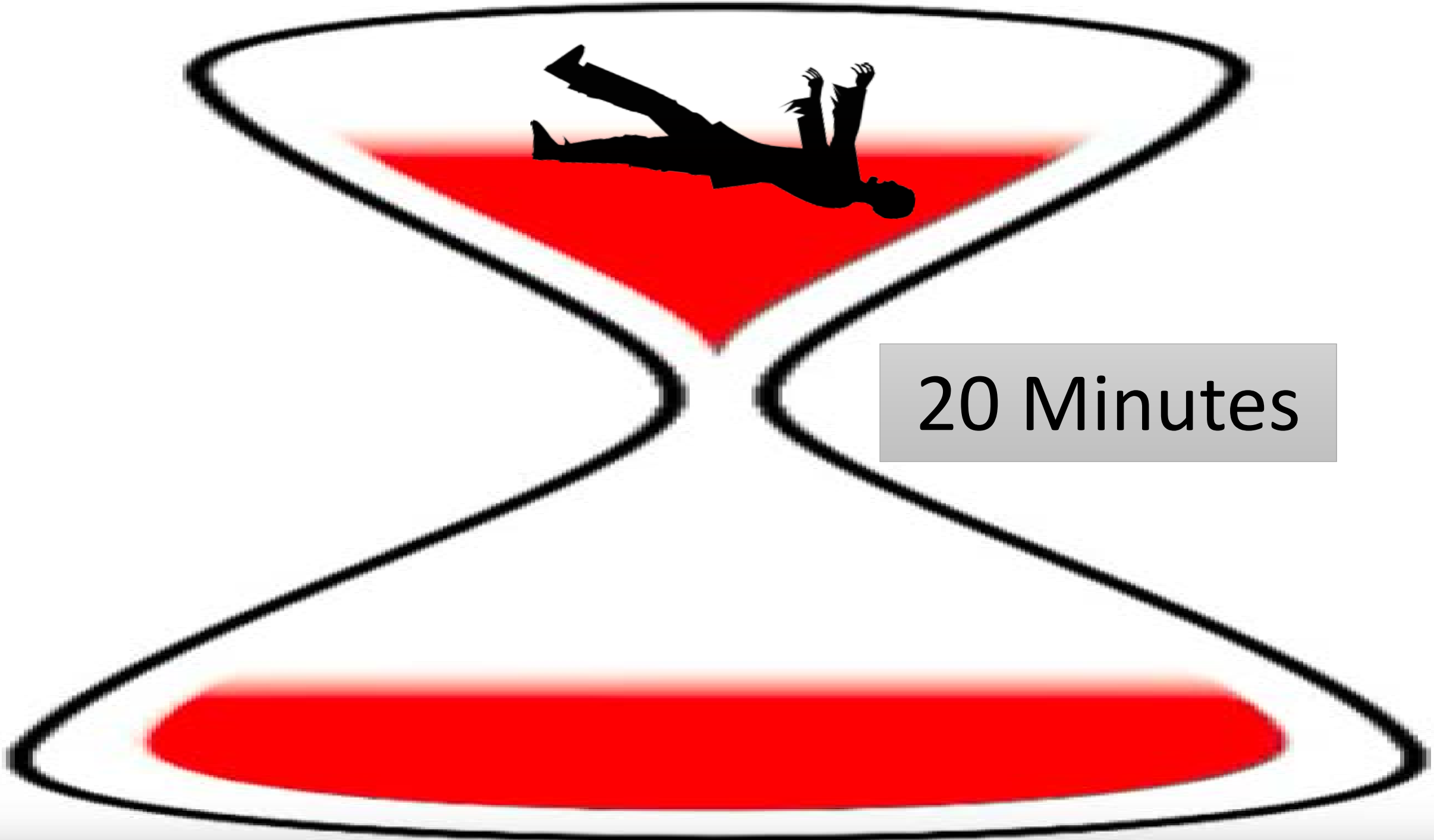
MiRoR
Methods in Research on Research

statcheck


0 Minutes


5 Minutes


10 Minutes


20 Minutes