Radical Pragmatism:
DOOR and SMART COMPASS for the Evaluation of Antibiotics

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FDA
November 19, 2019

A Leaky Roof…

- Created a water bubble in my wall
- In addition to a new roof, I had to re-paper the wall
- My neighbor recently papered a similar-sized room in his house. I asked:

  “How much paper did you buy?”

- He replied: “Six rolls.”

Upon finishing the papering of the wall…

- I had only used only 4 rolls
- I told my neighbor that I had 2 rolls left
- He replied:

"Oh. That happened to you too?"

Two Things I've Learned about Antibiotic Clinical Trials

1. They are rigorously conducted by experts closely adhering to the highest standards and fundamental principles of RCTs

2. They are essentially useless for helping clinicians make treatment decisions

Most clinical trials fail to provide the evidence needed to inform medical decision-making. However, the serious implications of this deficit are largely absent from public discourse.

DeMets and Califf, *JAMA*, 2011

Example Issues

- Drugs are compared in susceptible disease, but susceptibility status is unknown at the time of treatment initiation
- Patients are considered failures when they change therapy, though they may not fail
- We lose interest in patients that change therapy, despite therapeutic adjustments that can effectively treat the patient
- Population studied ≠ population applied
  - E.g., noninferiority trials exclude patients with recent prior therapy. Then these drugs are used in these patients, possibly representing a majority.

Question 1

- We define analysis populations
  - Efficacy: ITT population
  - Safety: safety population
- Efficacy population ≠ safety population
- We combine these two analyses into benefit:risk analyses
- To whom does this analysis apply?

Question 2

- We measure the duration of hospitalization
- Shorter duration is better … or is it?
- The faster the patient dies, the shorter the duration
- Outcome interpretation needs context of other outcomes

Question 3

- Trials typically use binary endpoints
- E.g., “cure”: patient survives, symptoms resolve, microbiological eradication, no changes to therapy
- Consider the following:
  - One patient fails because they die
  - Another patient fails because of lack of micro eradication
  - Primary analyses treats these patients equivalently (failure)
- Shouldn’t primary analysis recognize the difference?

FDA Advisory Committee Evaluation of Plazomicin in cUTI

Drug	Composite Cure				
Plazomicin	81.7%				
Meropenem	70.1%				

FDA Advisory Committee Evaluation of Plazomicin in cUTI

Drug	Composite Cure	Clinical Cure			
Plazomicin	81.7%	89.0%			
Meropenem	70.1%	90.4%			

FDA Advisory Committee Evaluation of Plazomicin in cUTI

Drug	Composite Cure	Clinical Cure	Micro Eradication		
Plazomicin	81.7%	89.0%	89.5%		
Meropenem	70.1%	90.4%	74.6%		

FDA Advisory Committee Evaluation of Plazomicin in cUTI

				Safety	
Drug	**Composite Cure**	**Clinical Cure**	**Micro Eradication**	**1-level Decrease in Creatinine Clearance**	**Last Serum Creatinine Increased ≥ 0.5 mg/dL**
Plazomicin	81.7%	89.0%	89.5%	13.7%	3%
Meropenem	70.1%	90.4%	74.6%	5.7%	1%

$$1 + 2 \times 3 \neq 9$$

Children in grade school have learned this.

Clinical trialists missed this class.

Question 4

- Suppose a loved one is diagnosed with a serious disease
- You are selecting treatment
- 3 treatment options: A, B, and C
- 2 outcomes, equally important
  - Treatment success: yes/no
  - Safety event: yes/no

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

They all have the same success rate.

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

They all have the same success rate.

A has the lowest safety event rate.

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
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Which treatment would you choose?

They all have the same success rate.

A has the lowest safety event rate.

B and C are indistinguishable.

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

They all have the same success rate.

A has the lowest safety event rate.

B and C are indistinguishable.

Choose A…right?

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

Safety event: 30%

		Success +	Success -
SE	+	15	15
	-	35	35

B (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	50	0
	-	0	50

C (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	0	50
	-	50	0

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

Safety event: 30%

		Success +	Success -
SE	+	15	15
	-	35	35

B (N=100)

Success: 50%

Safety event: 50%

	Success +	Success -
+	50	0
-	0	50

C (N=100)

Success: 50%

Safety event: 50%

	Success +	Success -
+	0	50
-	50	0

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

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Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	50	0
	-	0	50

C (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	0	50
	-	50	0

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

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		Success +	Success -
SE	+	15	15
	-	35	35

B (N=100)

Success: 50%

Safety event: 50%

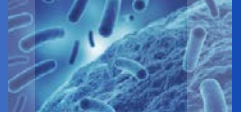
		Success +	Success -
SE	+	50	0
	-	0	50

C (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	0	50
	-	50	0



Our culture is to use patients to analyze the outcomes.

Shouldn’t we use outcomes to analyze the patients?

Scott's father (a math teacher) to his confused son many years ago:

"The order of operations is important…"

"The good physician treats the disease.
The great physician treats the patient."

William Osler

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2016, VOL. 8, NO. 4, 386–393
http://dx.doi.org/10.1080/19466315.2016.1207561

Taylor & Francis
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Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes: A Step Toward Pragmatism in Benefit:Risk Evaluation

Scott R. Evans[a,b] and Dean Follmann[c]

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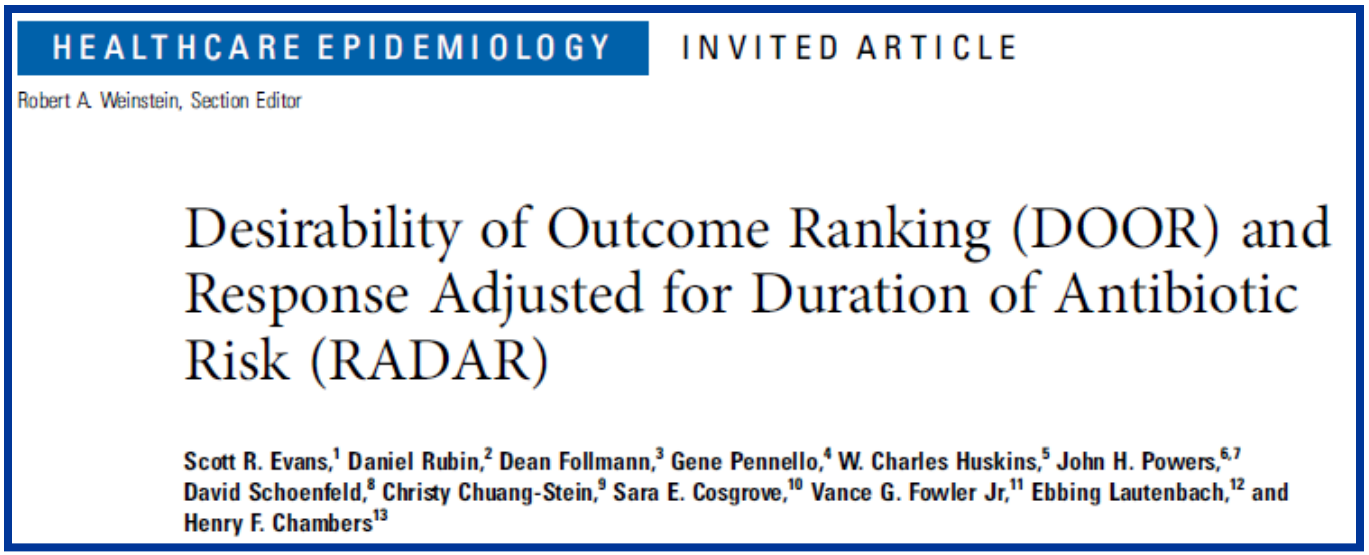


HEALTHCARE EPIDEMIOLOGY INVITED ARTICLE

Robert A. Weinstein, Section Editor

Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)

Scott R. Evans,[1] Daniel Rubin,[2] Dean Follmann,[3] Gene Pennello,[4] W. Charles Huskins,[5] John H. Powers,[6,7] David Schoenfeld,[8] Christy Chuang-Stein,[9] Sara E. Cosgrove,[10] Vance G. Fowler Jr,[11] Ebbing Lautenbach,[12] and Henry F. Chambers[13]

DOOR probability: probability of a more desirable global outcome when assigned to the new vs. the control treatment

Example

CRACKLE
Antibacterial Resistance Leadership Group

Should we use ceftazidime-avibactam or colistin for the initial treatment of CRE infection?

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

DOOR

- DOOR: 4 levels
  - Alive; discharged home
  - Alive; not discharged home; no renal failure
  - Alive; not discharged home; renal failure
  - Death

- Looking for northward migration of patients in these categories

DOOR

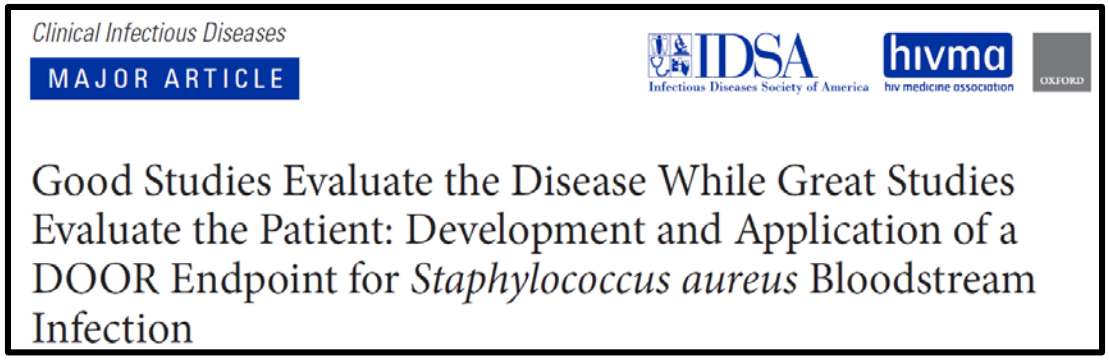
	Colistin (N=46)	Caz-Avi (N=26)
Discharged home	4 (9%)	6 (23%)
Alive; not discharged home; no renal failure	25 (54%)	17 (65%)
Alive; not discharged home; renal failure	5 (11%)	1 (4%)
Death	12 (26%)	2 (8%)

DOOR Probability: 64% (53%, 75%)

Summarizing the “Patient Journey”

Before we analyze several hundred patients,
we must understand how to analyze one.

An example strategy …

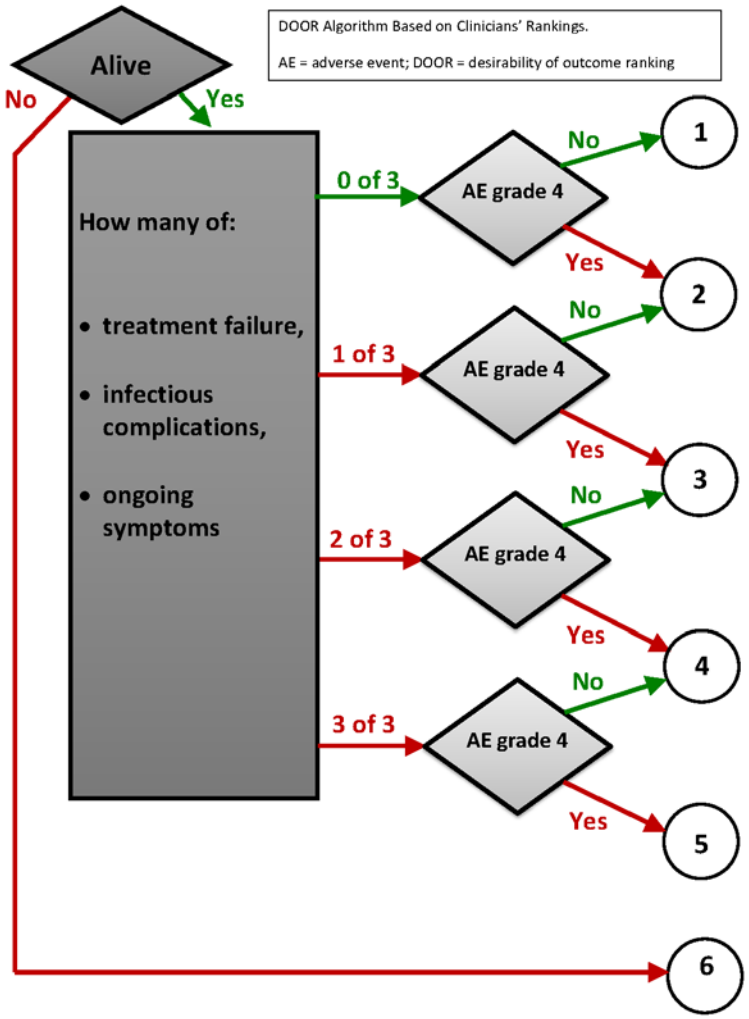


BAC DOOR

- Pre-trial sub-study to develop DOOR in *S. aureus* bacteremia
- 20 representative patient profiles (benefits, harms, and QoL) constructed based on experiences observed in prior trials
- Profiles sent to 43 expert clinicians
- They were asked to rank the profiles by *desirability of outcome*
- Examined components that drive clinician rankings

Decision Tree Algorithm

- Things that we learned
  - Cumulative effect
  - Symptoms important
  - Major non-fatal outcomes had similar importance



Can we account for:

1. **Potential unequal steps between categories?**

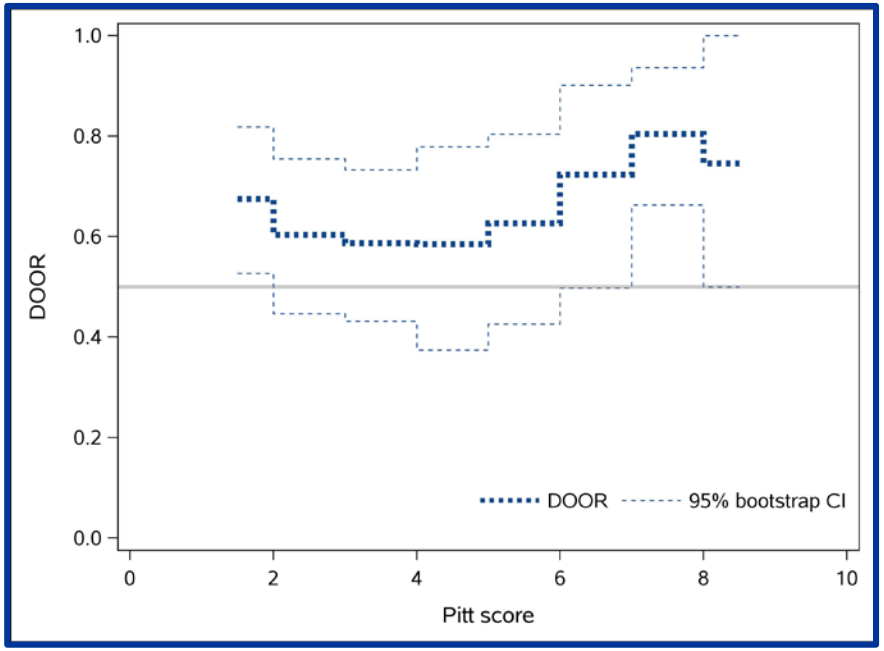
2. **Varying perspectives among patients / clinicians regarding the desirability of the categories?**

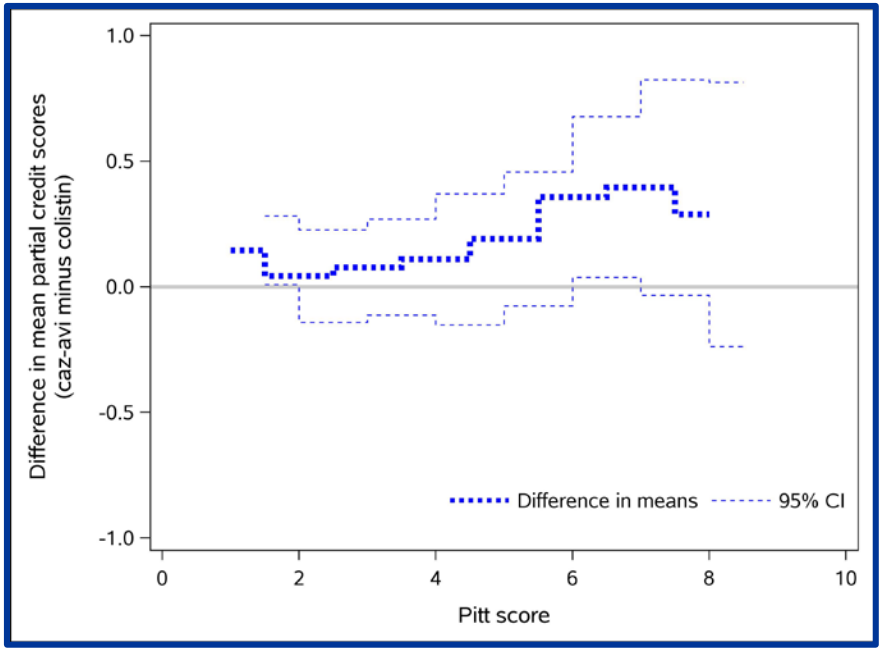
PARTIAL CREDIT

	Score
Discharged home	100
Alive; not discharged home; no renal failure	Partial credit
Alive; not discharged home; renal failure	Partial credit
Death	0

Tailoring Medicine

Who Benefits from Caz-Avi?





DOOR Probability

Partial Credit (80/60)

Largest differences are in the most severe patients.

DOOR STEPP

PROVIDE

- Prospective multi-center observational evaluation among adult hospitalized patients with MRSA bloodstream infections
- Research Question
  - What is the vancomycin pharmacodynamic exposure target associated with optimal treatment outcome?
- N=265

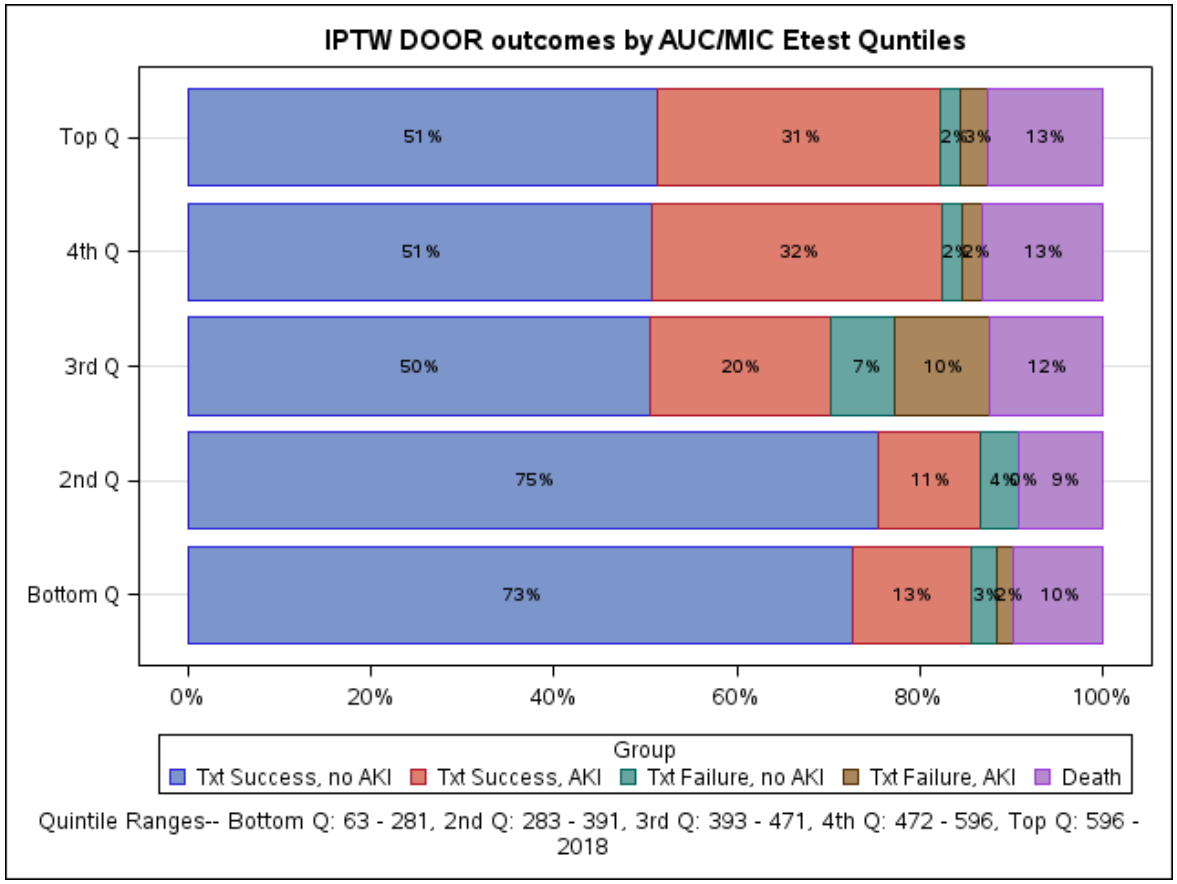
DOOR

Better outcome

Worse outcome

	Treatment success without AKI
	Treatment success with AKI
	Treatment failure (persistent bacteremia) without AKI
	Treatment failure with AKI
	Death

DOOR Outcomes by Dosing Quintiles



Higher doses bring toxicity but not greater treatment success.

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Presenting Risks and Benefits: Helping the Data Monitoring Committee Do Its Job

Scott R. Evans, PhD; Robert Bigelow, PhD; Christy Chuang-Stein, PhD; Susan S. Ellenberg, PhD; Paul Gallo, PhD; Weili He, PhD; Qi Jiang, PhD; and Frank Rockhold, PhD

Data monitoring committees (DMCs), or data and safety monitoring boards, protect clinical trial participants by conducting benefit-risk assessments during the course of a clinical trial. These evaluations may be improved by broader access to data and more effective analyses and presentation. Data monitoring committees should have access to all data, including efficacy data, at each interim review. The DMC reports should include graphical presentations that summarize benefits and harms in efficient ways. Benefit-risk assessments should include summaries that are consistent with the intention-to-treat principle and have a pragmatic focus. This article provides examples of graphical summaries that integrate benefits and harms, and proposes that such summaries become standard in DMC reports.

Ann Intern Med. 2020;172:xxx-xxx. doi:10.7326/M19-1491 **Annals.org**
For author affiliations, see end of text.
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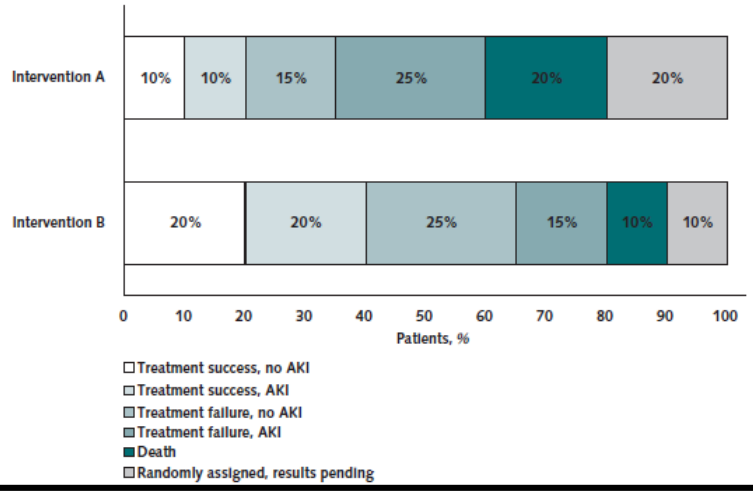
Figure 3. DOOR plot, by treatment.



ARLG 2.0

- Development of standardized syndrome-specific DOORs
  - ABSSSI
  - CABP
  - HABP/VABP
  - cIAI
  - cUTI

SMART COMPASS

Clinical Infectious Diseases

INVITED ARTICLE

IDEA: Scott R. Evans and Victor De Gruttola, Section Editors

Sequential, Multiple-Assignment, Randomized Trials for COMparing Personalized Antibiotic StrategieS (SMART-COMPASS)

Scott R. Evans,[1] Dean Follmann,[2] Ying Liu,[3] Thomas Holland,[4] Sarah B. Doernberg,[5] Nadine Rouphael,[6] Toshimitsu Hamasaki,[7] Yunyun Jiang,[1] Judith J. Lok,[8] Thuy Tien T. Tran,[1] Anthony D. Harris,[9] Vance G. Fowler Jr,[4] Helen Boucher,[10] Barry N. Kreiswirth,[11] Robert A. Bonomo,[12] David van Duin,[13] David L. Paterson,[14] and Henry Chambers[5]

[1]The Innovations in Design, Education, and Analysis Committee of the Biostatistics Center, George Washington Milken Institute School of Public Health; [2]National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; [3]Biogen, Inc., Cambridge, Massachusetts; [4]Duke University, Durham, North Carolina; [5]University of California at San Francisco; [6]Emory University, Atlanta, Georgia; [7]National Cerebral and Cardiovascular Center, Japan; [8]Boston University, Massachusetts; [9]University of Maryland School of Medicine, Baltimore; [10]Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; [11]New Jersey Medical School-Rutgers University, Newark; [12]Case Western Reserve University, Cleveland, Ohio; [13]University of North Carolina, Chapel Hill; and [14]University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital Campus, Australia.

SMART COMPASS

- Addresses several types of research questions
  - Identifies optimal strategies
  - Evaluates empiric therapies
  - Evaluates definitive therapies (licensure questions)
- Provides efficiencies compared to traditional multi-arm trials
- Pragmatic: mirrors clinical decision-making
  - Personalized medicine

NBA Coach Frank Layden

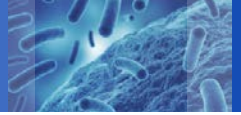
Had a player that was not producing.

Layden asked the player:

“Son, what is it with you? Is it ignorance or apathy?”

The player looked at Layden and said:

“Coach, I don't know and I don't care.”

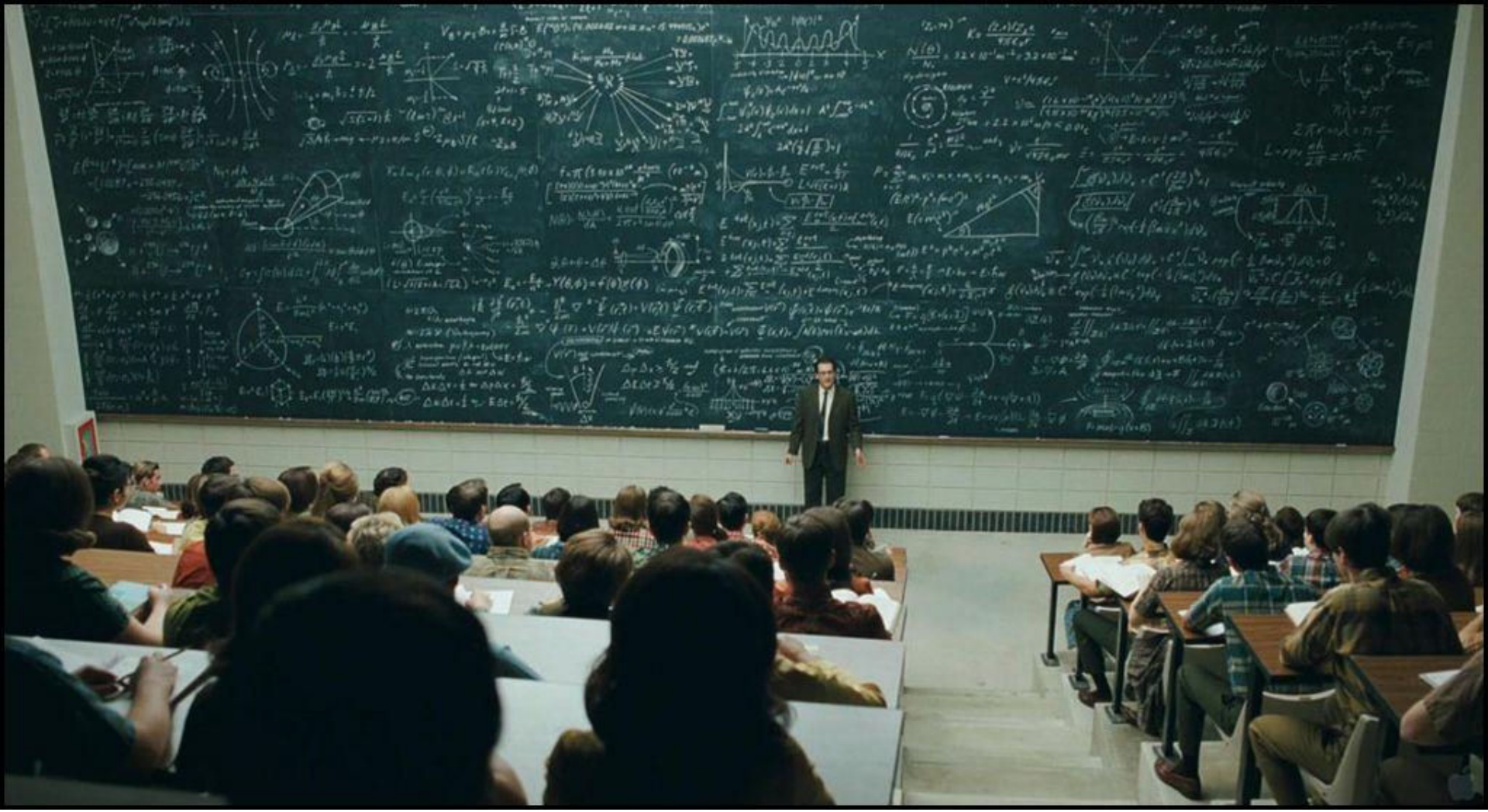


If people don’t know, then let’s educate them.

If they don’t care, then let’s motivate them.

Significant Contributors (p<0.001)

- Dean Follmann
- Dan Rubin
- Chip Chambers
- Vance Fowler
- The Antibacterial Resistance Leadership Group



I have no doubt that you will enthusiastically applaud now …
because you are so relieved that it is over.

Thank you.