DEVICE
DirEct versus VIdeo laryngosCopE trial

PRAGMATIC CRITICAL CARE RESEARCH GROUP

The DEVICE Trial:
An Embedded, Pragmatic Trial of Emergency Airway Management

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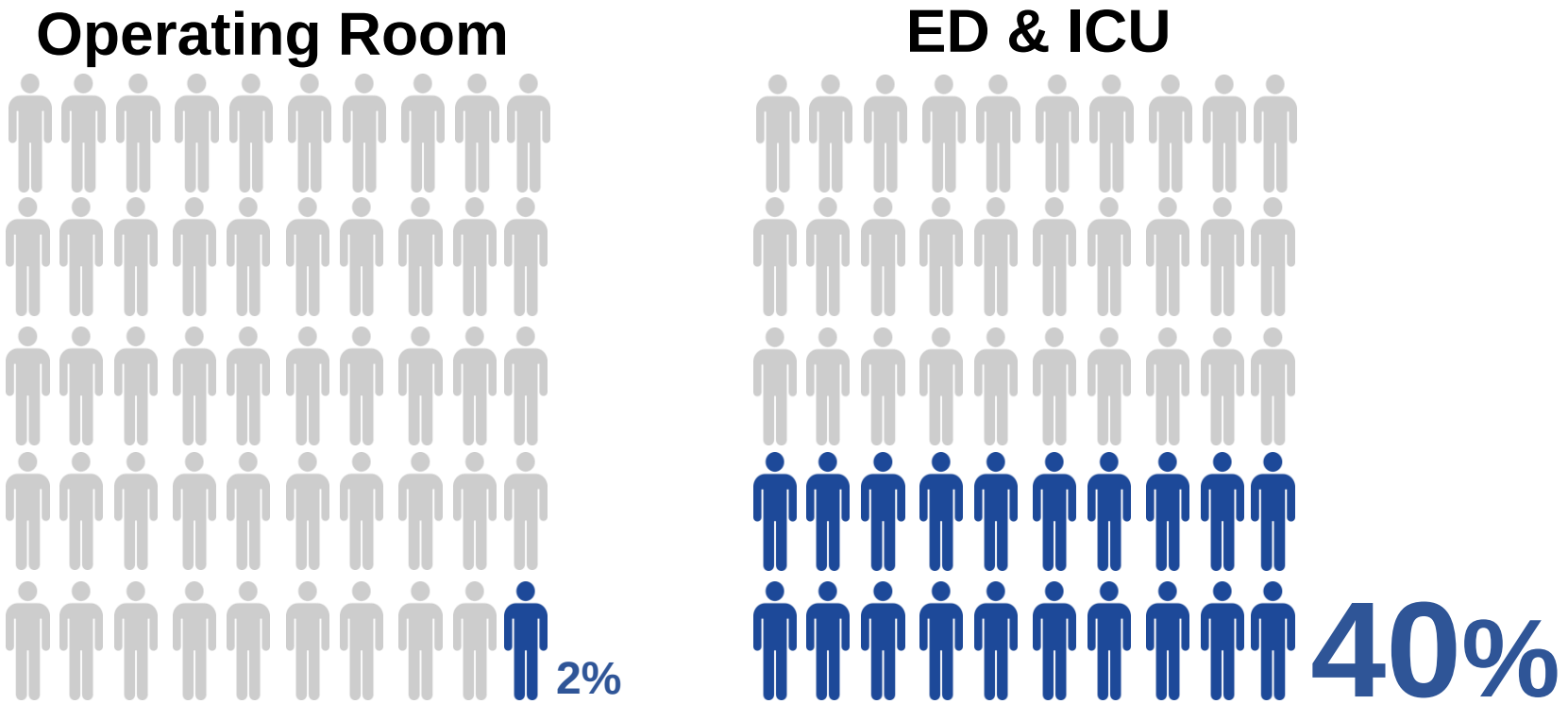
Disclosures

- Funding:
  - U.S. Department of Defense

- Conflicts of interest:
  - none

Emergency tracheal intubation is a common and high-risk procedure

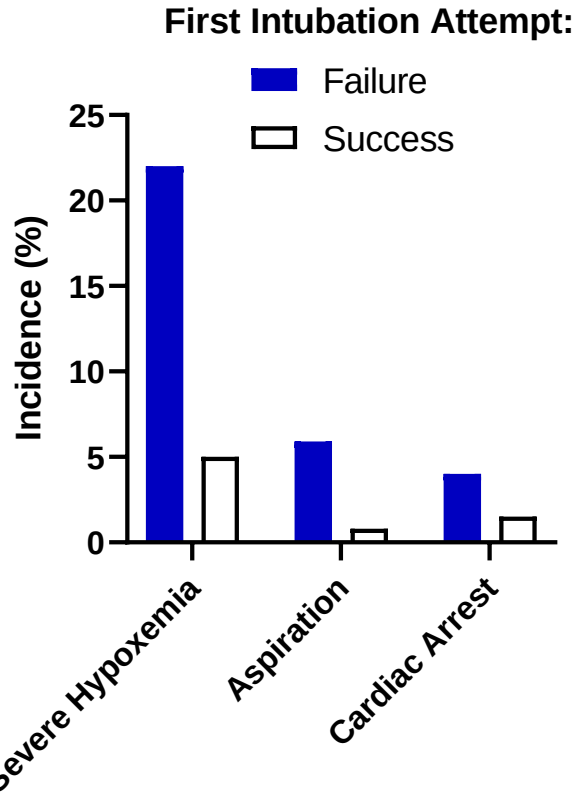


Russotto et al. JAMA 2021

Failure of the First Intubation Attempt

- Failure to intubate on the first attempt occurs in 20-30% of tracheal intubations in the ED or ICU.[1]

- Failure to intubate on the first attempt is associated with life-threatening complications.[1-3]



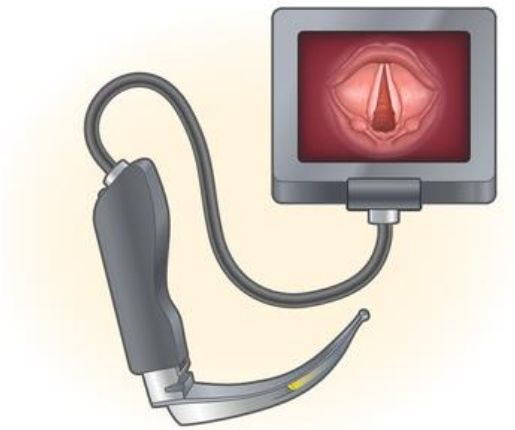
[1] Russotto et al. JAMA, 2021
[2] De Jong et al. Intensive Care Med 2020
[3] Sakles et al. Acad Emerg Med, 2013

Laryngoscopes

- Two devices are commonly used to perform tracheal intubation

DIRECT LARYNGOSCOPE

VIDEO LARYNGOSCOPE

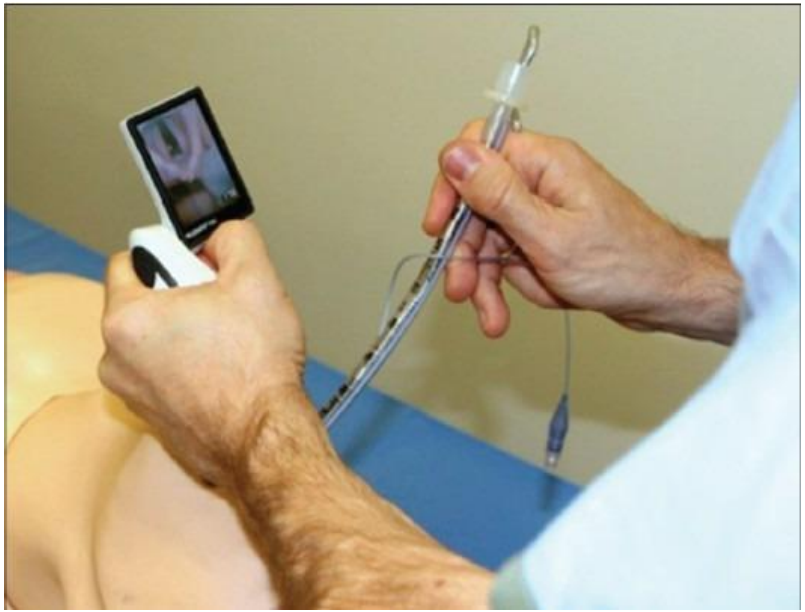


Direct Laryngoscope

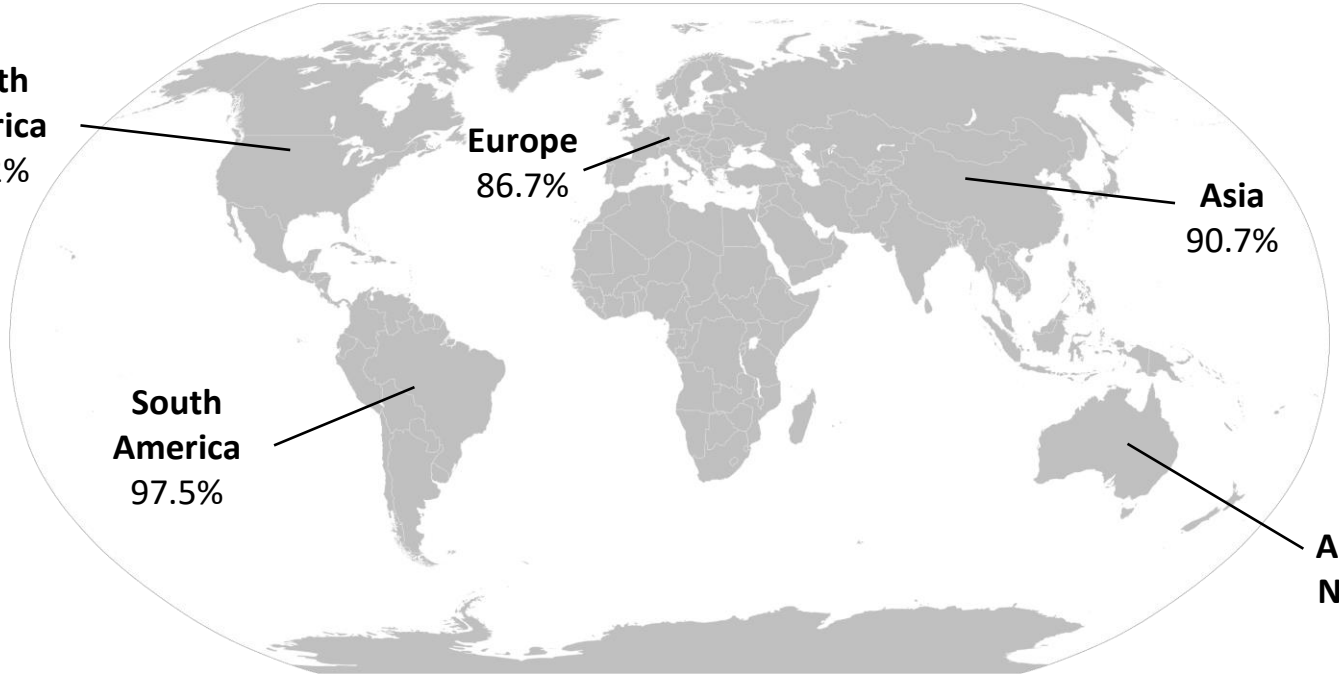
- A handle, a blade, and a light
- Vocal cords are visualized through the mouth
- Endotracheal tube passed with **direct, line-of-site** visual inspection

Video Laryngoscope

- Camera near the tip of the blade
- Vocal cords visualized on video screen (indirect laryngoscopy)
- Clinician can pass an endotracheal tube through the vocal cords **without creating a direct line of sight from the mouth**



A direct laryngoscope is used for approximately 80% of ED and ICU intubations worldwide

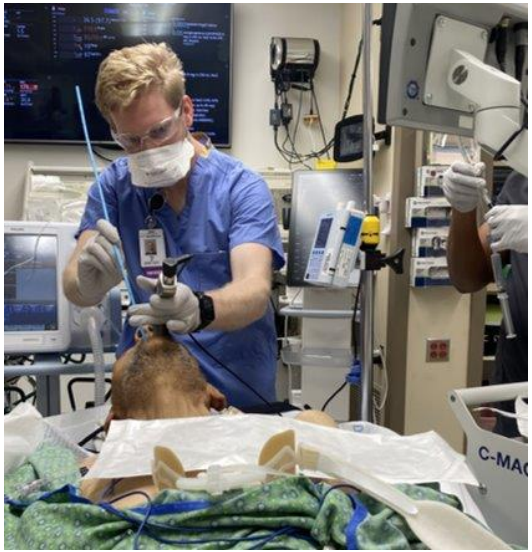


Russotto et al. Br J Anaesth, 2023

Current guidelines and evidence

- Tracheal intubation guidelines state that use of either a video laryngoscope or a direct laryngoscope is acceptable.[1,2]

- Prior randomized trials in the ED & ICU:
  - All conducted at a single center, except one[3]
  - Sample sizes of 40 to 623 patients
  - Clinicians had limited prior experience using a video laryngoscope[3,4]



[1] Higgs et al. Br J Anesth, 2018
[2] Myatra et al. Indian J Anaseth, 2016
[3] Lascarrou et al. JAMA, 2017
[4] Janz et al. Crit Care Med, 2016

DEVICE Trial Hypothesis

- Use of a video laryngoscope will increase the incidence of successful intubation on the first attempt.

- Clinical trial network
- Multidisciplinary investigators
  - Emergency medicine, anesthesiology, and critical care
- EDs and ICUs at 20 centers across the U.S.
- Pragmatic trials comparing effectiveness of emergency interventions

Methods

- **Design:** multicenter, parallel-group, unblinded, pragmatic, randomized trial comparing the use of a video laryngoscope with the use of a direct laryngoscope for tracheal intubation of critically ill adults
- **17 sites:** 7 EDs and 10 ICUs across the United States
- **Inclusion Criteria:**
  - Adults undergoing orotracheal intubation using a laryngoscope
- **Exclusion Criteria:**
  - Pregnant or prisoner
  - Immediate need for tracheal intubation that precluded randomization
  - Clinicians determined that video or direct laryngoscope required or contraindicated
- **IRB approval:** waiver of informed consent, patient information sheet

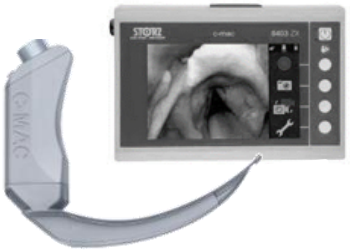
Randomization and Blinding

- Allocation concealed until randomization using opaque envelopes containing trial group assignment
- 1:1 randomization in blocks of variable size, stratified by trial site
- Not blinded after randomization

Interventions

VIDEO

Use a **video laryngoscope** on the first attempt.
Use the **screen** to view the cords.



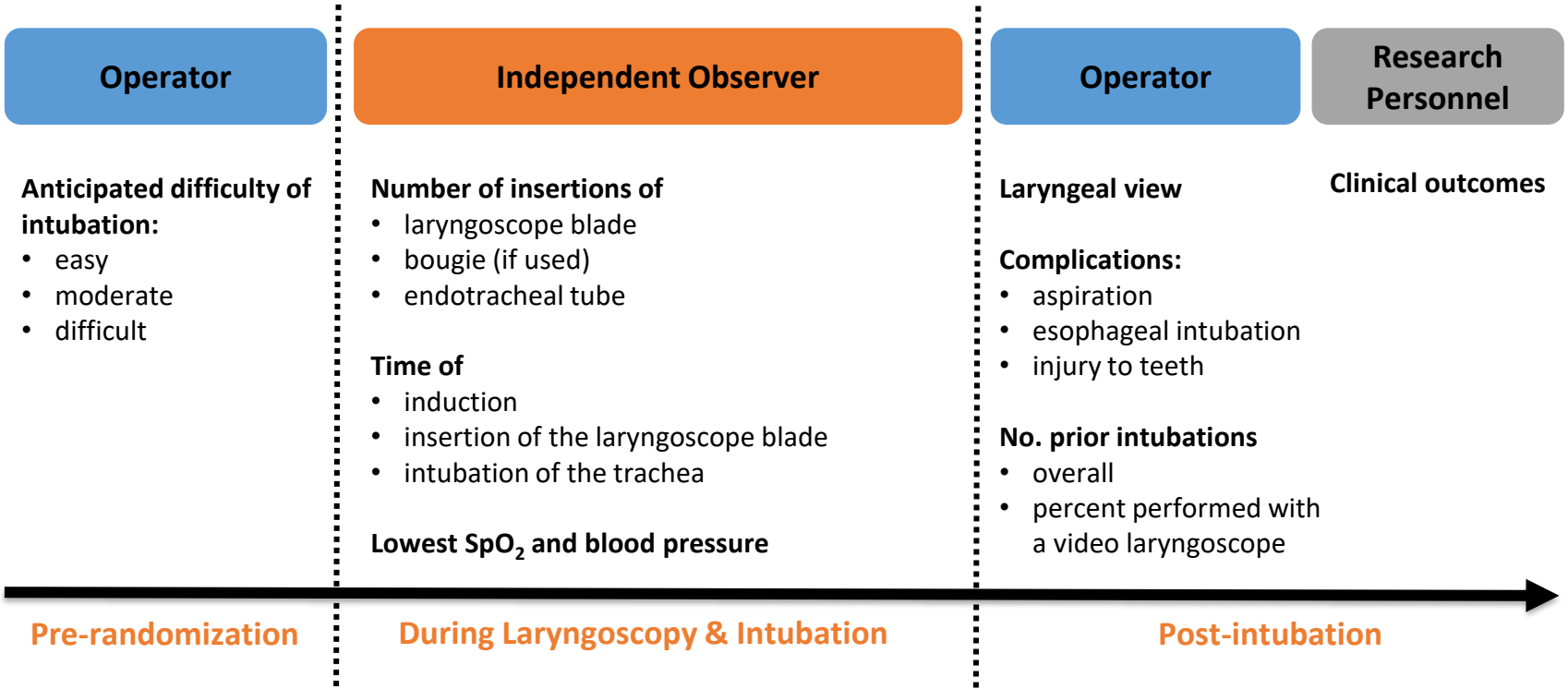
If the first attempt fails, use any device or approach on subsequent attempts.

DIRECT

Use a **direct laryngoscope** on the first attempt.
Laryngoscope CANNOT have a camera or screen.

If the first attempt fails, use any device or approach on subsequent attempts.

Data Collection



Primary and Secondary Outcomes

Primary Outcome

- Successful intubation on the first attempt

Secondary Outcome

- Severe complications between induction and 2 min after intubation:
  - Severe hypoxemia (SpO_2 < 80%); severe hypotension (SBP < 65 mmHg); new or increased vasopressor administration; cardiac arrest; or death

Sample Size

- Sample size of 2,000 patients
  - Successful intubation on the first attempt in DL group = 80%
  - Power = 90%
  - Alpha = 0.05
  - Missing data ≤ 4%
  - Absolute difference in successful intubation on first attempt detectable = **5%**

Data Analysis

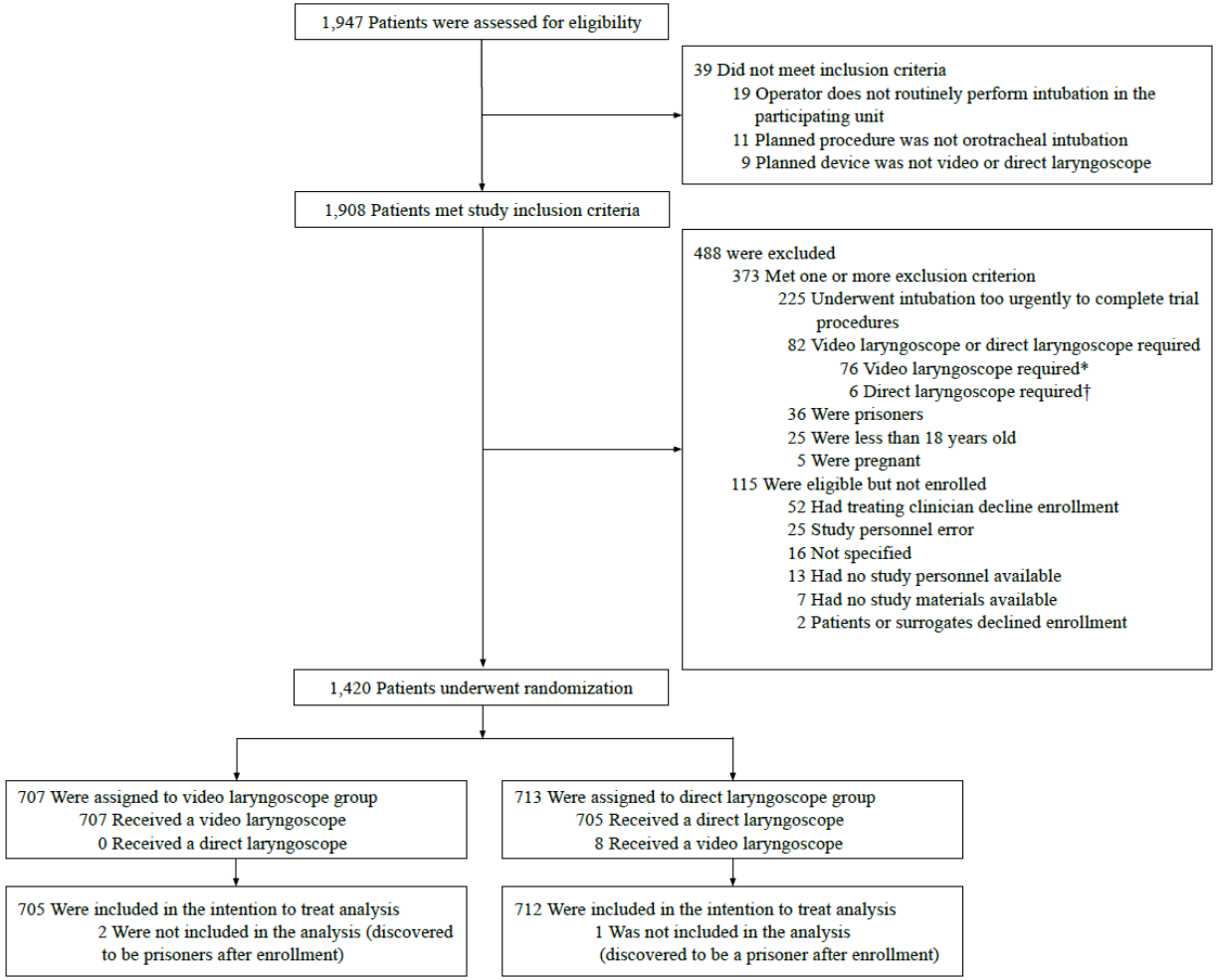
- Primary analysis
  - Unadjusted, intention-to-treat comparison of successful intubation on the first attempt between trial groups using a Chi-square test

- Single, planned interim analysis after 1,000 patients enrolled
  - Stop for efficacy if P-value ≤ 0.001 for comparison of primary outcome between trial groups using a Chi-square test

Trial Stopping

- On November 17, 2022 (at the time of the single, pre-specified interim analysis), trial enrollment was stopped at the recommendation of the data and safety monitoring board because the prespecified stopping criterion for ***efficacy*** had been met.

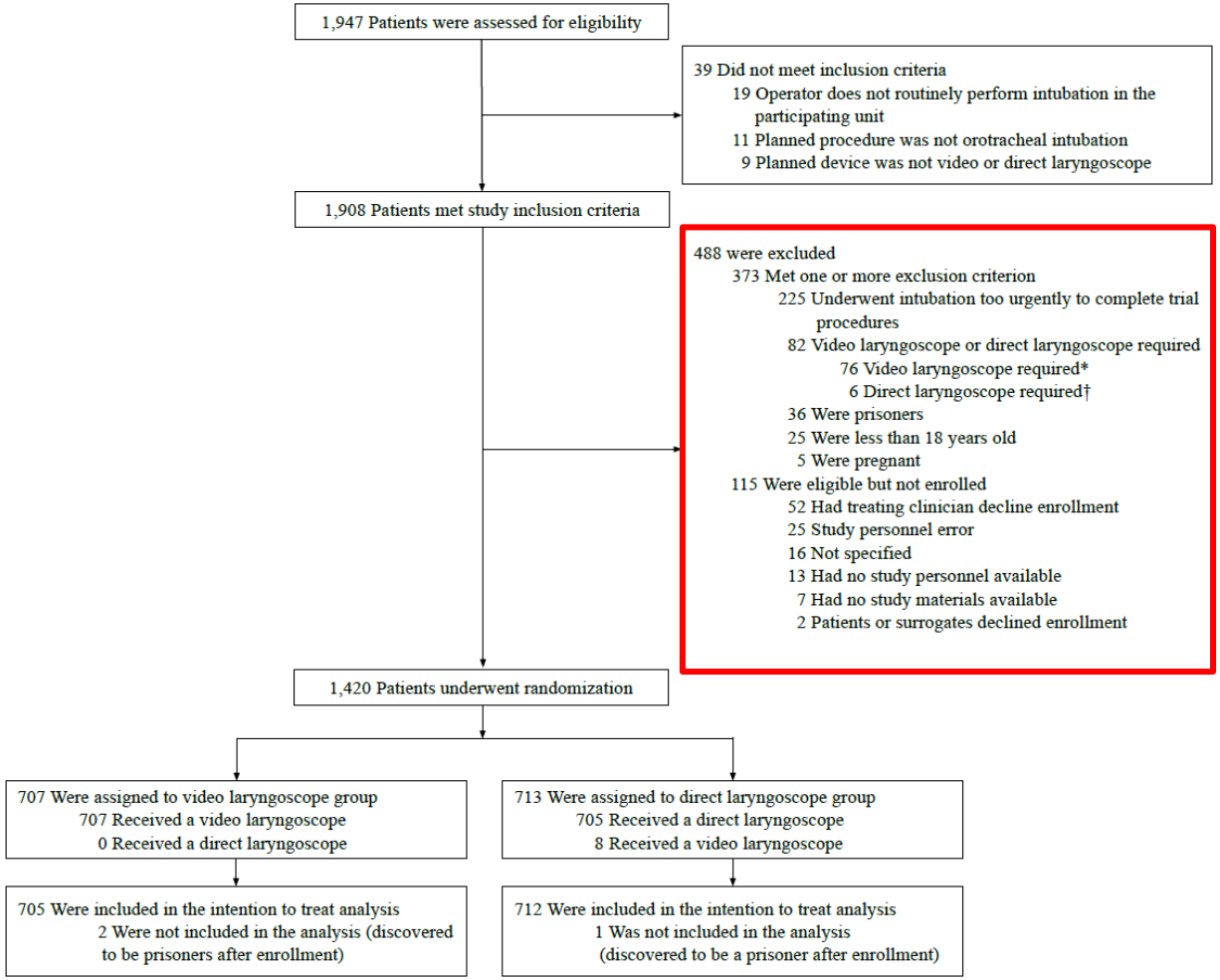
Results



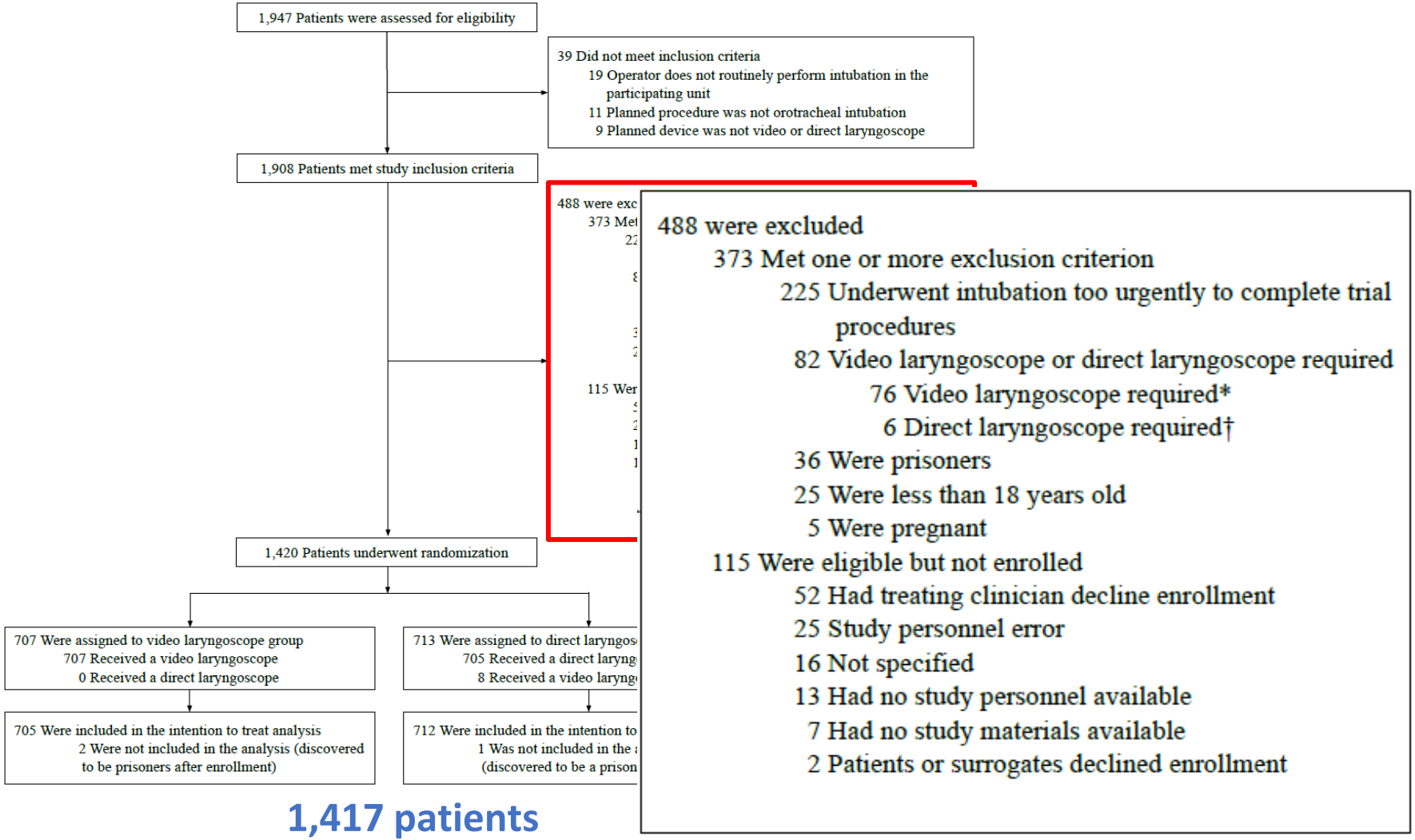
1,947 patients assessed for eligibility

1,420 patients (73%) randomized

1,417 patients



1,417 patients



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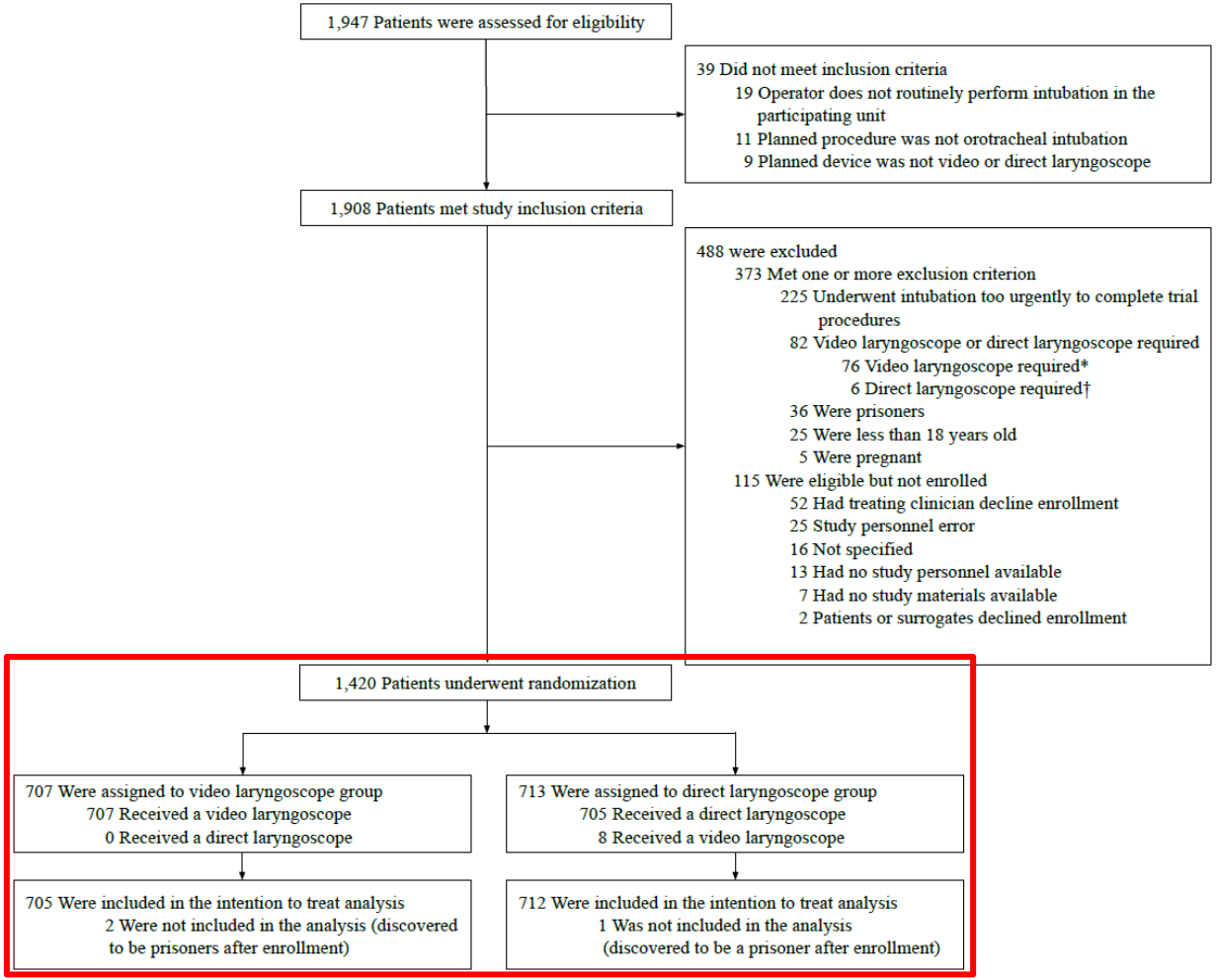

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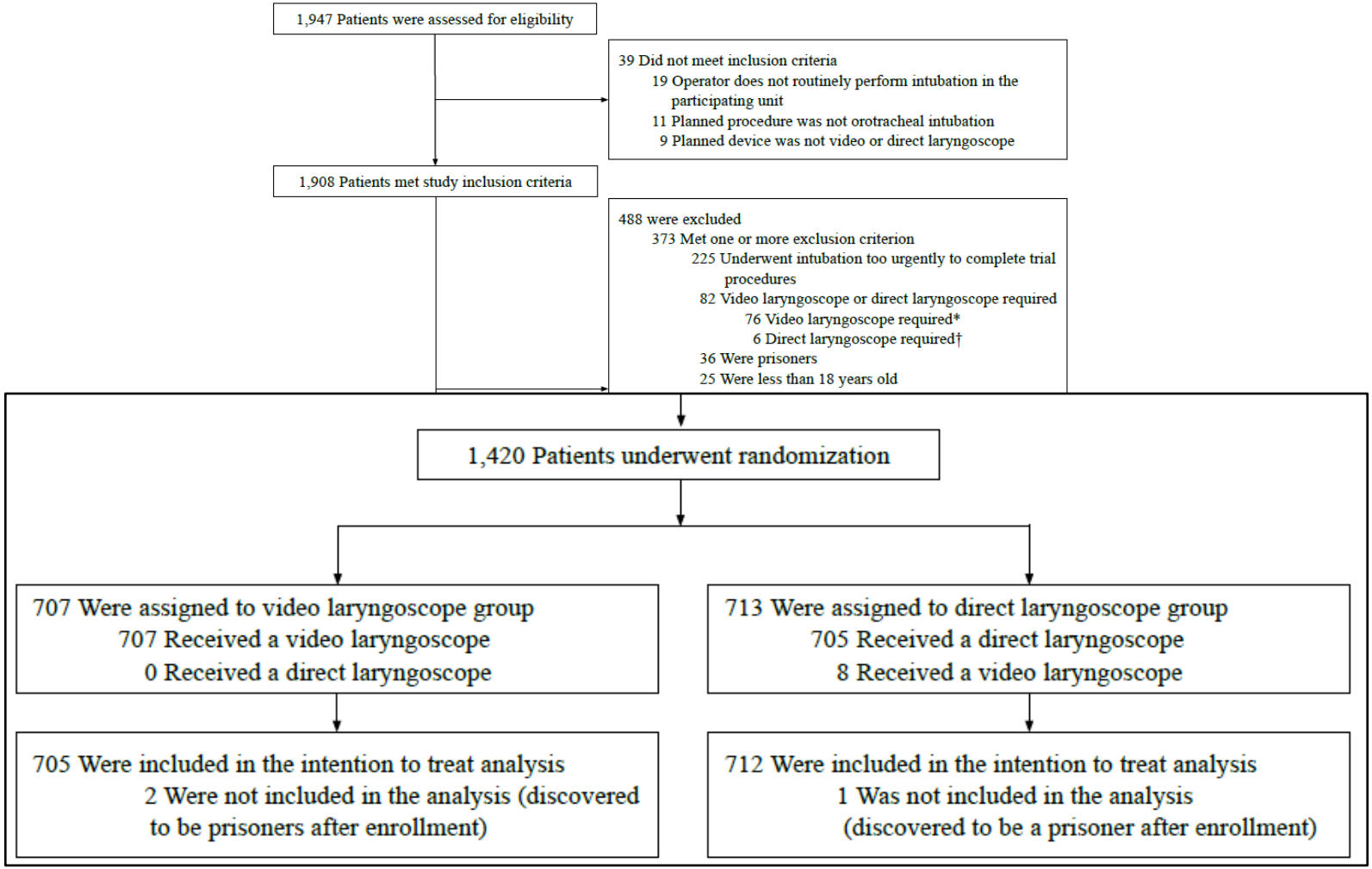


1,417 patients

Patient Characteristics	Video Laryngoscope (N= 705)		Direct Laryngoscope (N= 712)	
Age, years	54	[36-66]	55	[39-67]
Female sex	240	(34.0%)	228	(36.2%)
Body mass index, kg/m^2	26	[23-31]	27	[23-32]
Indication for intubation				
Altered mental status	318	(45.1%)	324	(45.5%)
Acute respiratory failure	215	(30.5%)	216	(30.3%)
Other	172	(24.4%)	172	(24.2%)
Location: Emergency Department	495	(70.2%)	493	(69.2%)
Traumatic injury	171	(24.3%)	167	(23.5%)
Anticipated Difficulty				
Easy	232	(32.9%)	223	(31.3%)
Moderate	317	(45.0%)	331	(46.5%)
Difficult	67	(9.5%)	62	(8.7%)

Data given as no. (%) or median [IQR]

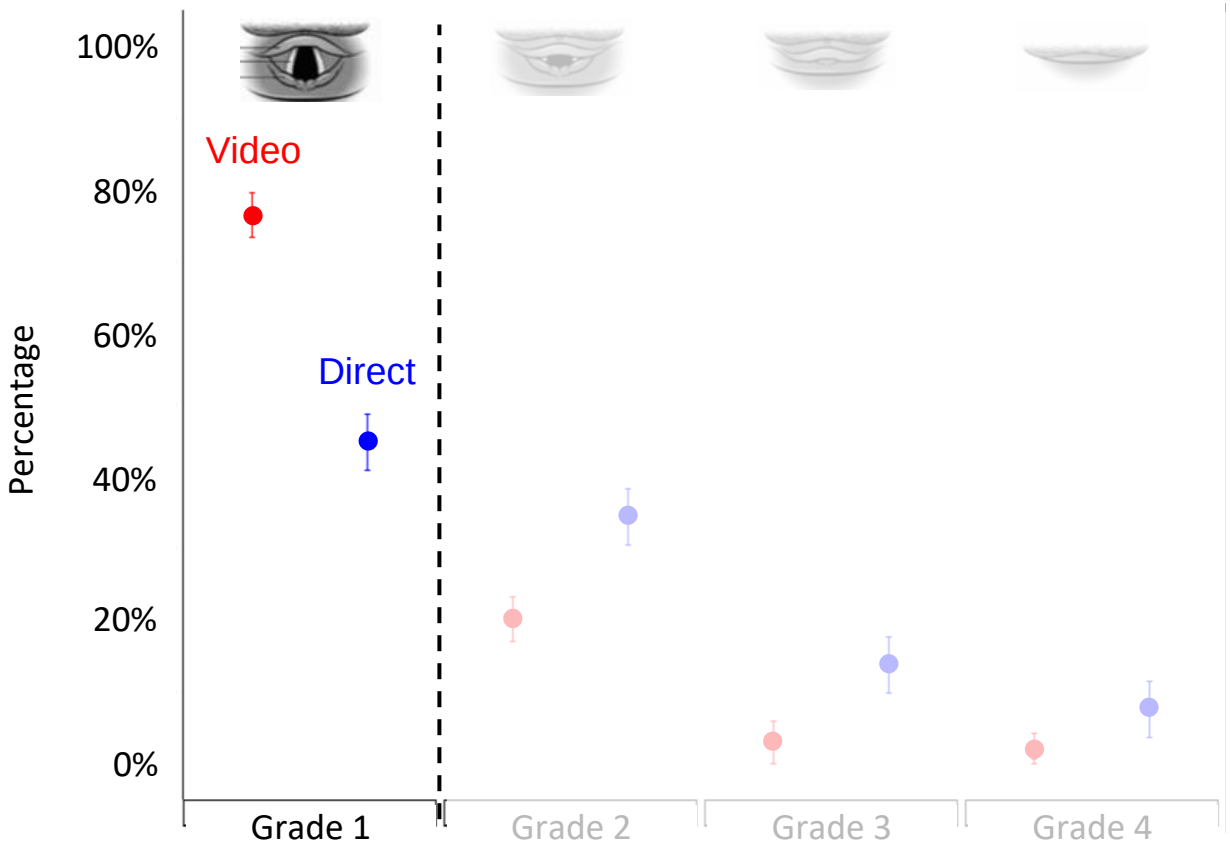
Operator Characteristics	Video Laryngoscope (N= 705)		Direct Laryngoscope (N= 712)	
No. of previous intubations	50	[25-90]	50	[26-99]
Proportion of prior intubations performed with VL				
<0.25 – Primarily experienced with a direct laryngoscope	44	(6.2%)	34	(4.8%)
0.25 to 0.75 – Similar experience with both	398	(56.5%)	429	(60.3%)
>0.75 – Primarily experienced with a video laryngoscope	262	(37.2%)	248	(34.9%)
Training level				
Resident Physician	513	(72.8%)	502	(70.5%)
Fellow Physician	164	(23.3%)	173	(24.3%)
Specialty				
Emergency medicine	496	(70.4%)	497	(69.8%)
Critical care medicine	177	(25.1%)	182	(25.6%)
Anesthesiology	18	(2.6%)	25	(3.5%)

Data given as no. (%) or median [IQR]

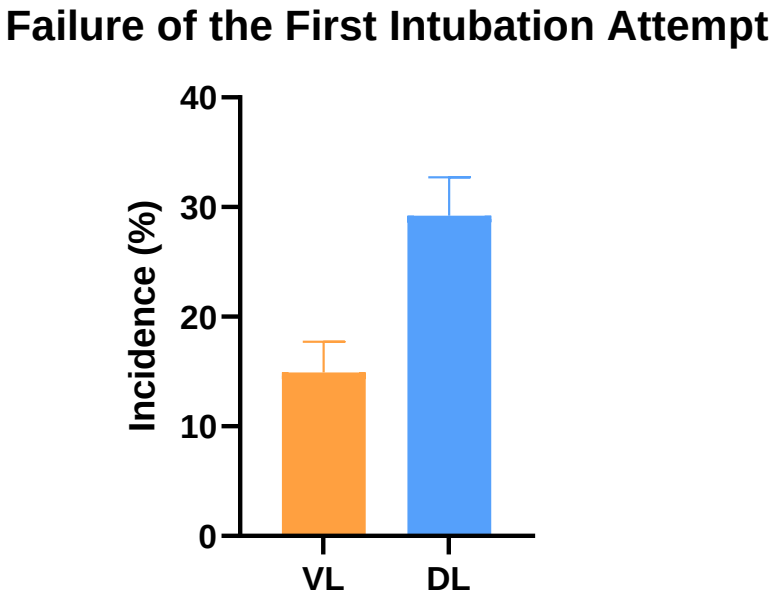
Laryngoscope used on the first attempt

	Video Laryngoscope Group (N= 705)		Direct Laryngoscope Group (N= 712)	
Video Laryngoscope	**705**	**(100.0%)**	8	(1.1%)
Direct Laryngoscope	0	(0.0%)	**704**	**(98.9%)**

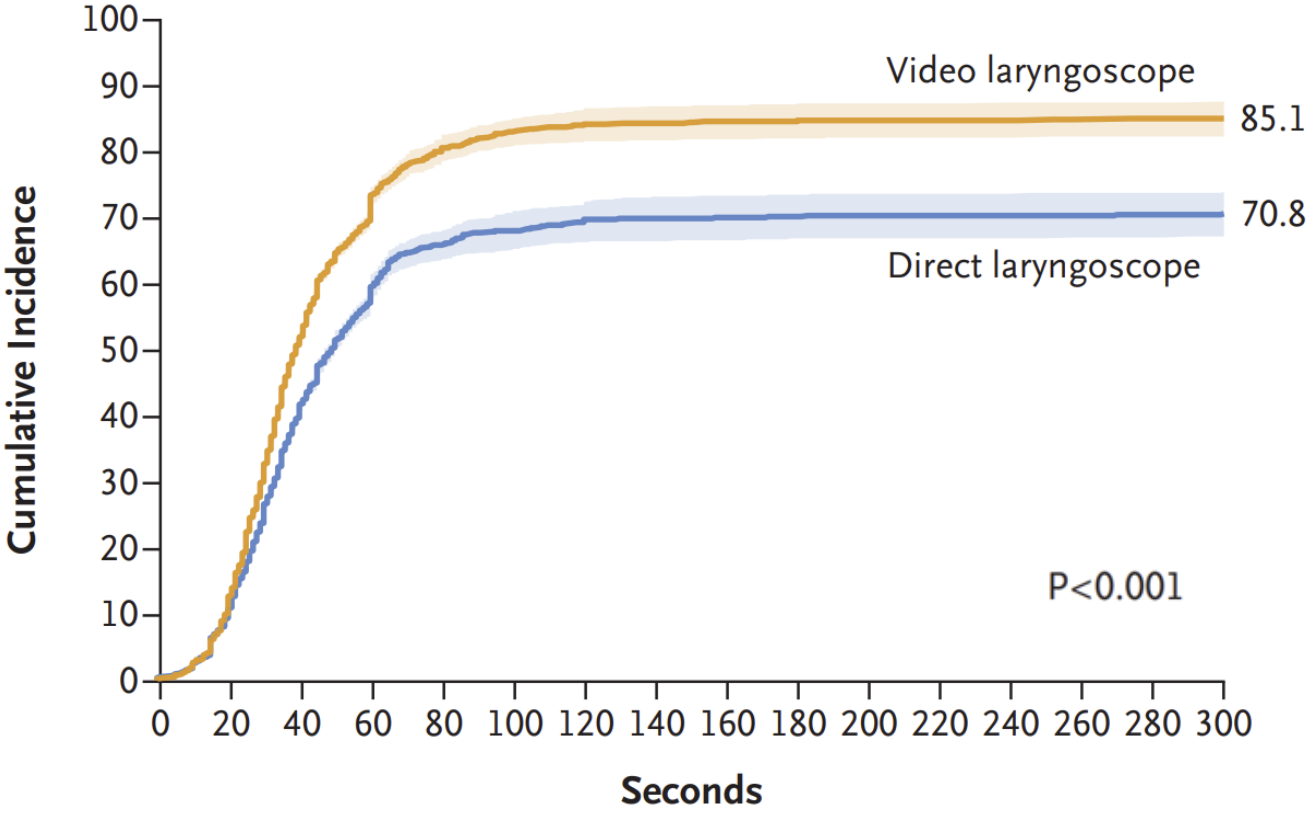
Video laryngoscope use improved Cormack-Lehane grade of laryngeal view



	Video Laryngoscope (N= 705)	Direct Laryngoscope (N= 712)	Absolute risk difference (95% CI)	P value
Primary outcome: Successful intubation on first attempt	600 (85.1%)	504 (70.8%)	**14.3%** (9.9% to 18.7%)	<0.001



Primary Outcome



All subgroups favor video laryngoscope use

Subgroup	Video Laryngoscope	Direct Laryngoscope
	no. of events/total no. (%)	
Overall	600/705 (85.1)	504/712 (70.8)
Location in hospital		
Emergency department	425/495 (85.9)	352/493 (71.4)
Intensive care unit	175/210 (83.3)	152/219 (69.4)
Body-mass index		
<30	402/468 (85.9)	343/483 (71.0)
≥30	179/217 (82.5)	155/216 (71.8)
Traumatic injury		
Yes	151/171 (88.3)	114/167 (68.3)
No	449/534 (84.1)	390/545 (71.6)
Anticipated difficulty of intubation		
Easy	206/232 (88.8)	172/223 (77.1)
Moderate	266/317 (83.9)	235/331 (71.0)
Difficult	51/67 (76.1)	30/62 (48.4)
Not reported	77/89 (86.5)	67/96 (69.8)
No. of operator's previous intubations		
<25	128/160 (80.0)	83/154 (53.9)
25–100	379/441 (85.9)	330/448 (73.7)
>100	93/104 (89.4)	91/109 (83.5)
Proportion of previous intubations performed with a video laryngoscope		
<0.25	39/44 (88.6)	27/34 (79.4)
0.25–0.75	335/398 (84.2)	303/429 (70.6)
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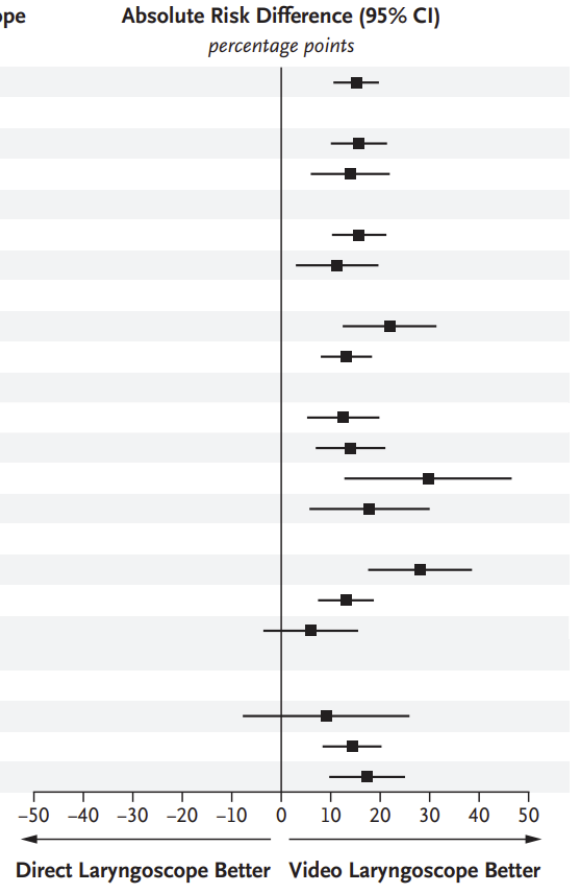

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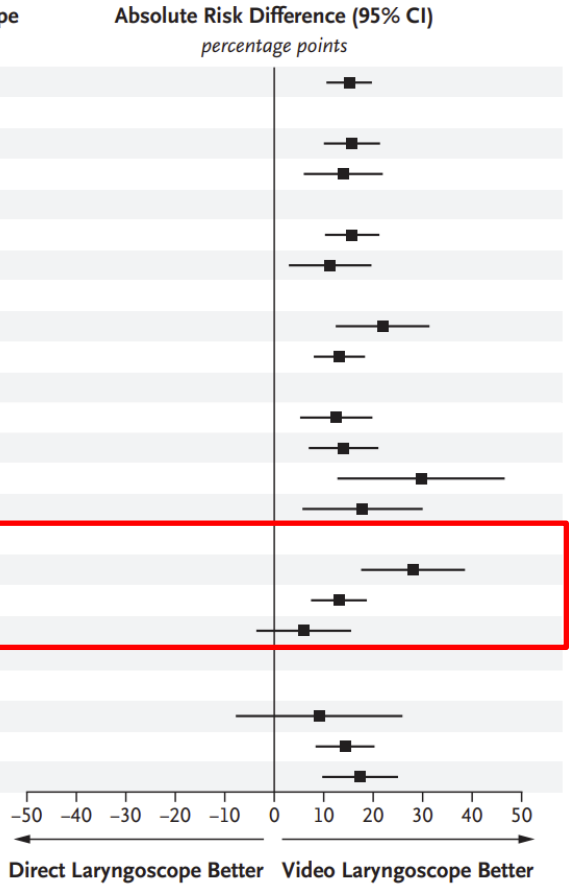

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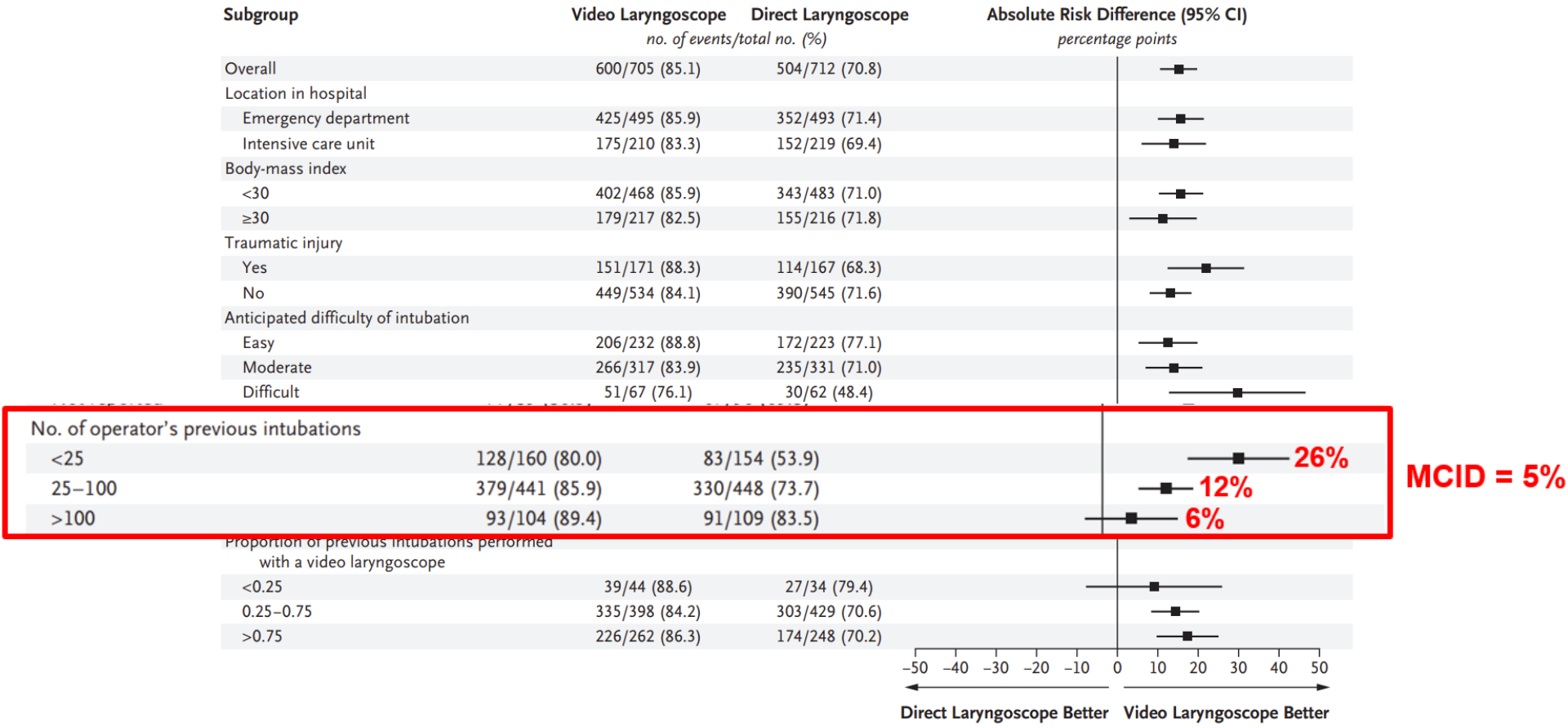

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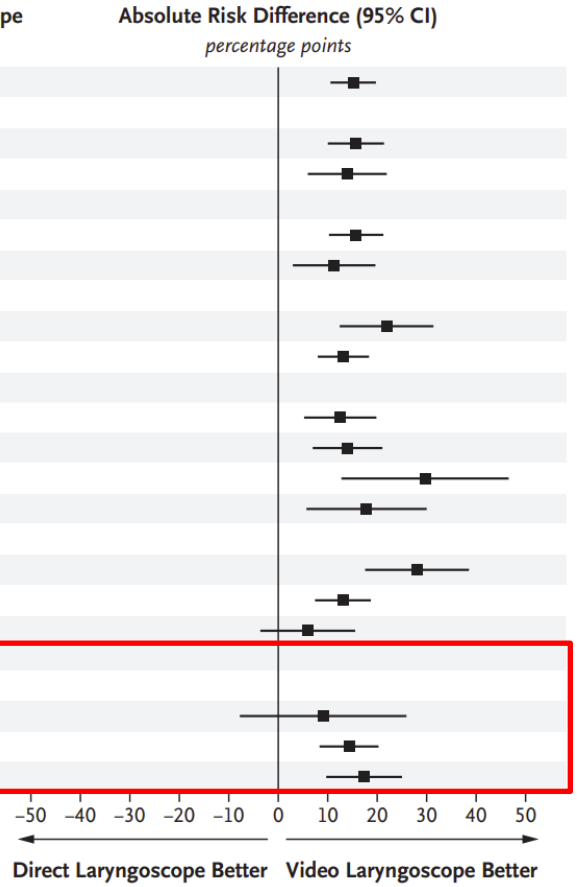

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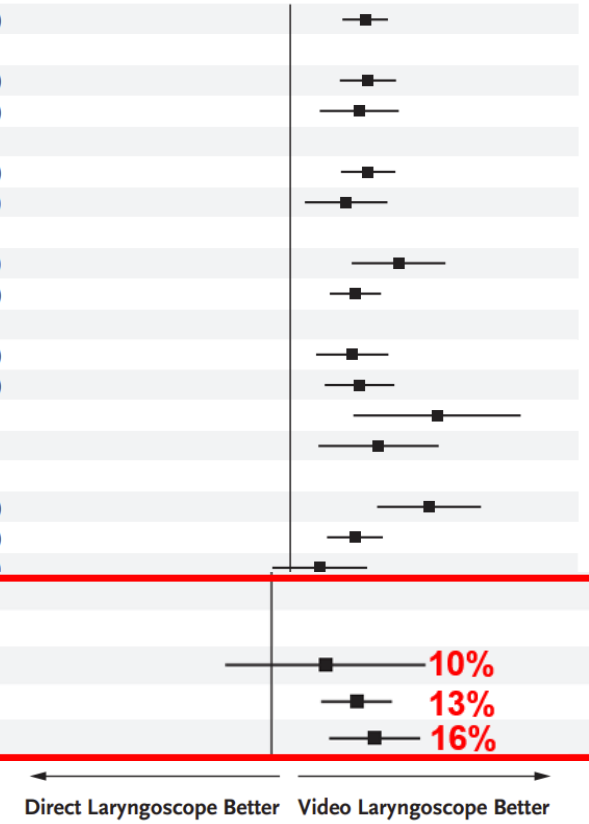
Absolute Risk Difference (95% CI)
percentage points



MCID = 5%

Exploratory Procedural Outcomes	Video Laryngoscope (N= 705)	Direct Laryngoscope (N= 712)	Absolute Difference or Median Difference (95% CI)
Duration of intubation, seconds	38 [26-60]	46 [30-83]	-8 (-12 to -4)
Intubation on 1st laryngoscope blade insertion	636 (90.3%)	546 (77.3%)	13.0% (9.1% to 16.9%)
Reason for failure on the first attempt			
Inadequate view of the vocal cords	26 (3.7%)	123 (17.3%)	-13.6% (-16.8% to -10.3%)
Inability to pass an endotracheal tube or bougie	49 (7.0%)	51 (7.2%)	-0.2% (-3.0% to 2.6%)

Data given as no. (%) or median [IQR]

Secondary Outcome	Video Laryngoscope (N= 705)		Direct Laryngoscope (N= 712)		Absolute difference (95% CI)
Severe complications	151	(21.4%)	149	(20.9%)	0.5% (-3.9% to 4.9%)
SpO_2 < 80%	64	(9.7%)	69	(10.5%)	-0.7% (-4.2% to 2.7%)
SBP < 65 mm Hg	20	(3.2%)	29	(4.5%)	-1.3% (-3.6% to 1.0%)
New or increased vasopressor	91	(12.9%)	87	(12.2%)	0.7% (-2.9% to 4.3%)
Cardiac arrest	2	(0.3%)	0	(0.0%)	0.3% (-0.3% to 0.8%)
Death	1	(0.1%)	3	(0.4%)	-0.3% (-1.0% to 0.4%)

Safety & Exploratory Clinical Outcomes	Video Laryngoscope (N= 705)		Direct Laryngoscope (N= 712)		Absolute difference (95% CI)
Safety Outcomes					
Aspiration	7	(1.0%)	12	(1.7%)	-0.7% (-2.0% to 0.6%)
Esophageal intubation	6	(0.9%)	9	(1.3%)	-0.4% (-1.6% to 0.8%)
Injury to teeth	3	(0.4%)	2	(0.3%)	0.1% (-0.6% to 0.9%)
Exploratory Clinical Outcomes					
ICU-free days	20	[0-25]	19	[0-24]	1 (-1 to 3)
Ventilator-free days	24	[0-26]	23	[0-26]	1 (0 to 2)
Death by 1 hour	15	(2.1%)	27	(3.8%)	-1.7 (-3.6 to 0.2)
Death by 28 days	184	(26.1%)	191	(26.8%)	-0.7 (-5.5 to 4.0)

Data given as no. (%) or median [IQR]

Summary

- 1,417-patient randomized trial in 17 EDs and ICUs
- Use of a video laryngoscope increased successful intubation on the first attempt from 71% to 85%
- Importance
  - Failure to intubate on the first attempt may result in life-threatening complications
  - In current clinical care globally, 80% of critically ill adults are intubated using a direct laryngoscope

The next 7 ED or ICU patients undergoing intubation…

Cannot intubate on the first attempt with either VL or DL.

Can intubate on the first attempt with either VL or DL.

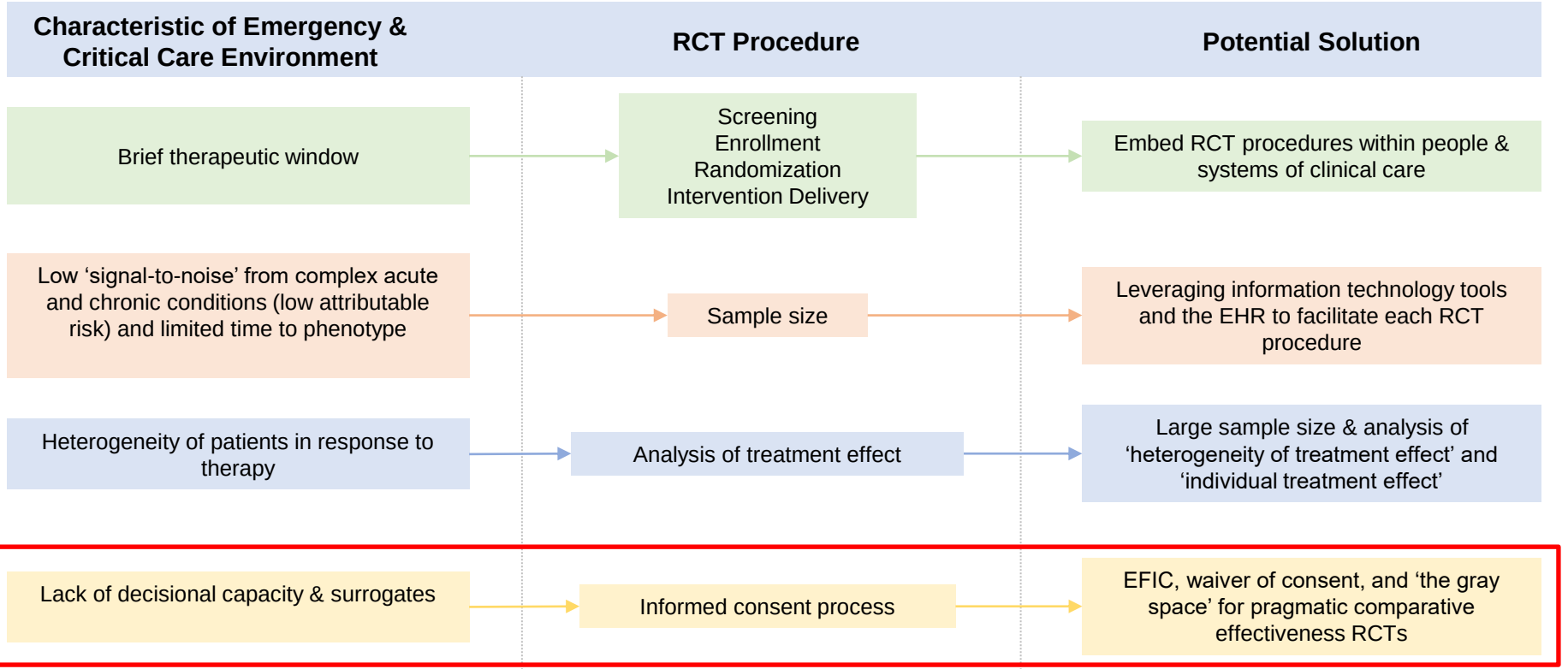
Can intubate on the first attempt with VL but not with DL.

Why did it take 20 years to prove VL superior?

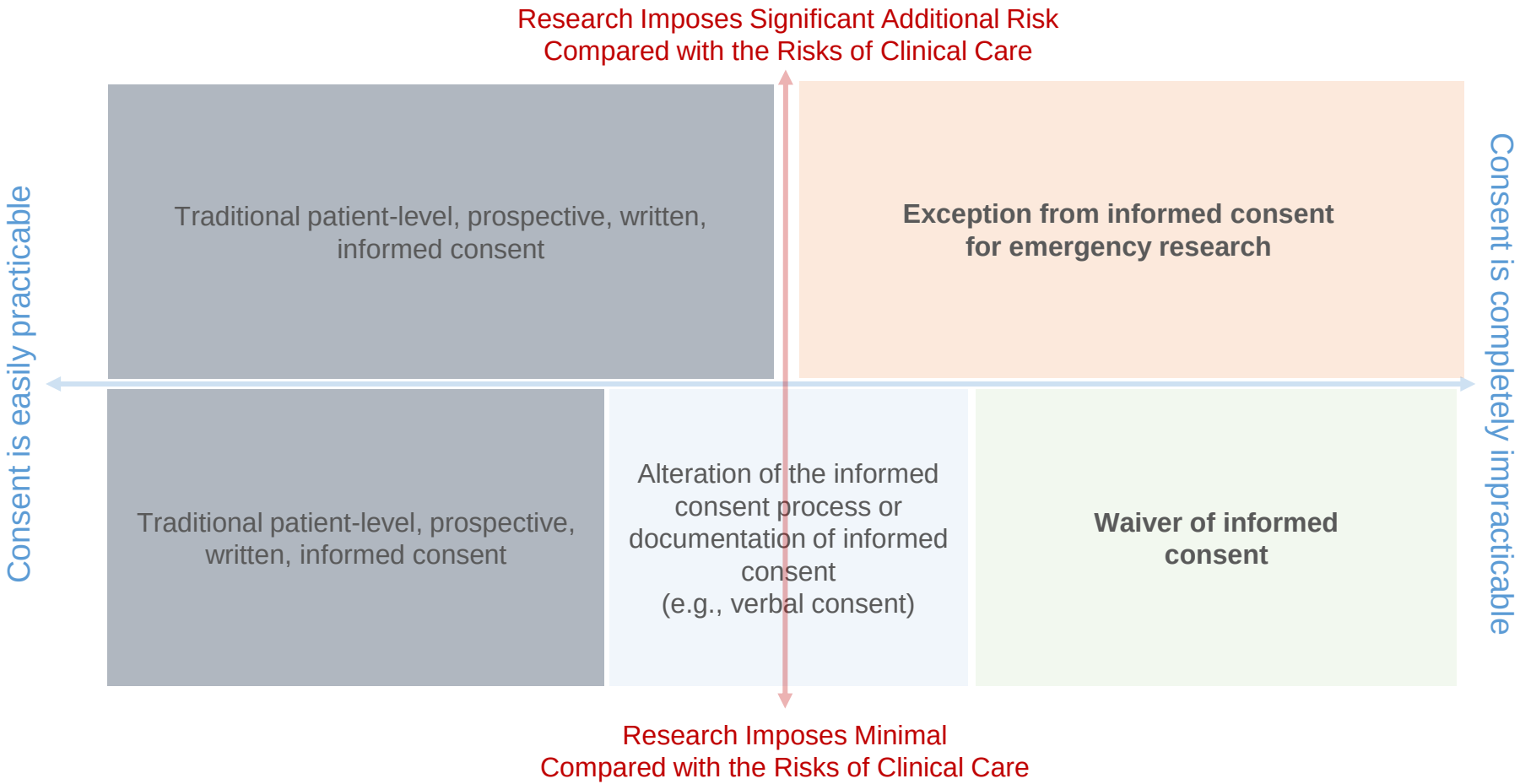
(Despite ~40 million critically ill adults in the US being intubated with either a VL or a DL during that time)

- Confounding by indication in observational studies?
- Improvement in technology?
- Increased comfort and experience with video laryngoscope use?
- **Challenges to conducting trials of emergency procedures?**

Challenges to conducting RCTs in emergency procedures & critical care



Current Regulations for Informed Consent



Exception from Informed Consent (EFIC)

- Implemented in 1996 to standardize the approach to research in emergency settings and procedures

- Attempts to demonstrate transparency and "respect for persons" (principle of the *Belmont Report,* 1979) when therapeutic window is too short to allow prospective informed consent and:
  - The condition being studied is **life-threatening**
  - Existing treatments are **unproven or unsatisfactory**
  - Research involves **more than minimal risk**

Exception from Informed Consent (EFIC)

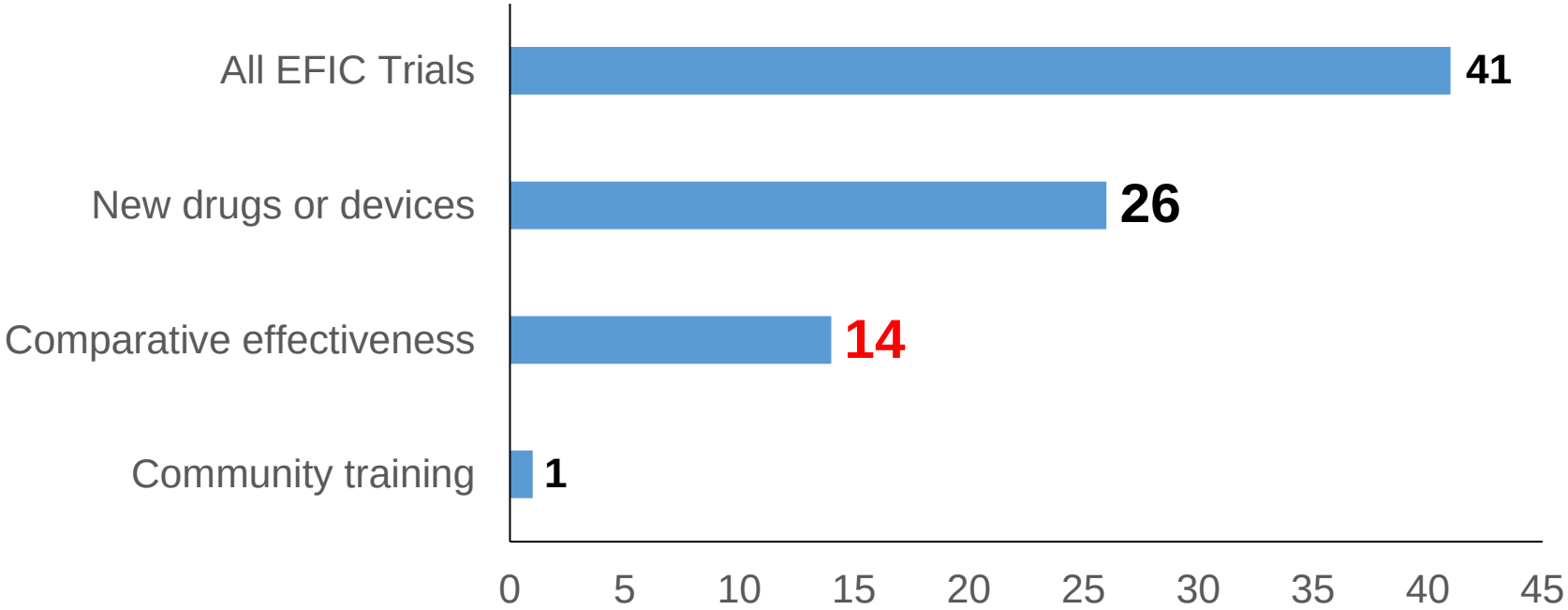
Pre-Trial:

1. Community consultation
   - Opportunity for affected communities to provide meaningful input to investigators and the IRB
   - Two-way communication: town hall meetings, focus groups, one-on-one meetings
2. Public disclosure
   - Maximize transparency
   - One-way communication: press releases, radio/newspaper/social media advertisements
3. FDA oversight through an Investigational New Drug Application

Cost and duration: 1-3 years and $50,000 per site

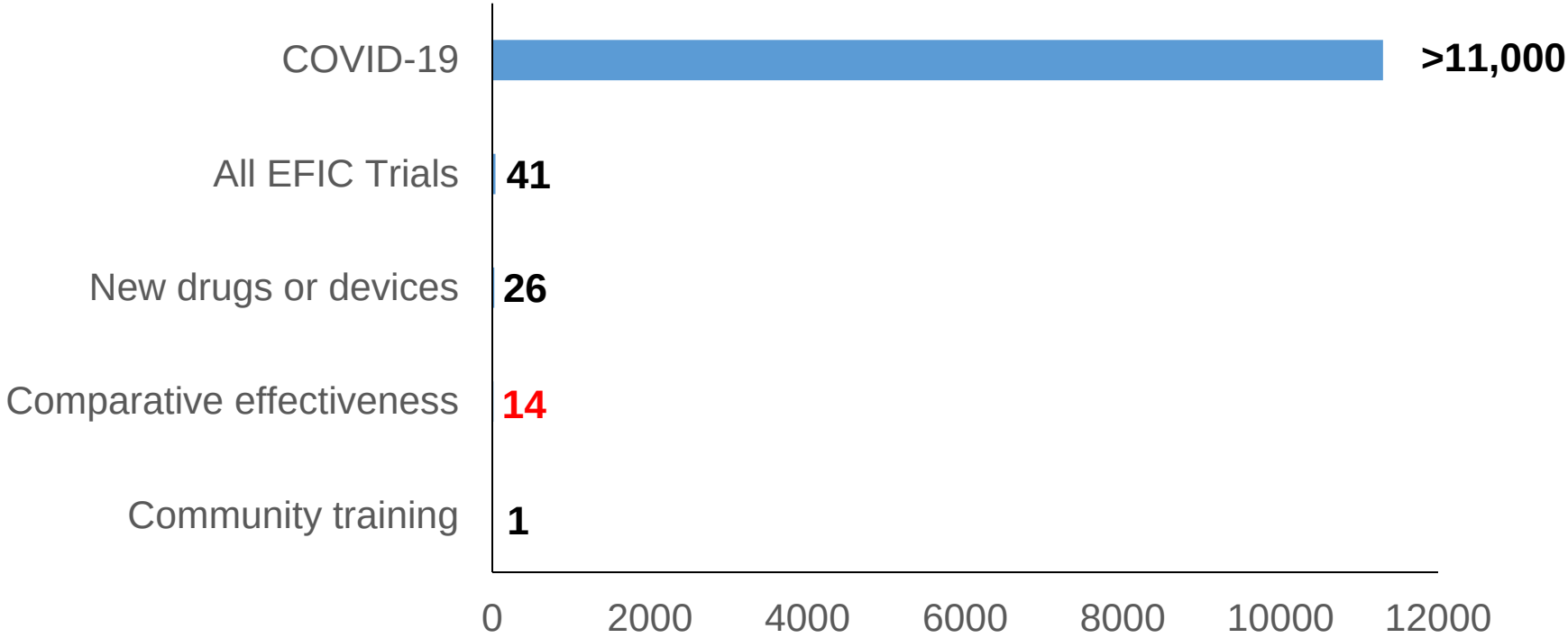
Silbergleit R, et al. Acad Emerg Med. 2012

20 Years of EFIC Trials



Feldman WB, et al. Health Aff. 2018

Number of Trials in the First 18 Months of COVID



Statistica: Number of COVID-19 clinical trials as of October 25, 2021

Waiver of Informed Consent

Criteria for waiver of informed consent (45 CFR 46.116(f))

1. No more than minimal risk to patients
2. Could not be carried out without the waiver;
3. Only uses identifiable private health information if such information is required to conduct the study
4. Does not adversely affect patients' rights or welfare
5. Whenever appropriate, additional pertinent information is provided after participation.

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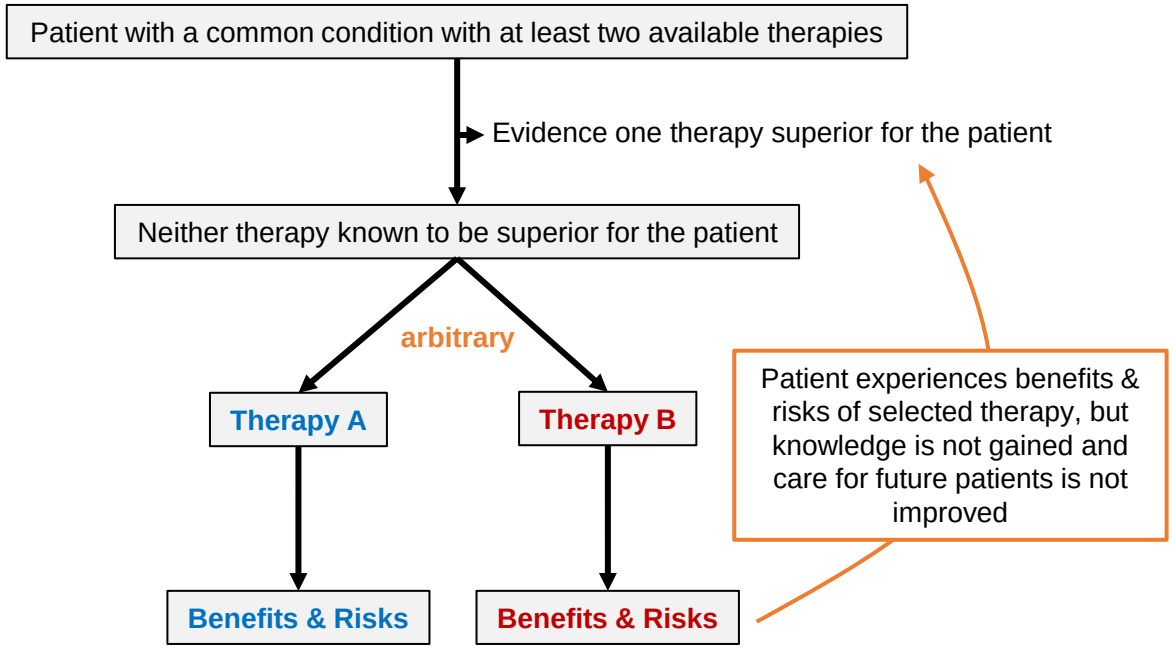
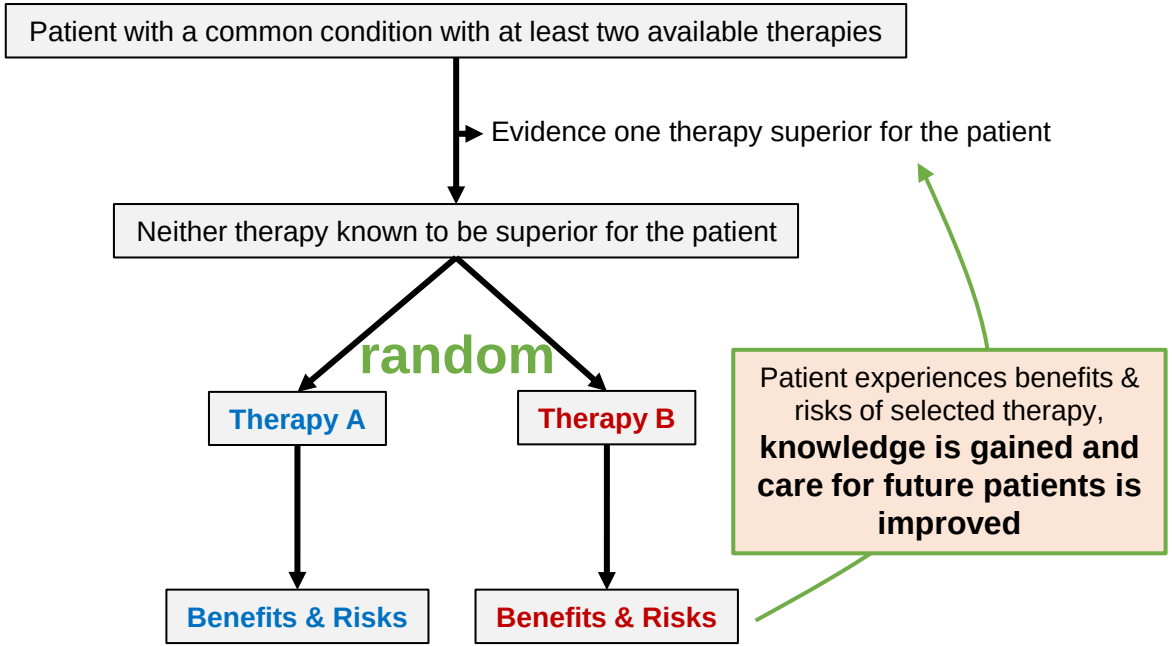
Treatment decisions in **Clinical Care**



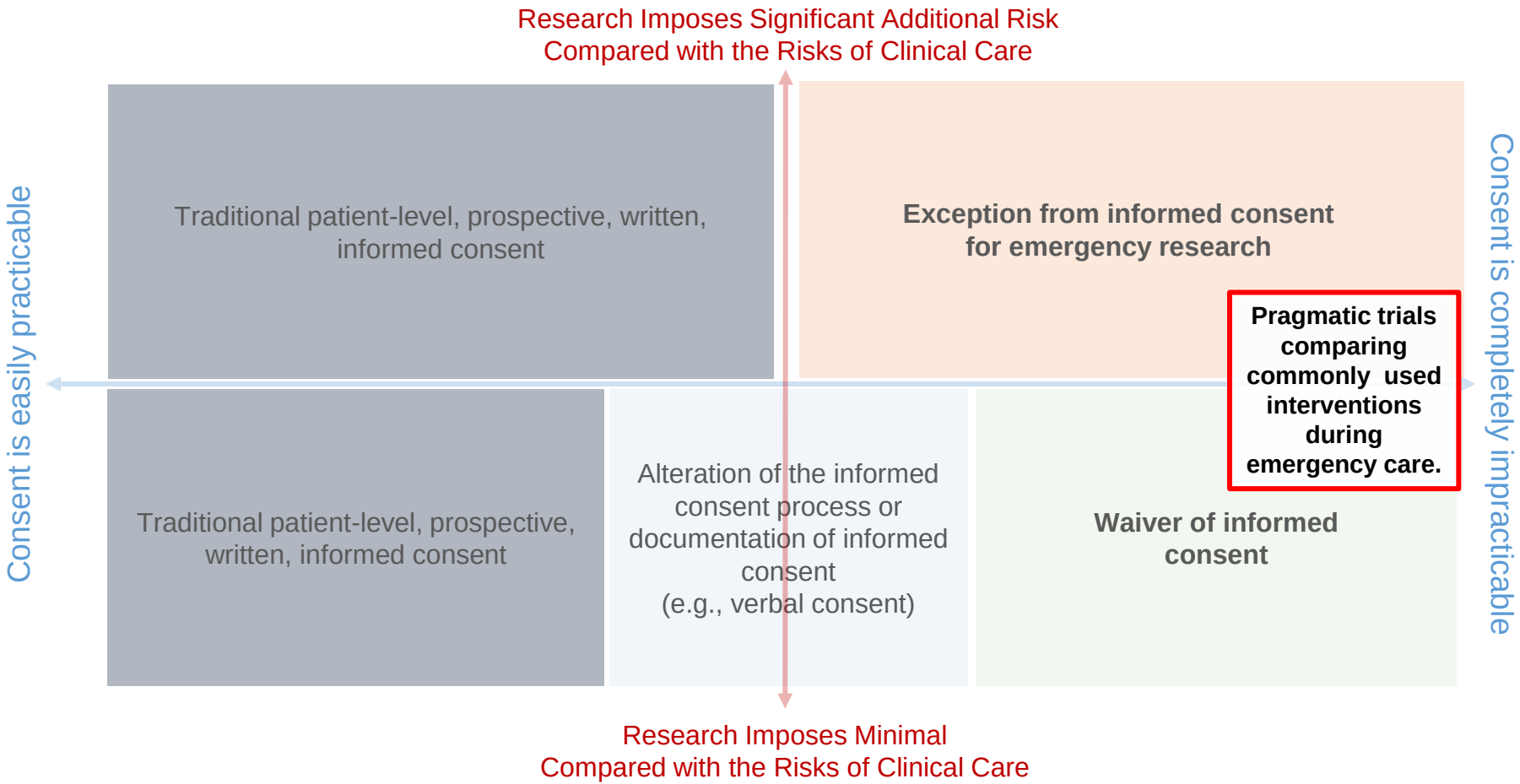
Arbitrary variation (different clinicians choosing different treatments for the same patient) = Clinical Equipoise

Treatment decisions in a **Comparative Effectiveness Trial**

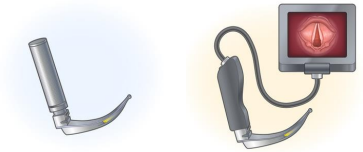
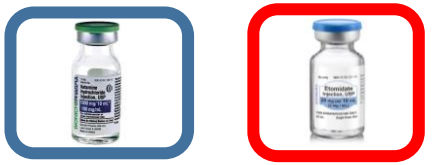


When two interventions are commonly used in clinical care and neither is known to be superior, having the choice between the two made randomly rather than based on arbitrary factors unrelated to knowledge of which therapy is best for a given patient may represent **no more than minimal incremental risk**, compared to the risk of routine clinical care

Current Regulations for Informed Consent



Comparison of two PCCRG airway trials

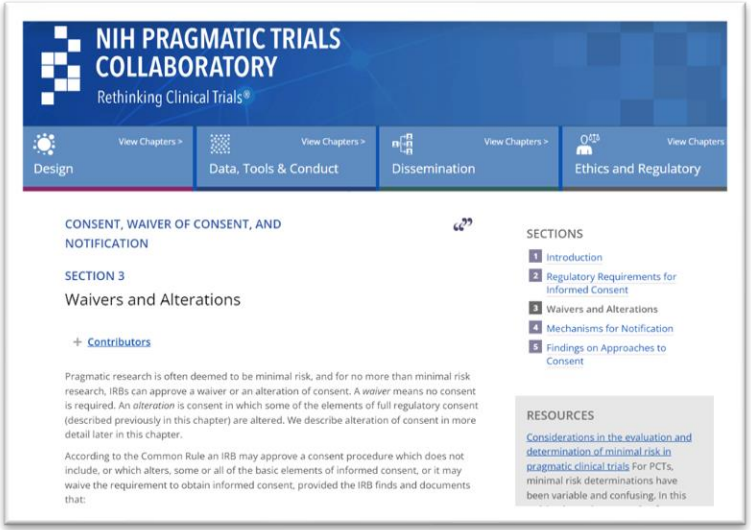
	DEVICE Trial	RSI Trial
Topic		 Ketamine Etomidate
Mechanism	Waiver of Informed Consent	Exception from Informed Consent
Pre-Trial	IRB approval	IRB & FDA approval (IND), CC & PD
Patient Notification	IRB-approved form provided by clinician	IRB-approved form provided by research team
Patient Self-withdrawals	0/1420	1/390* (actively enrolling)
Duration	Less than 1 year	8 years
Cost	$1.5 million	$9 million

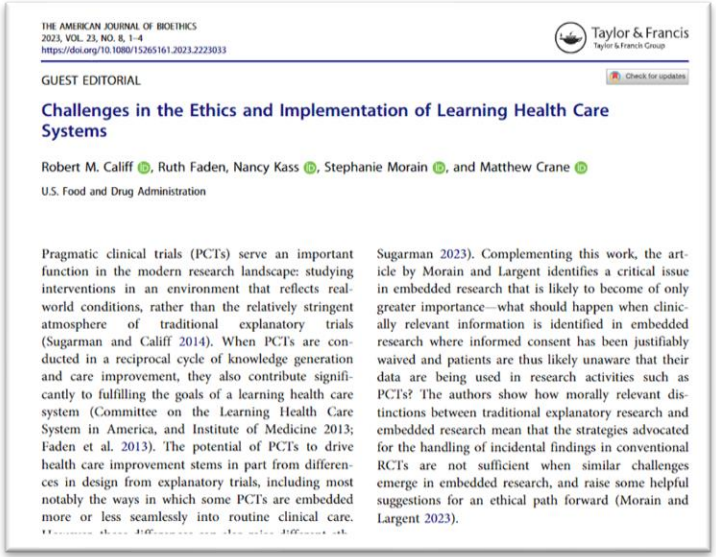
Neither Regulatory Pathway Fits Pragmatic Comparative Effectiveness Research

- Waiver of informed consent
  - Envisioned for retrospective observational research
  - How should we define minimal risk and in what circumstances is waiver of consent an appropriate mechanism for pragmatic RCTs?
  - How should patients be notified of participation?

- EFIC
  - Envisioned for new drug and device trials in cardiac arrest
  - No mechanism to conduct RCTs for conditions not immediately life-threatening (e.g., severe agitation, alcohol withdrawal).
  - Community Consultation and Public Disclosure are prohibitively expensive and time-consuming and require expertise not available at most centers.

Regulation of Pragmatic RCTs: Ongoing Uncertainty





- FDA Commissioner: "***Neither HHS nor FDA regulations currently have guidance on whether or when [pragmatic trials] might be categorized as minimal risk . . . These issues need the joint attention of federal agencies, the research community, the health care delivery ecosystem, and patient advocates***"

Moral Imperative to Develop an Ethical and Regulatory Framework for Pragmatic CER

- "Insofar as contemporary research ethics and oversight interfere with learning activities that could reduce errors and improve clinical effectiveness, the **overprotection is itself a source of harm to patient's interests**" – Ruth Faden
- For example:
  - Over the last 20 years: more than 20 million critically ill adults were intubated with a direct laryngoscope
  - If a lack of regulatory framework had prevented the DEVICE trial from being conducted, one million critically ill adults each year would have continued to be intubated with an inferior device **INDEFINITELY**

Conclusion

Among critically ill adults undergoing tracheal intubation in an ED or ICU, use of a video laryngoscope increased successful intubation on the first attempt compared to use of a direct laryngoscope.

There is a moral imperative to develop an ethical and regulatory framework for pragmatic comparative effectiveness research.

Thank you!

Matthew E. Prekker, Brian E. Driver, Stacy A. Trent, Daniel Resnick-Ault, Kevin P. Seitz, Derek W. Russell, John P. Gaillard, Andrew J. Latimer, Shekhar A. Ghamande, Kevin W. Gibbs, Derek J. Vonderhaar, Micah R. Whitson, Christopher R. Barnes, Jeremy P. Walco, Ivor S. Douglas, Vijay Krishnamoorthy, Alon Dagan, Jill J. Bastman, Bradley D. Lloyd, Sheetal Gandotra, Jordan Kugler Goranson, Steven H. Mitchell, Heath D. White, Jessica A. Palakshappa, Alyssa Espinera, David B. Page, Aaron Joffe, Sydney J. Hansen, Christopher G. Hughes, Tobias George, J. Taylor Herbert, Nathan I. Shapiro, LTC Steven G. Schauer, Maj. Brit J. Long, Brant Imhoff, Li Wang, Jillian P. Rhoads, Kelsey N. Womack, David R. Janz, Wesley H. Self, Todd W. Rice, Adit A. Ginde, Jonathan D. Casey, Matthew W. Semler.