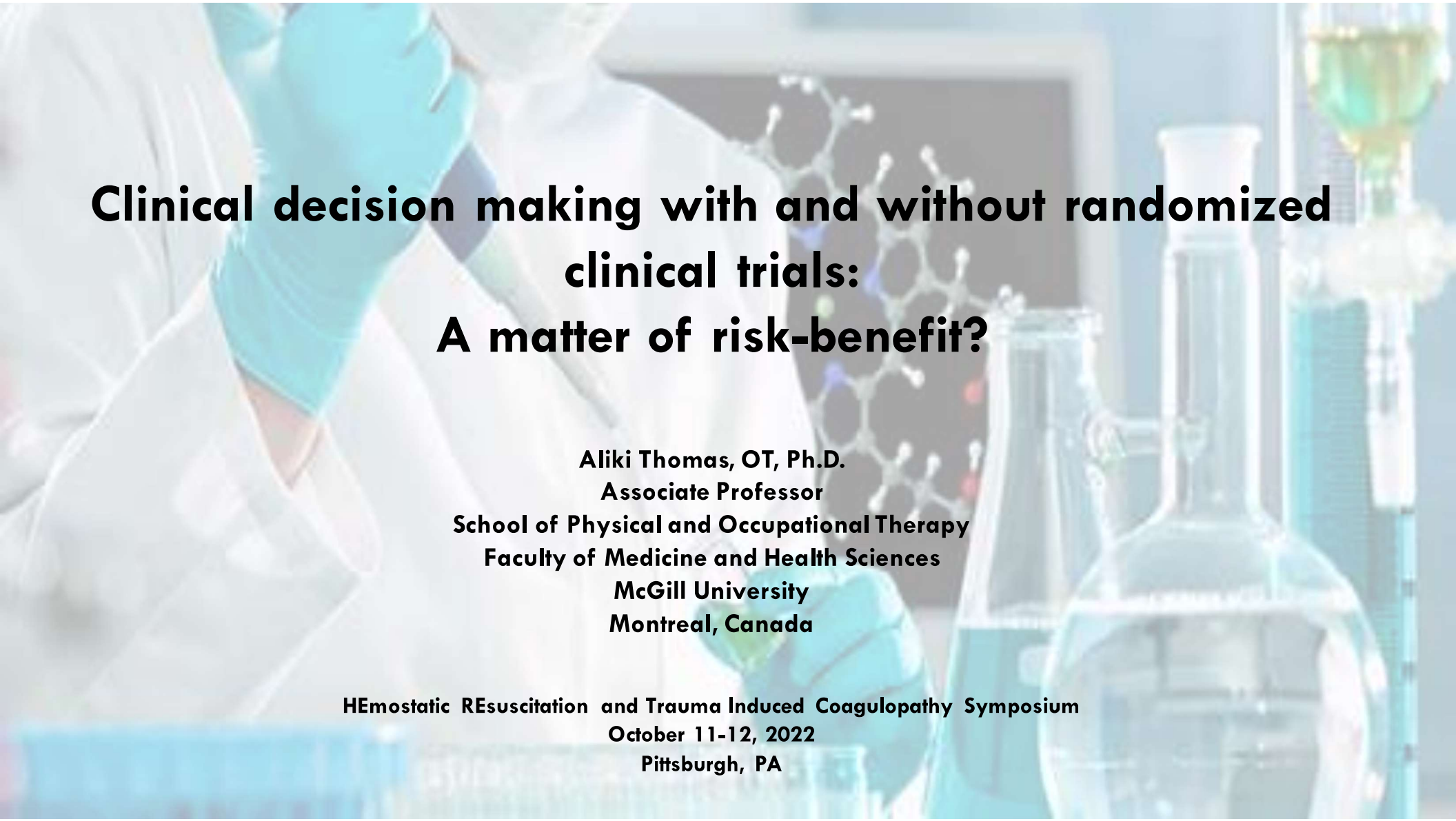


Clinical decision making with and without randomized clinical trials: A matter of risk-benefit?

Aliki Thomas, OT, Ph.D.
Associate Professor
School of Physical and Occupational Therapy
Faculty of Medicine and Health Sciences
McGill University
Montreal, Canada

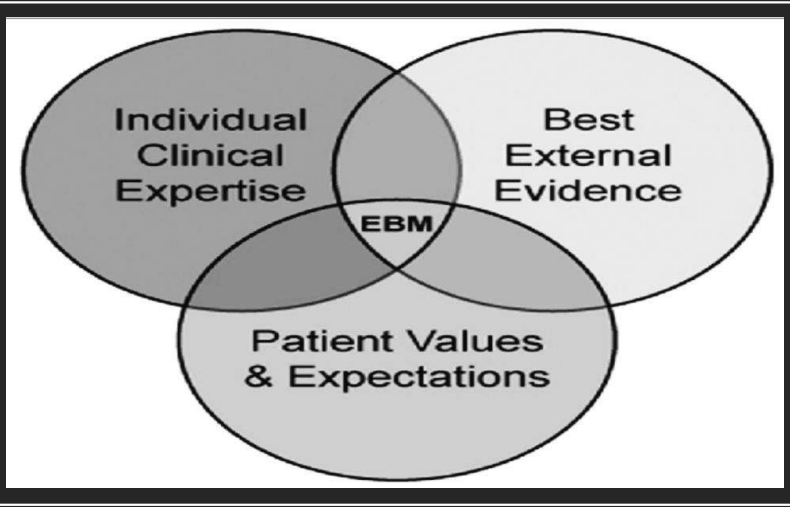
HEmostatic REsuscitation and Trauma Induced Coagulopathy Symposium
October 11-12, 2022
Pittsburgh, PA

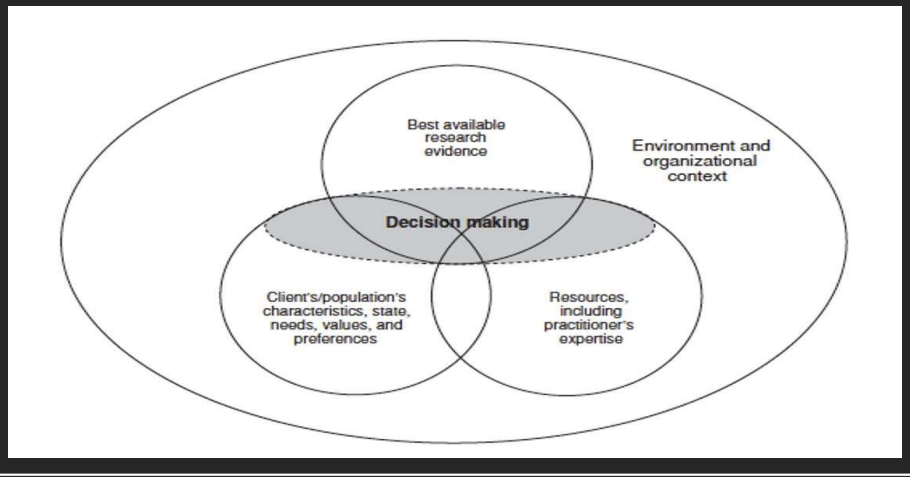

Disclosure

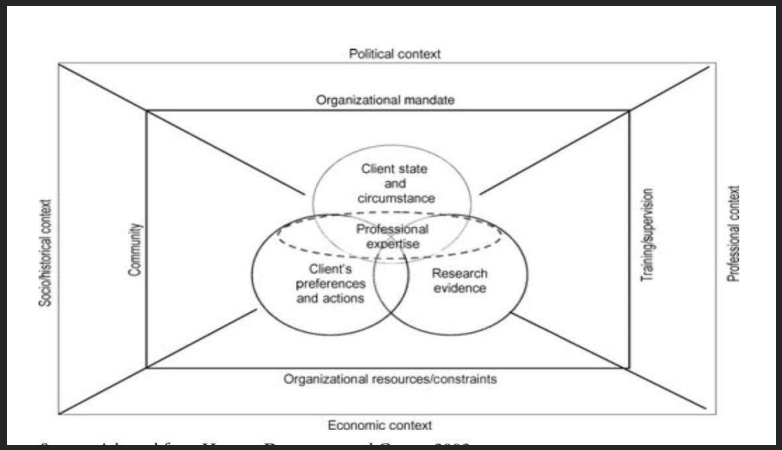

Does it take an RCT to change practice?

Evidence-based medicine

Guyatt et al., 1992; Sackett et al., 1996







Guyatt et al., 1992; Satterfield et al, 2009;

Plurality of knowledge

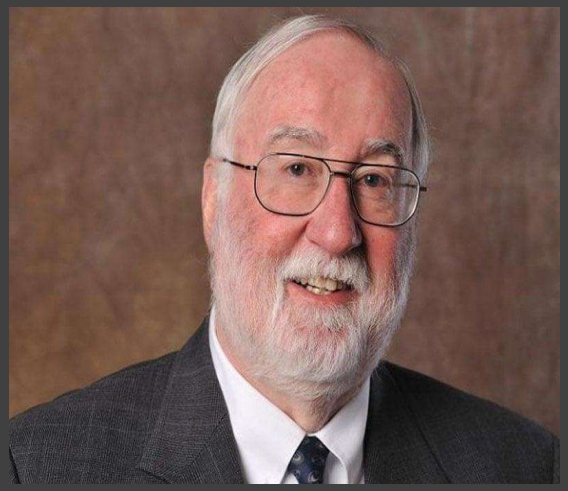
Value of various research designs in generating actionable evidence

Patient oriented research and shared decision-making

Population-level trials do not translate to practice and to individual patient

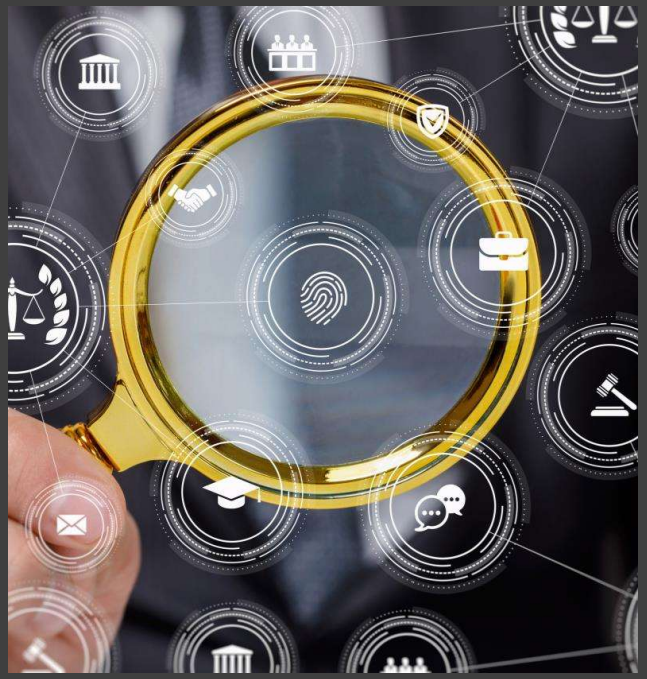
Context-specificity

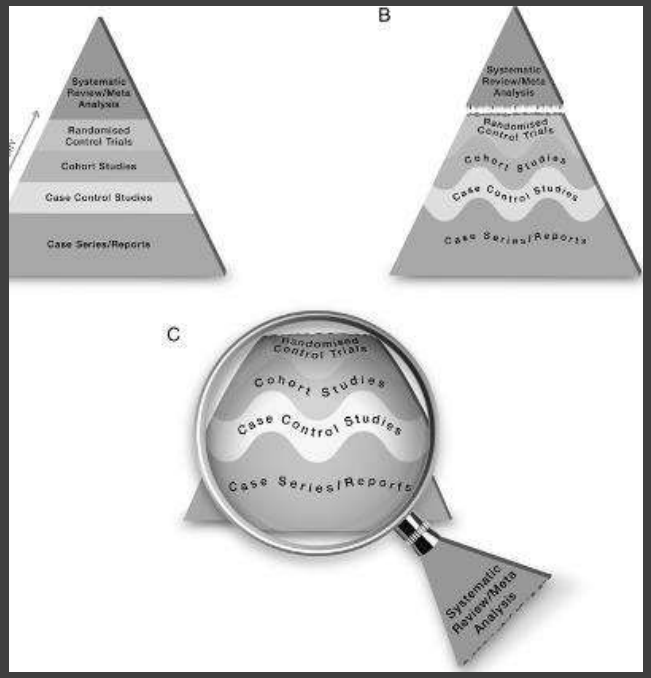
Mercuri & Baigrie, 2018; Greenhalgh et al., 2015;
Das et al., 2008; Kalitzkus & Matthiessen, 2009;
Neuman & Neuman, 2009;
Kuper et al., 2017;
Satterfield et al., 2009

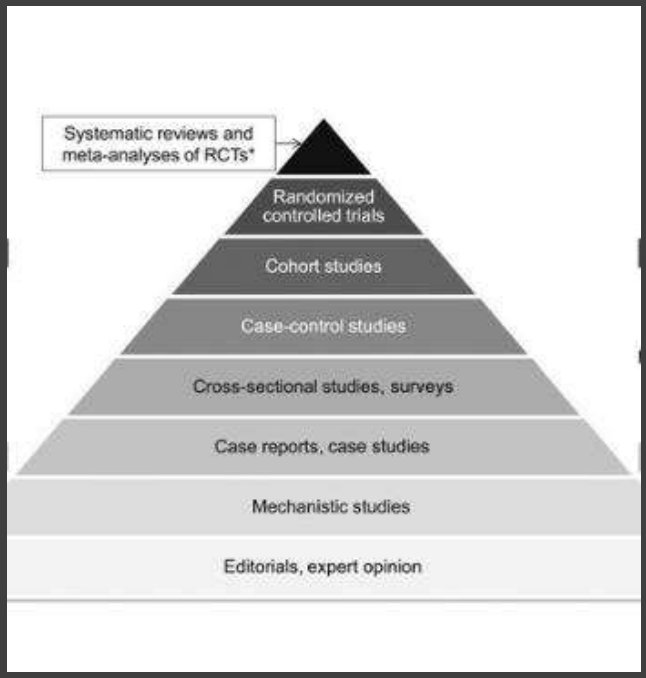


Evidence doesn't make decisions people do

(D. Sackett)

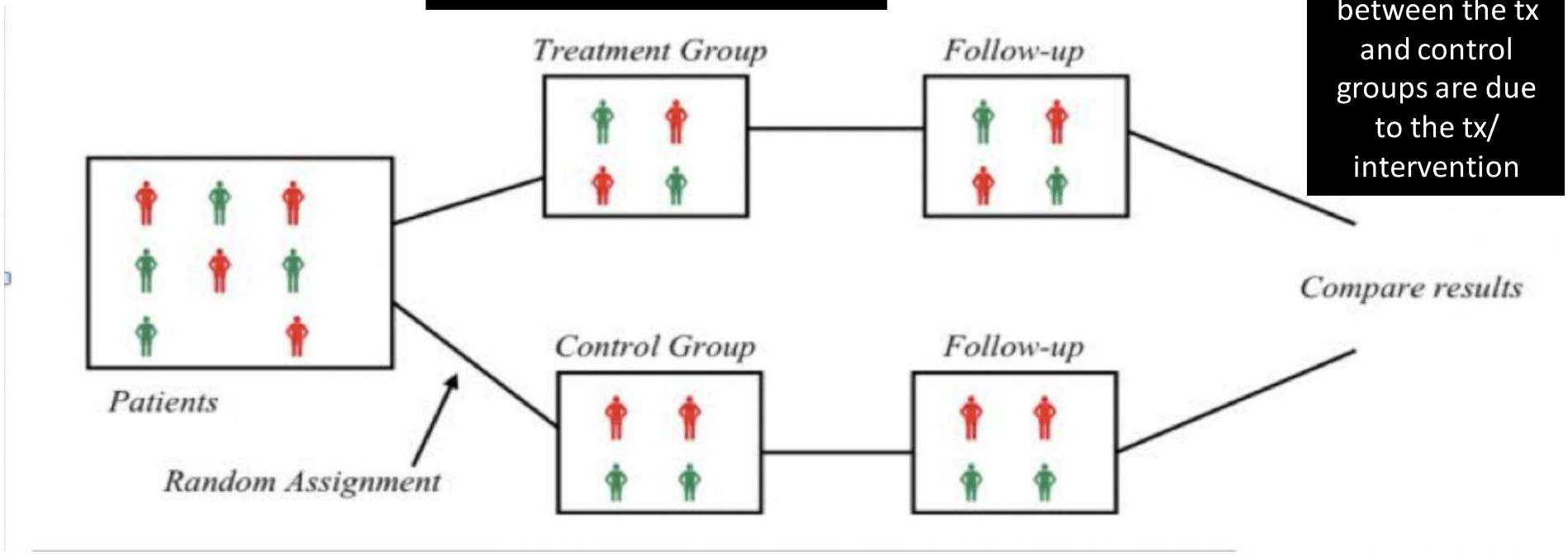






Evidence in Clinical Decision-Making

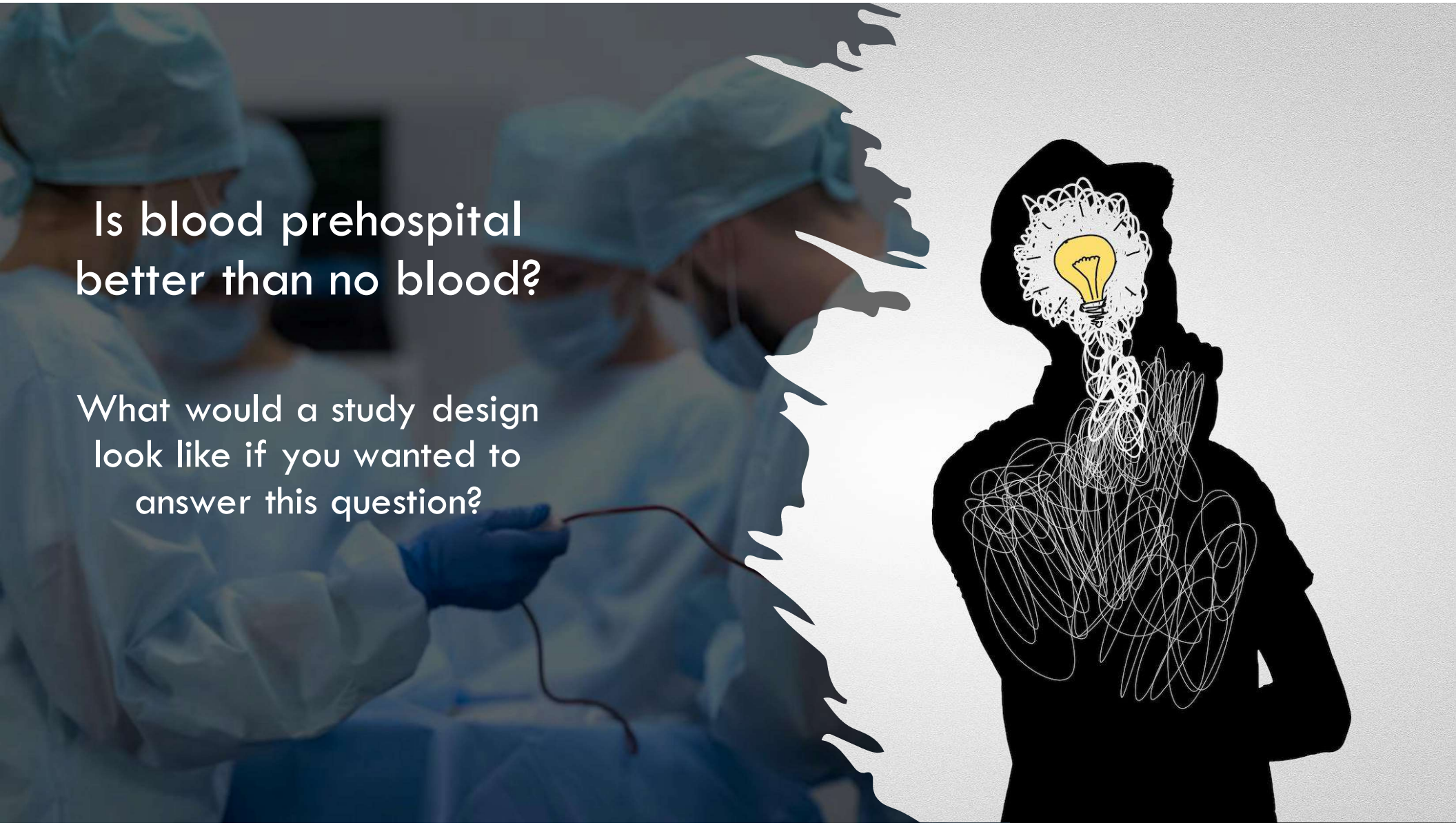
If randomization is successful and the groups are balanced at baseline…



…can conclude that the differences between the tx and control groups are due to the tx/ intervention

Is blood prehospital better than no blood?

What would a study design look like if you wanted to answer this question?



Strengths of the RCT

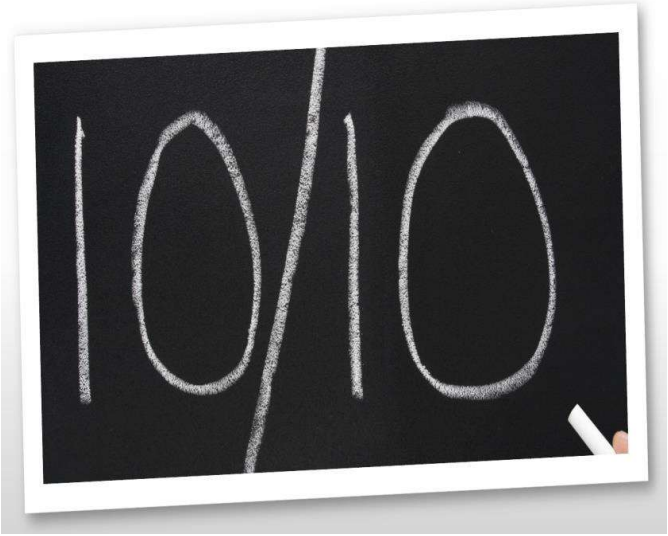
Comparative

Minimizes biases (selection, information, confounding)

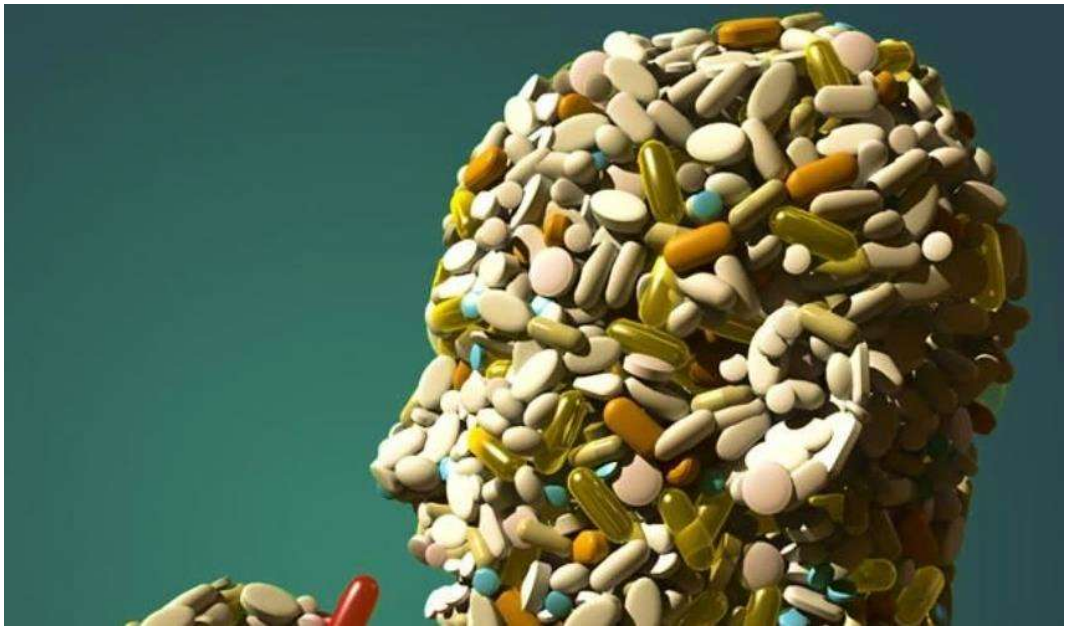
Statistical reliability

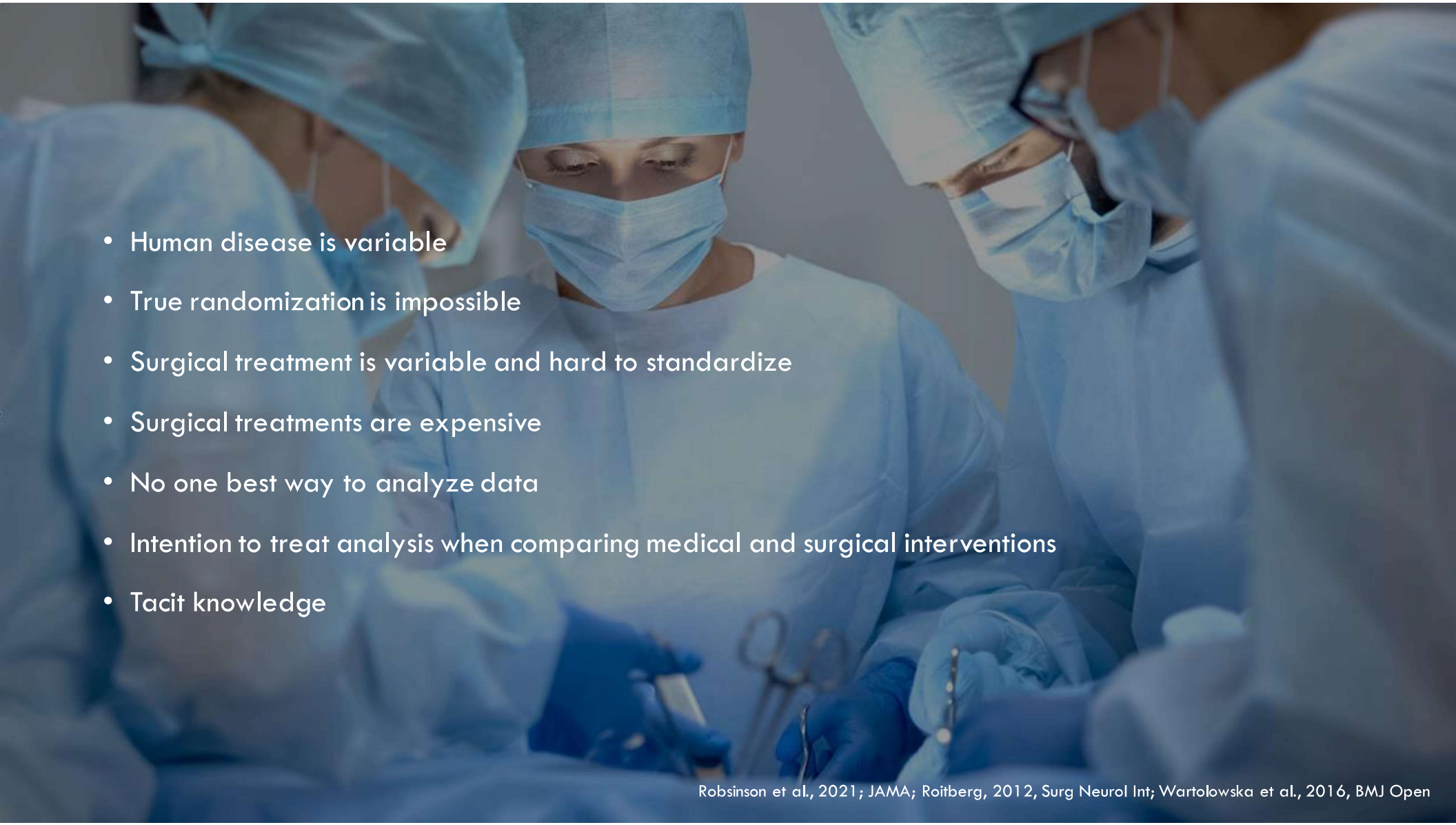
Findings meant to generalize

They yield estimate of the effect of an intervention that is unbiased and consistent

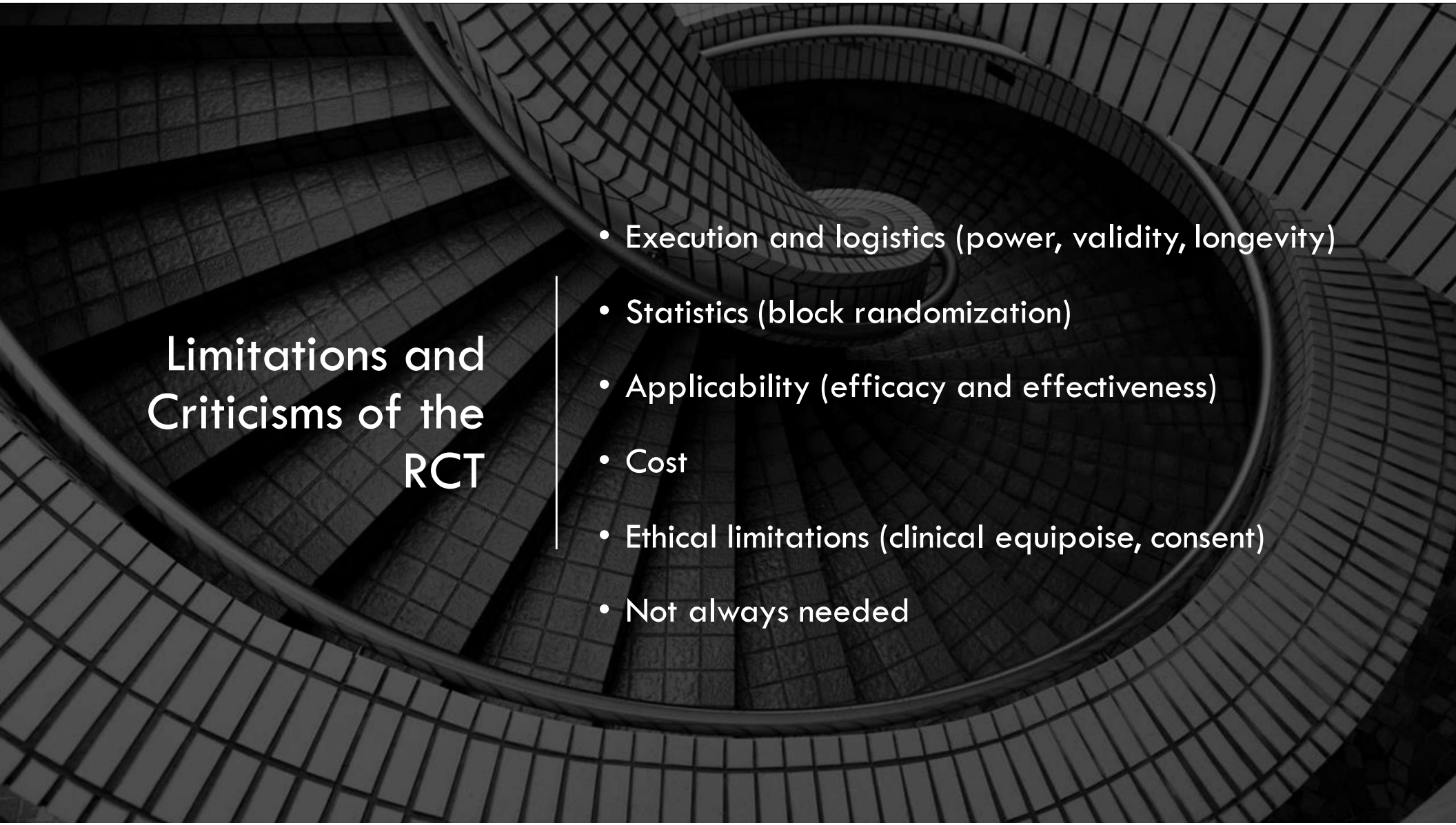


RCT





Robsinson et al., 2021; JAMA; Roitberg, 2012, Surg Neurol Int; Wartolowska et al., 2016, BMJ Open



Limitations and Criticisms of the RCT

- Execution and logistics (power, validity, longevity)
- Statistics (block randomization)
- Applicability (efficacy and effectiveness)
- Cost
- Ethical limitations (clinical equipoise, consent)
- Not always needed

EXECUTION AND LOGISTICS

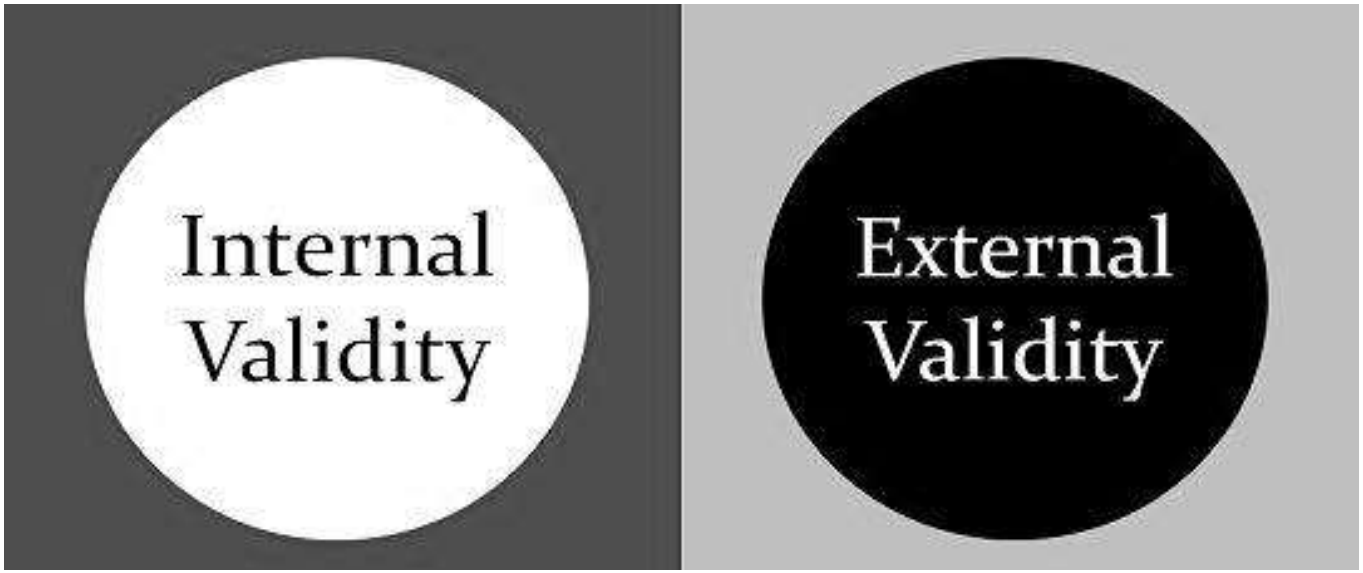
power, validity, time

Trial participants

- Tried many other treatments
- Co-morbidities

TIME

Trace causal inferences to the intervention



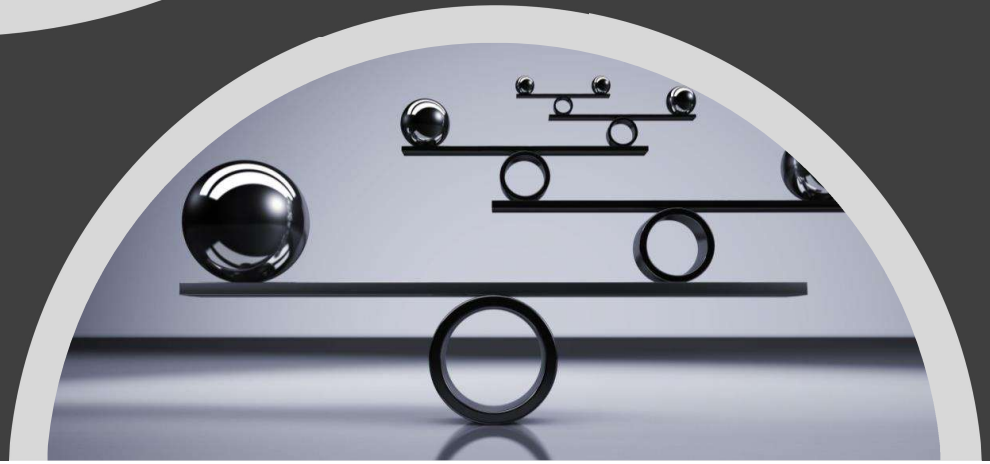
Generalizability of results

Applicability

Efficacy vs. Effectiveness

(along a continuum)

Results many not "mimic" real life treatment situation

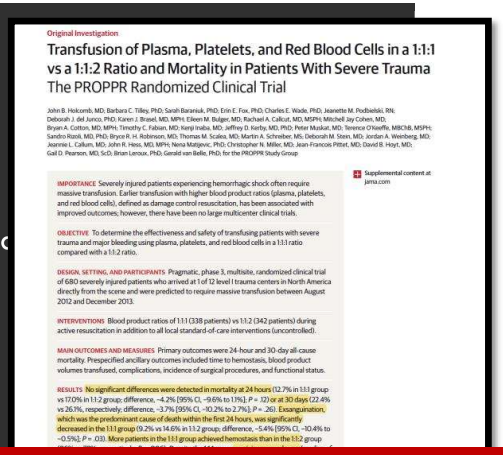


There are RCTs, and then there are RCTs. Not all RCTs are the same.

Streiner, 2002

OBJECTIVE

Effectiveness and safety of transfusing patients with severe trauma & major bleeding using plasma, platelets, & red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio.



Original Investigation

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma

The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy C. Fabian, MD; Hanji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O'Keeffe, MBChB, MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jeannie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

Supplemental content at jama.com

IMPORTANCE Severely injured patients experiencing hemorrhagic shock often require massive transfusion. Earlier transfusion with higher blood product ratios (plasma, platelets, and red blood cells), defined as damage control resuscitation, has been associated with improved outcomes; however, there have been no large multicenter clinical trials.

OBJECTIVE To determine the effectiveness and safety of transfusing patients with severe trauma and major bleeding using plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio.

DESIGN, SETTING, AND PARTICIPANTS Pragmatic, phase 3, multisite, randomized clinical trial of 680 severely injured patients who arrived at 1 of 12 level I trauma centers in North America directly from the scene and were predicted to require massive transfusion between August 2012 and December 2013.

INTERVENTIONS Blood product ratios of 1:1:1 (338 patients) vs 1:1:2 (342 patients) during active resuscitation in addition to all local standard-of-care interventions (uncontrolled).

MAIN OUTCOMES AND MEASURES Primary outcomes were 24-hour and 30-day all-cause mortality. Prespecified ancillary outcomes included time to hemostasis, blood product volumes transfused, complications, incidence of surgical procedures, and functional status.

RESULTS No significant differences were detected in mortality at 24 hours (12.7% in 1:1:1 group vs 17.0% in 1:1:2 group; difference, −4.2% [95% CI, −9.6% to 1.1%]; $P = .12$) or at 30 days (22.4% vs 26.1%, respectively; difference, −3.7% [95% CI, −10.2% to 2.7%]; $P = .26$). Exsanguination, which was the predominant cause of death within the first 24 hours, was significantly decreased in the 1:1:1 group (9.2% vs 14.6% in 1:1:2 group; difference, −5.4% [95% CI, −10.4% to −0.5%]; $P = .03$). More patients in the 1:1:1 group achieved hemostasis than in the 1:1:2 group

MAIN OUTCOMES AND MEASURES

Primary: 24-hour and

Ancillary: time to hem
complications, incidence
status

NO MATTER HOW HARD WE TRY

THERE WILL BE LIMITATIONS THAT WILL THREATEN THE GENERALIZABILITY OF THE RESULTS

CONCLUSIONS

- No sign. diff. in mortality at 24 hours or at 30 days.
- More patients in the 1:1:1 group achieved hemostasis and fewer died from exsanguination by 24 hours.
- Even though there was an increased use of plasma and platelets
- Transfused in the 1:1:1 group, no other safety differences were identified between the 2 groups.

Holcomb et al., 2015; JAMA

- Power to detect differences N ~ 3000
- Inability to completely exclude patients with an unsurvivable BI; 23% deaths - 24 hours & 38% at 30 days associated with TBI

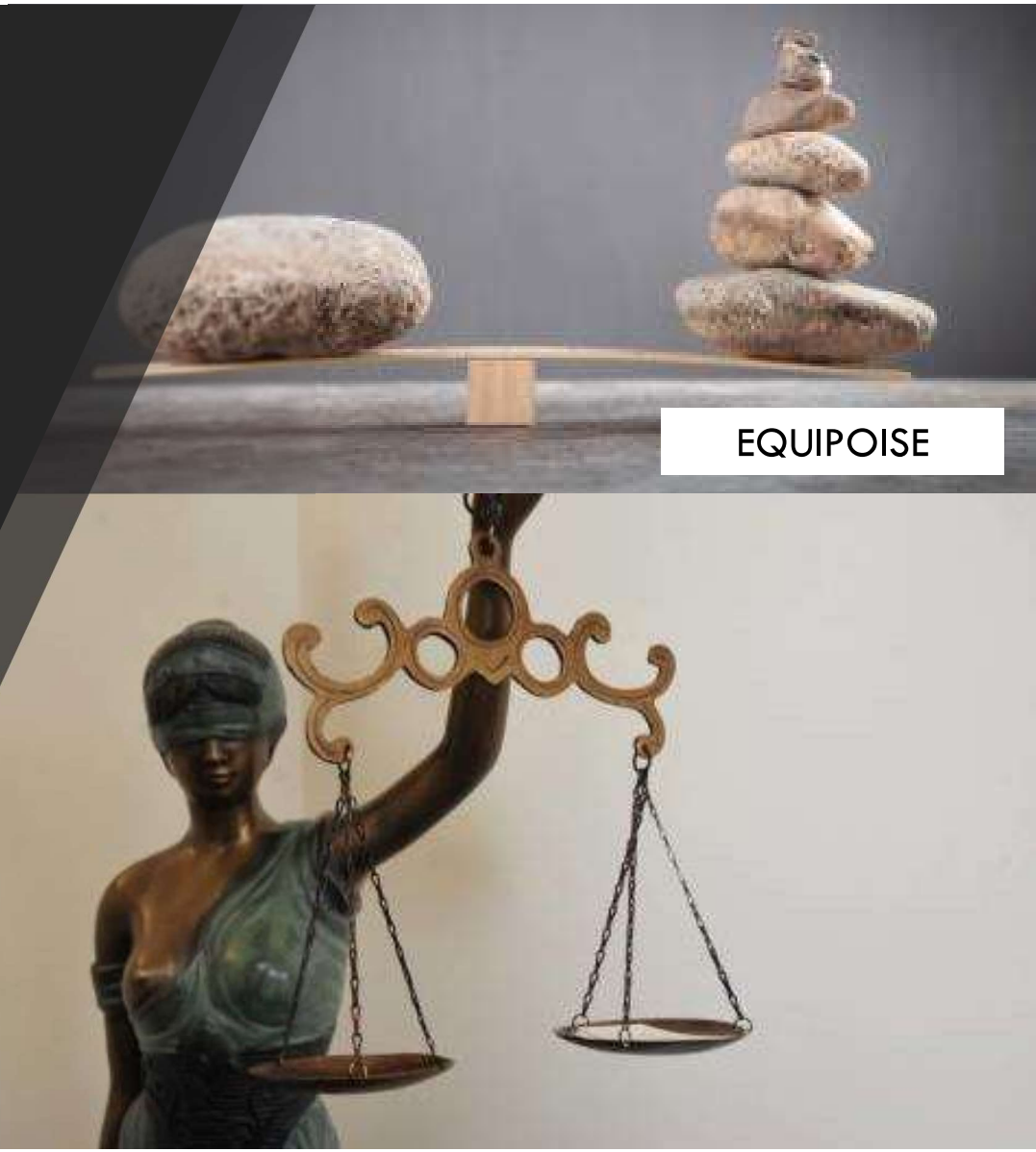
e opened

ffects of

beting risks of death from hemorrhage and TBI


Phase I, II, III: $4M, $13M, $20M
Sertkaya et al. 2014

- Smoking
- Flossing
- Radiation
- Breastfeeding
- Sudden Infant Death Syndrome
- Informed consent not always possible



Rh(D) and Haemolytic Disease of the Newborn

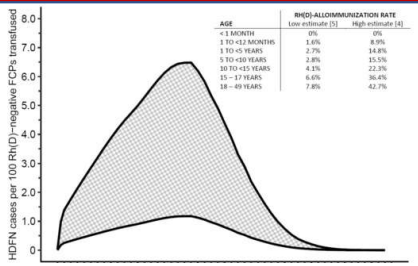
SHOULD CLINICAL PRACTICE CHANGE TO ALLOW RH+ WHOLE BLOOD TO WOMEN WITH CHILDBEARING POTENTIAL WHEN NO DEFINITIVE EVIDENCE ON BENEFITS OF WHOLE BLOOD AND RISK OF HDHF?

Received: 30 March 2021 | Revised: 24 May 2021 | Accepte
DOI: 10.1111/vox.13169

LETTER TO THE EDITOR

Risk of future haemolytic following the transfusion to Rh(D)-negative childre

Recently, the risks of an Rh(D)-negative female of child-bearing potential (FCP) developing haemolytic disease of the newborn (HDFN) following receipt of Rh(D)-positive red blood cells (RBCs) or low-titre group O whole blood during her trauma resuscitation was modelled using her age at the time of transfusion and several other important societal factors that impact the development of HDFN [1]. In that study, the FCP age range was 18–49 years. Since its publication, questions have arisen about the future HDFN potential following the transfusion of Rh(D)-positive units to injured Rh(D)-negative children. The previously published model was adapted for, and applied to, patients between 0 and 17 years [1]. For this new model, the Rh(D) alloimmunization risk had to be



AGE	RH(D)-ALLOIMMUNIZATION RATE	
	Low estimate [5]	High estimate [4]
< 1 MONTH	0%	0%
1 TO <12 MONTHS	1.6%	8.9%
1 TO <5 YEARS	2.7%	14.8%
5 TO <10 YEARS	2.8%	15.5%
10 TO <15 YEARS	4.1%	22.3%
15 – 17 YEARS	6.6%	36.4%
18 – 49 YEARS	7.8%	42.7%

Vox Sanguinis (2021)
Society of Blood Transfusion
DOI: 10.1111/vox.13065

-negative
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t on

Jansen N. Seheult,[1,2] Michelle N. Stram,[3] Thomas Pearce,[1] Carolina B. Bub,[4] Stephen P. Emery,[5] Jose Kutner,[4] Naoko Watanabe-Okochi,[6] Jason L. Sperry,[7] Minoko Takanashi,[8] Darrell J. Triulzi[1,2] & Mark H. Yazer[1,2]
[1]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[2]Vitalant, Pittsburgh, PA, USA
[3]New York University School of Medicine, New York, NY, USA
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[6]Japanese Red Cross Society, Kanto-Koshinetsu Block Blood Center, Saitama, Japan
[7]Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[8]Japanese Red Cross Society Blood Service Headquarters, Tokyo, Japan

Yazer et al., 2022; Seheult et al., 2021

al

implistic

NOT ALL RCTs ARE MADE EQUAL
DIFFERENT RCTs WILL YIELD DIFFERENT RESULTS


THE LANCET

ARTICLES | VOLUME 392, ISSUE 10144, P283-291, JULY 28, 2018

Plasma-first resuscitation to treat haemorrhagic shoc
ground transportation in an urban area: a randomisec

Hunter B Moore, MD · Prof Ernest E Moore, MD · Michael P Chapman, MD · Kev
Gary Bryskiewicz · Robert Blechar · et al. Show all authors

Published: July 19, 2018 · DOI: https://doi.org/10.1016/S0140-6736(18)31553-8 ·

DIRECT COMPARISON IS DIFFICULT BUT CAN GUIDE FUTURE RESEARCH

1. **What is optimal blood quantity prehospital transfusion (pht), given different transport times, different environments, different patient pathologies?**
2. **When should pht cease?**
3. **Which patients benefit most pht?**

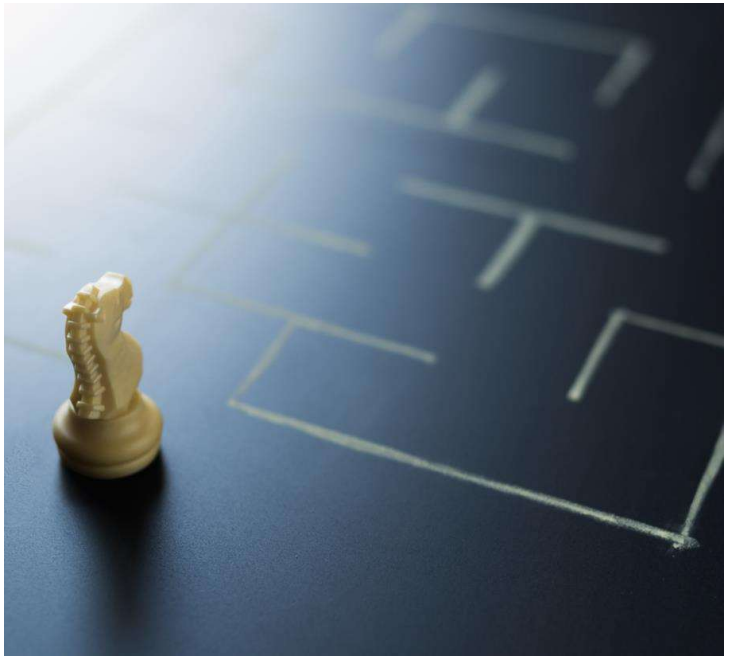
LESSONS LEARNED

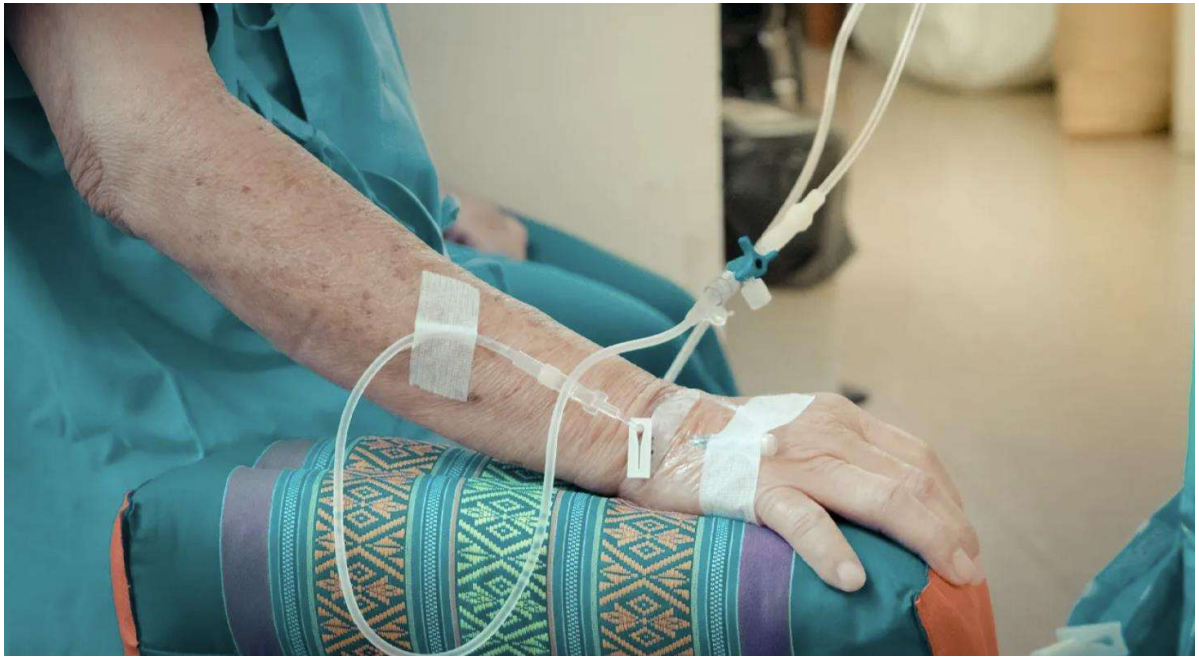
DON'T CONDEMN PHT!!!

Help better identify those who may not benefit

Develop better tools to assess the patient phenotype using data available at the start of resuscitation

Sperry et al., 2018, *N Engl J Med;*
Moore et al., 2018, *Lancet;*
Crombie et al., 2022, *Lancet Haematol.*
Yazer et al., 2022, *Transfusion*





Need for RCT and Hard Cases

- Resuscitation
- O^2

Are there hard cases in transfusion?

Overreliance on the RCT…

Hubble: Visible Light

Another: X-Rays

Another: Gamma Rays

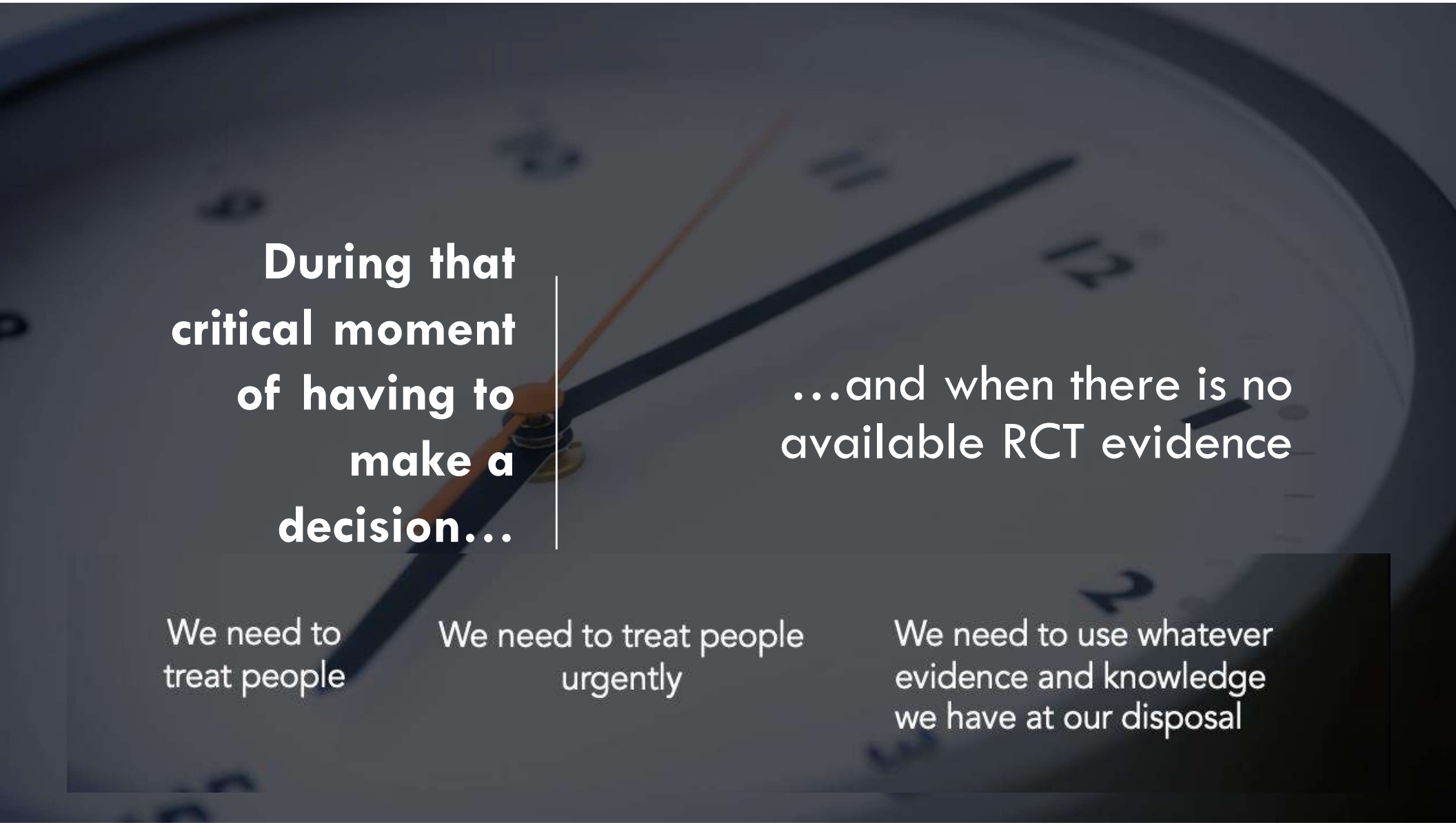
"If you can do an RCT,

by all means do it"

William Shaddish, PhD

Professor Psychological Sciences

University of California at Merced


During that critical moment of having to make a decision…
…and when there is no available RCT evidence
We need to treat people
We need to treat people urgently
We need to use whatever evidence and knowledge we have at our disposal

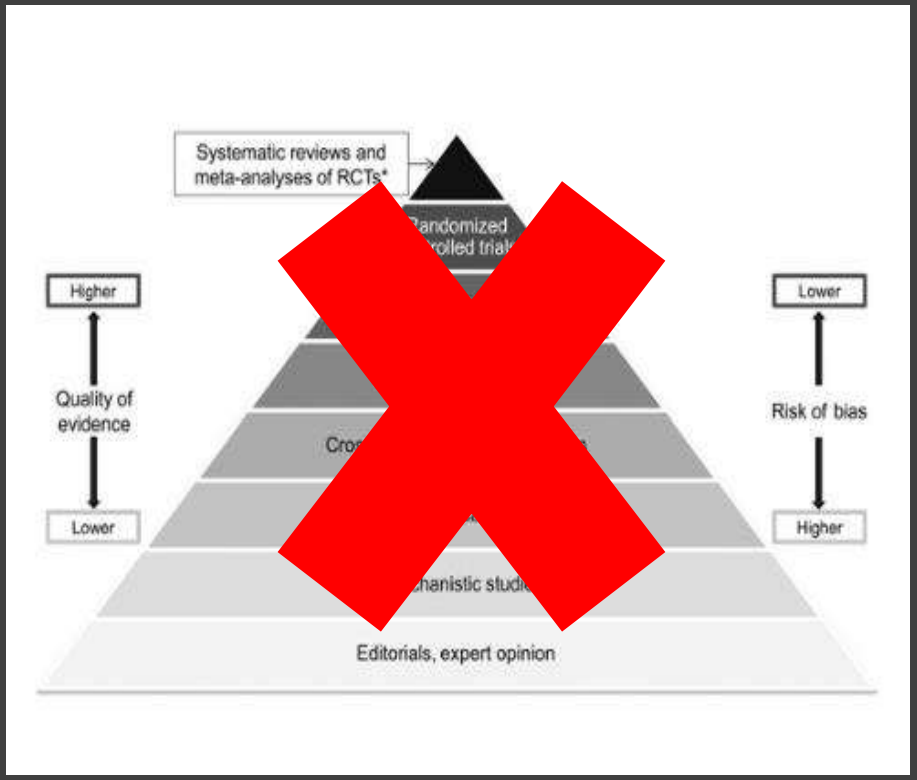
When is it reasonable to change practice?

Lessons from Implementation Science


Public Health


When faced with changing, imperfect and conflicting evidence… clinicians may behave differently
Jaeschke, et al., 2020

Is the 'Evidence-Pyramid' now dead?



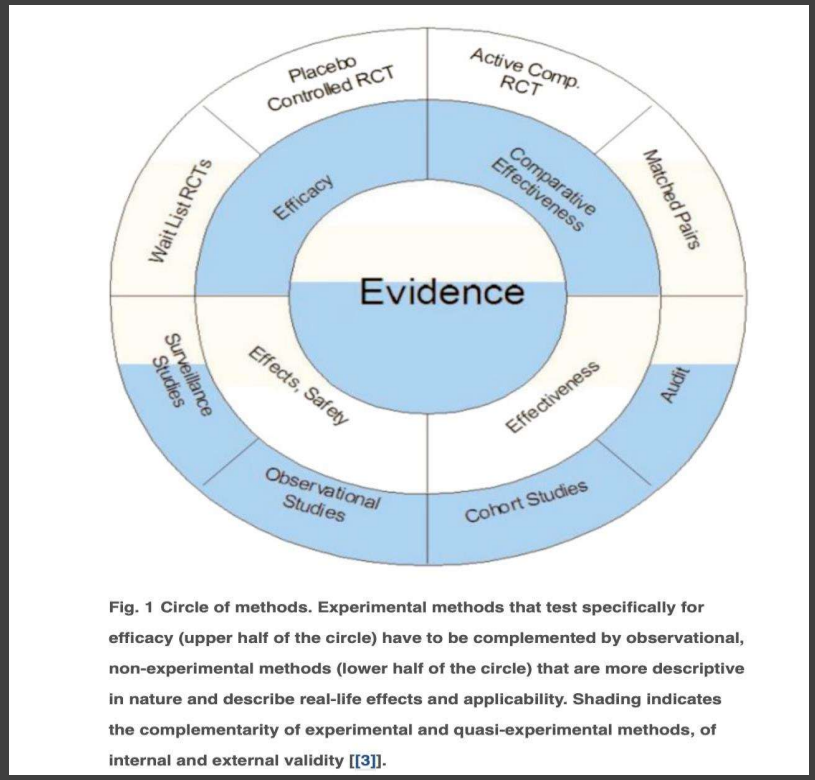


Fig. 1 Circle of methods. Experimental methods that test specifically for efficacy (upper half of the circle) have to be complemented by observational, non-experimental methods (lower half of the circle) that are more descriptive in nature and describe real-life effects and applicability. Shading indicates the complementarity of experimental and quasi-experimental methods, of internal and external validity [[3]].

Tugwell & Knottnerus, 2015; Walach *et al.* (2006)

Other sources

- observational studies (+ routinely collected data ***)
- phase II trial data
- epidemiological data
- qualitative data
- single case experiments
- historical controls
- reports from the field/clinicians using an intervention
- design incorporating adaptive and Bayesian principles

Hemkens, Contopoulos-Ioannidis & Ioannidis, 2016; Jansen et al., 2017

Big data

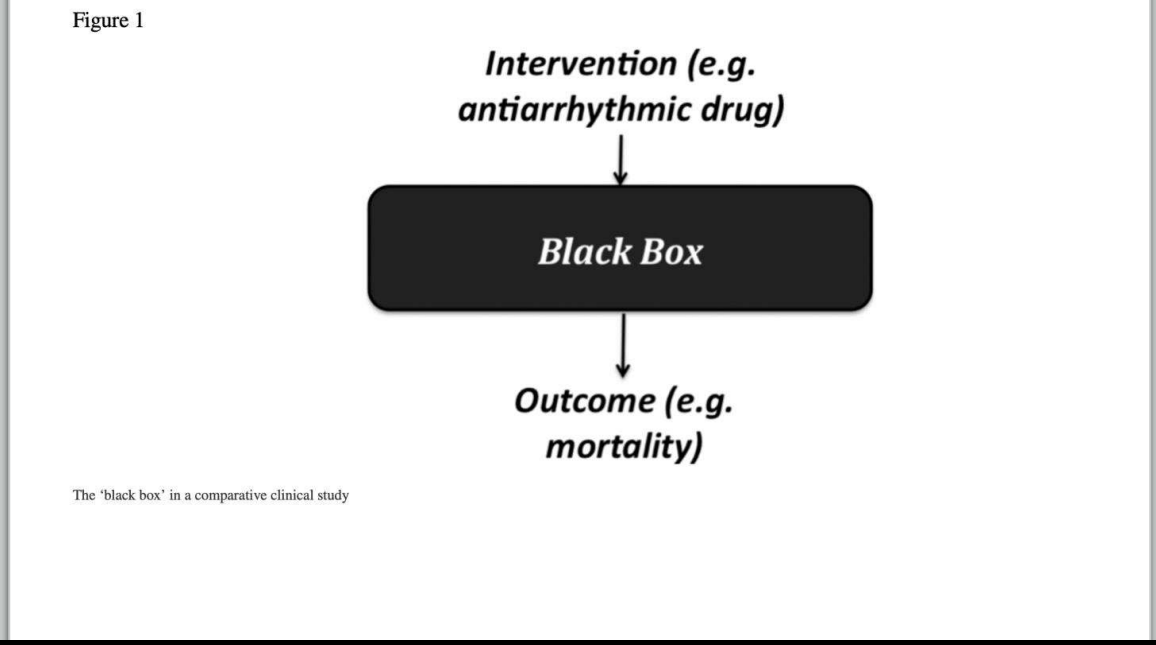
Mechanistic Reasoning

The inference from mechanisms to claims that an intervention produced a patient-relevant outcome

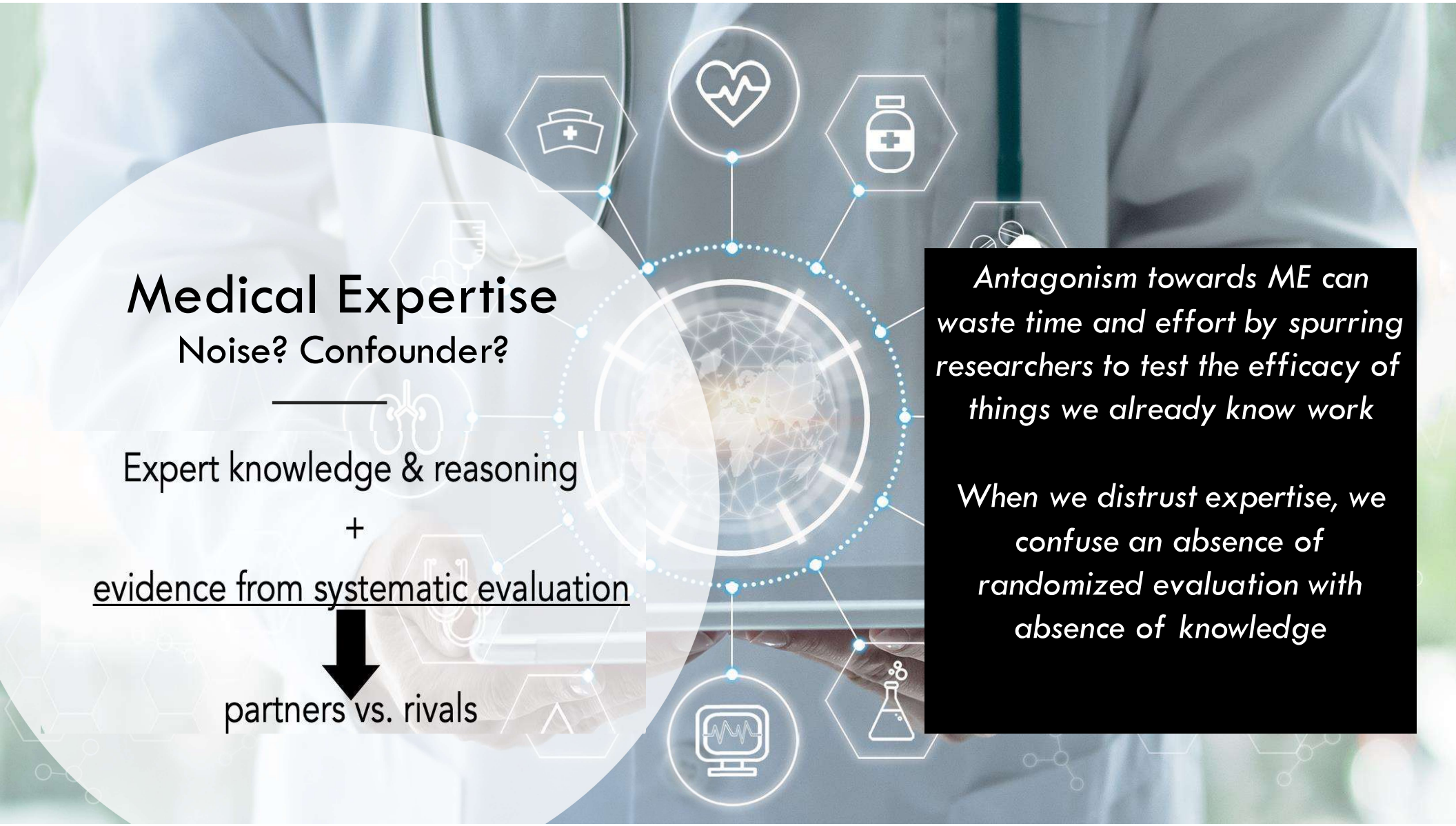
Such reasoning will involve an inferential chain linking the intervention with the outcome

(Howick, Glasziou & Aronson, 2010)

REQUIREMENT:
no gaps in the inferential chain linking the intervention to the clinically relevant outcome and evidence for the links



Introduction of useful treatments such as antisepsis and AB for peptic ulcers was delayed because of a failure to consider mechanisms properly



Medical Expertise

Noise? Confounder?

Expert knowledge & reasoning

+

evidence from systematic evaluation

partners vs. rivals

Antagonism towards ME can waste time and effort by spurring researchers to test the efficacy of things we already know work

When we distrust expertise, we confuse an absence of randomized evaluation with absence of knowledge

Borgman et al.,2007: J of Trauma
Spinella et al., 2009; J of Trauma

Eastridge et al., 2012; J Trauma Acute Care Surg
Eastridge et al., 2011; J of Trauma

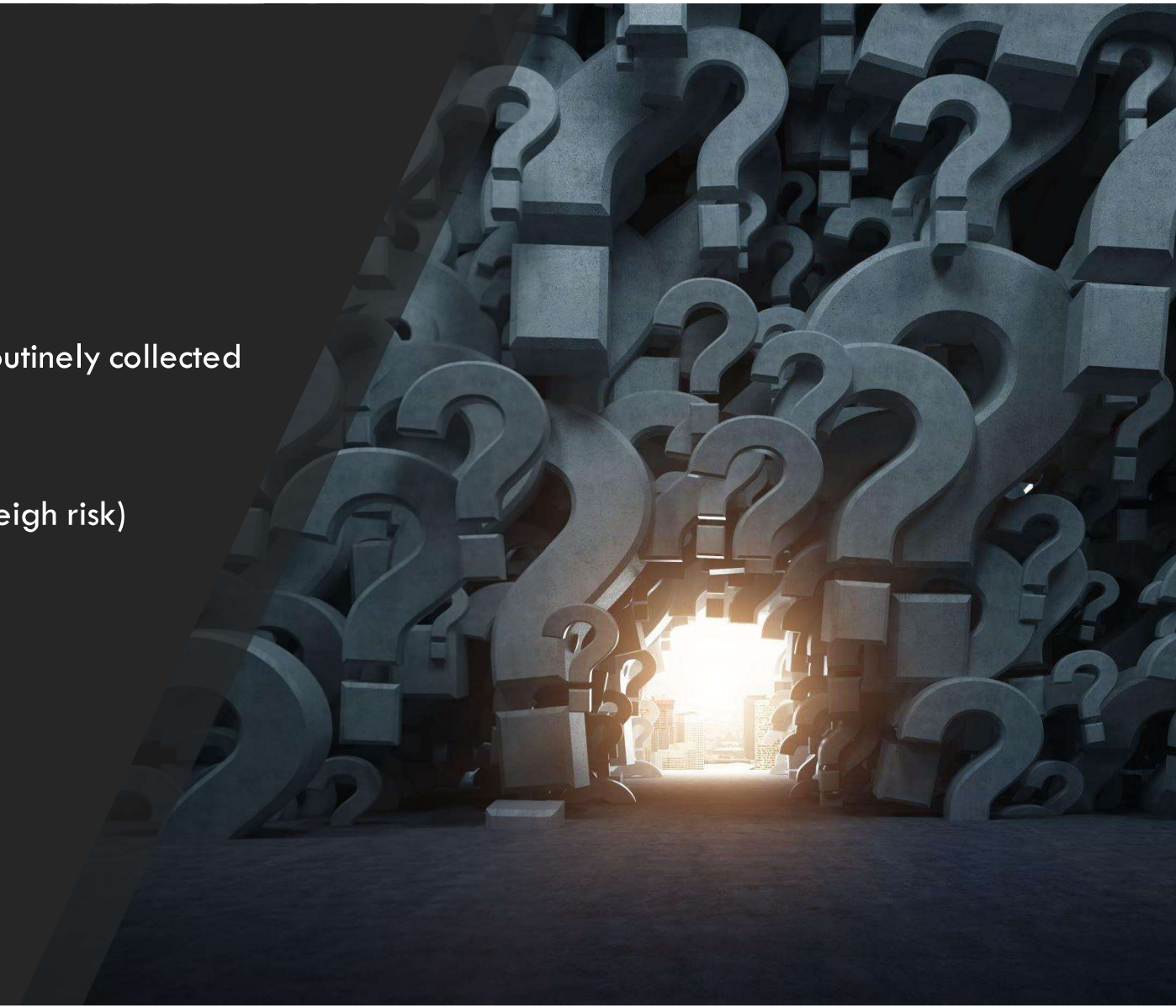
Shackelford et al., 2017; JAMA
Berwick et al., 2016; JAMA

When is it reasonable to change practice?

Lessons from Implementation Science

When…

- Learning health systems data
- Good observational studies with routinely collected data
- Situation is dire and urgent
- Acceptable risk (benefit may outweigh risk)
- Underlying mechanisms are solid
- Patient/family input
- Context is facilitating (resources)
- Clinical experience supports it
- Importantly…..



Practitioners

Policymakers

Administrators

Patients/families

Researchers

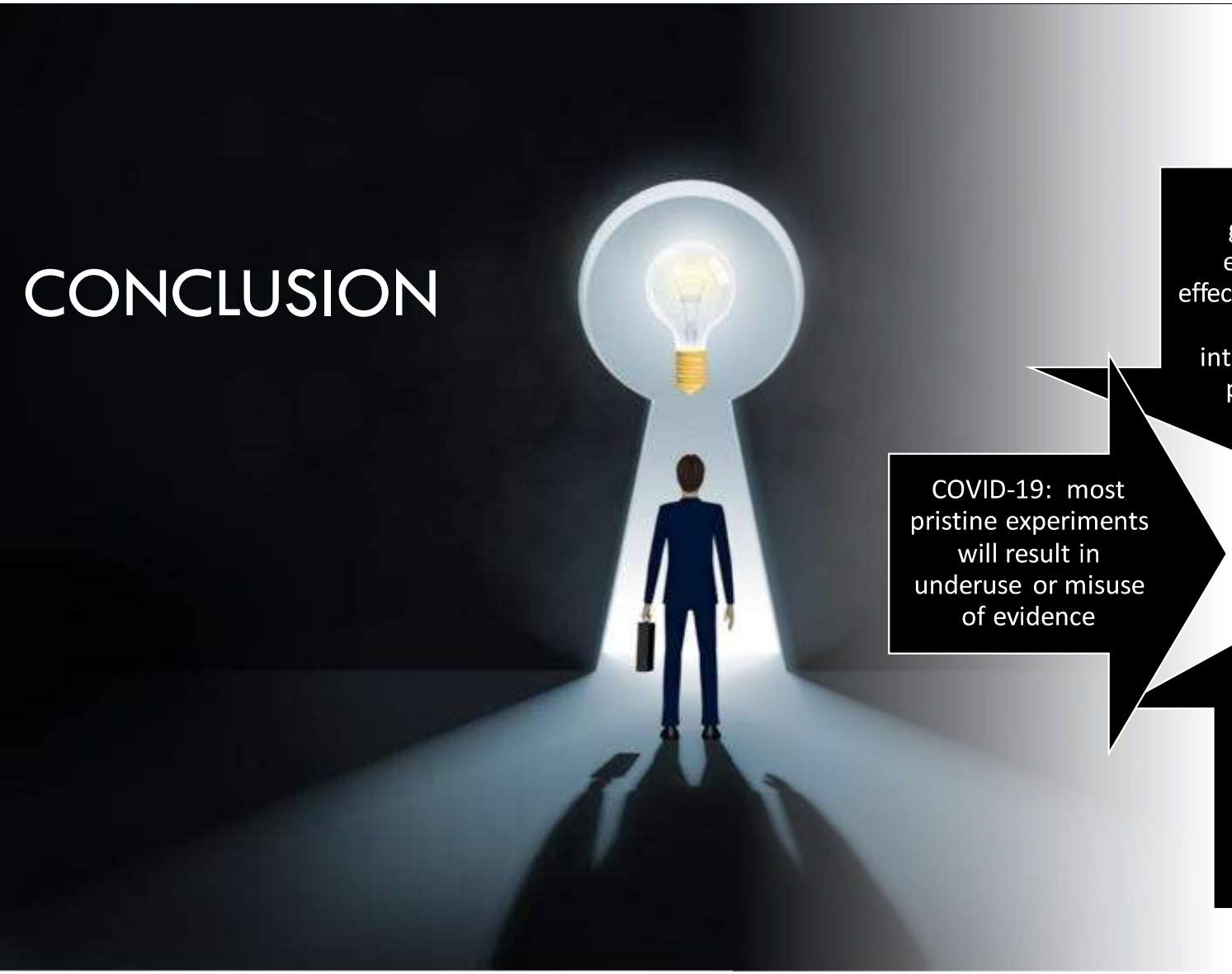
Funders

EVIDENCE DOES NOT ALWAYS DRIVE PRACTICE

What counts as evidence?
Who is asking for the evidence?
Who is producing the evidence?
What is done with or without evidence?

Bussieres et al., 2016
Eilayyan et al., 2018;2019
Peters et al., 2020
Thomas et al., 2020
Thomas & Ellaway, 2021
Thomas, Chin-Yee, & Mercuri, 2021

CONCLUSION



Vital role generating evidence of effectiveness of life saving interventions & procedures

COVID-19: most pristine experiments will result in underuse or misuse of evidence

Advantages and drawbacks

HC is complex; patients are complex

ACKNOWLEDGEMENTS

Dr. Mathew Mercuri

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