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Evidenced Based Medicine: The Value of Randomized Controlled Trials versus Administrative Databases

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Evidence based medicine (EBM)

The conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients

Evidence based medicine (EBM)

EBM is a movement to increase the use of high quality clinical research in clinical decision making

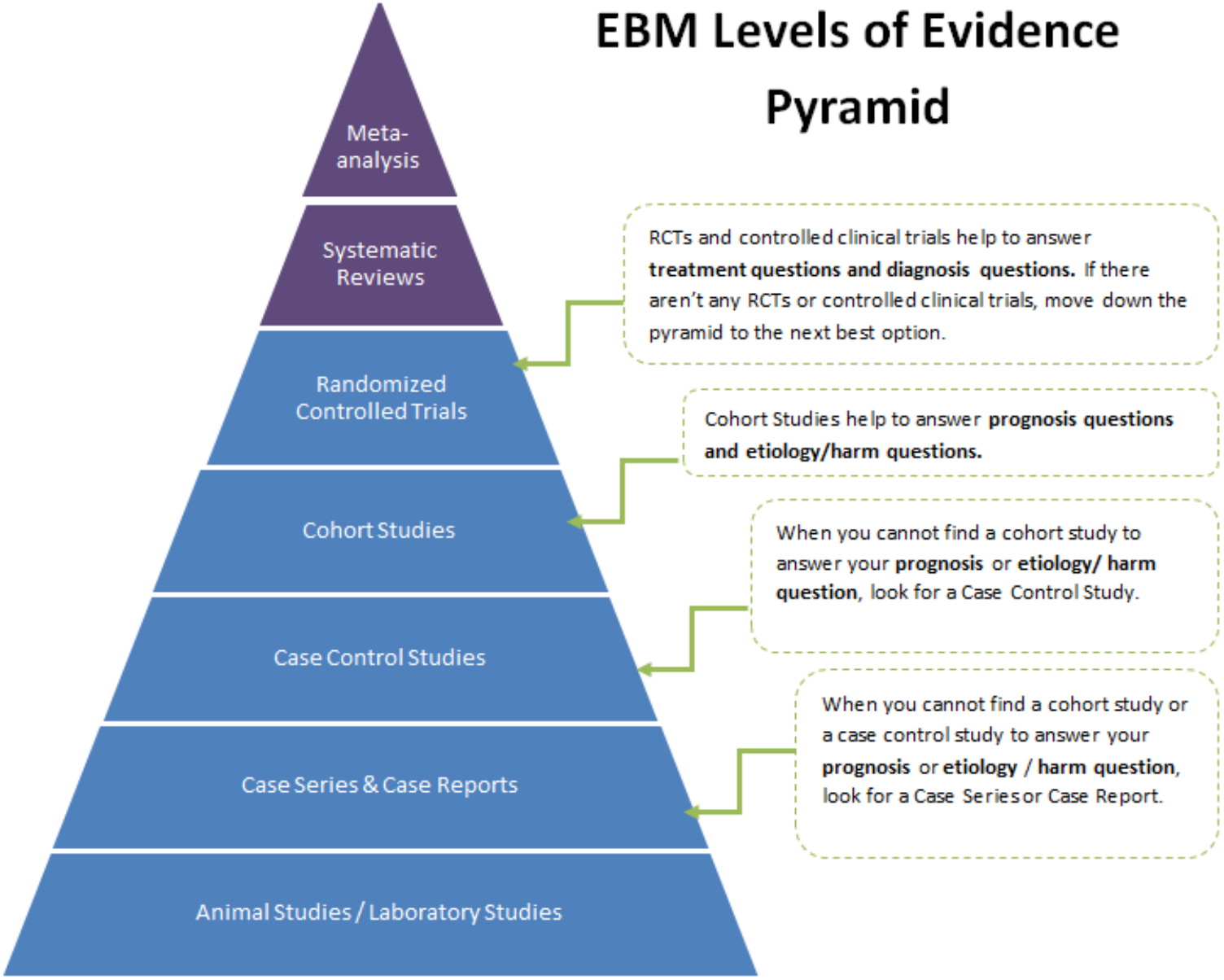
Evidence based medicine (EBM)

EBM integrates clinical experience and patient values with the best available research information

Evidence based medicine (EBM)

Requires additional skills of the clinician including efficient literature-searching, and the application of formal rules of evidence in evaluating the literature

EBM Levels of Evidence Pyramid



Weakest level at the base progressively, stronger sources as one moves to the peak
Evidence exists as a continuum of rigor with that derived from the RCT as the most rigorous

RCT is the Gold Standard

Well designed, rigorously executed, properly analyzed and properly interpreted RCT provide the best evidence for ***comparing treatments***

Randomization

Allows an **unbiased** assessment of comparative treatment benefit

Balance: On average, *all covariates* are balanced across treatment groups

Unbiased assignment: Treatment assignment entirely at random

All RCTs are challenging

Surgical trials are especially challenging

- Recruitment of patients
- Retention of patients
- Defining treatments
- Adherence to treatments
- Masking (blinding)
- Unexpected problems

RCTs not always feasible

Ethical reasons - **Lack of Equipoise**

Practical reasons

- ***Cost***
- *Rare disease or outcome*
- *Clinician/Patient resistance to randomization*

The Need for Large Volume Databases

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Surgical procedures represent one of the largest expenditures in healthcare

Projected to constitute over 7% of US gross domestic product by 2025

Vested interest among many stakeholders in the expected risks and benefits of a given procedure in a particular cohort of patients

Two classifications of LVD

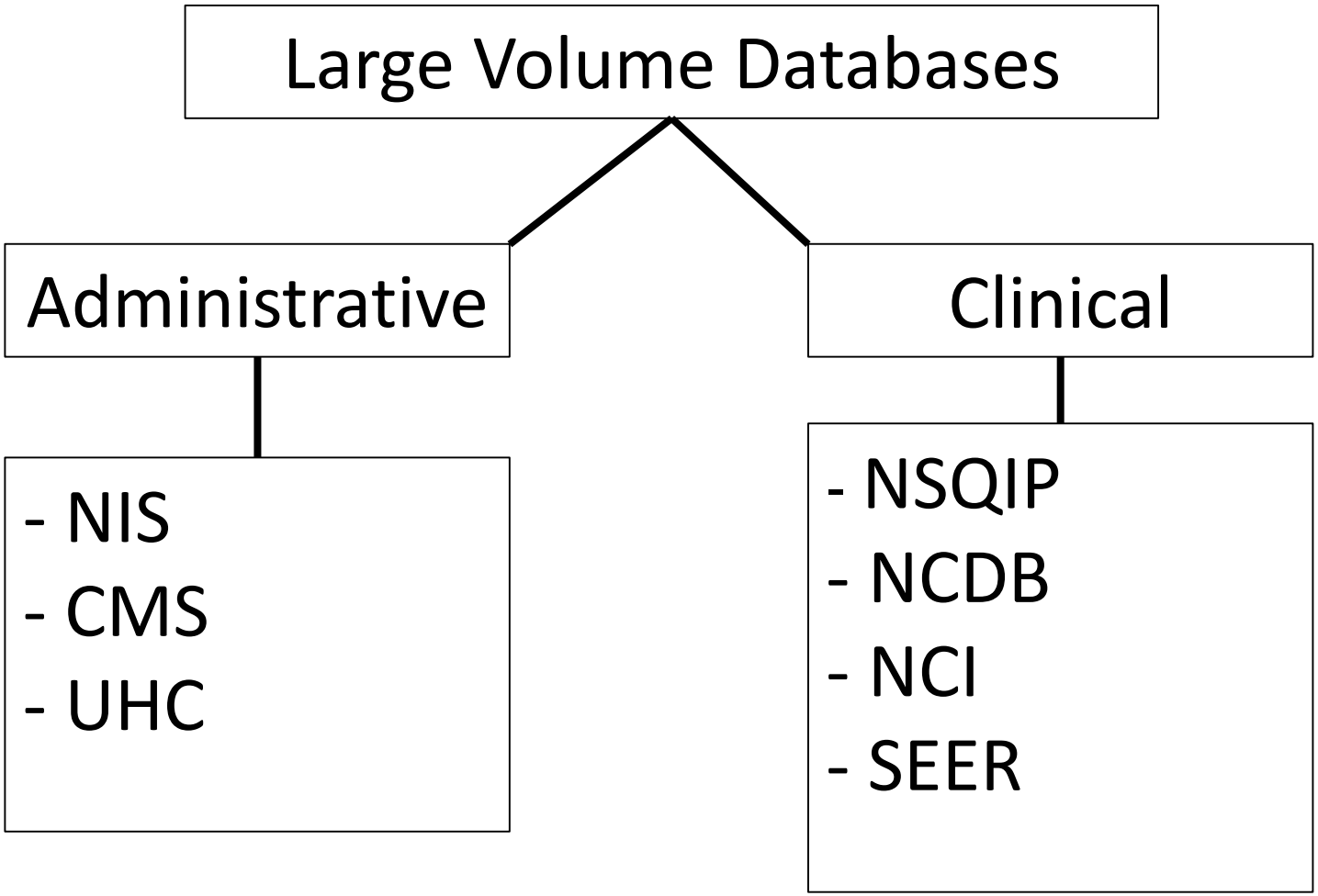
Administrative – Payments/Billing

Requests to insurers for healthcare payments and claims for clinical services (CMS, NIS)

Clinical – Patients

Composed of a given patient population with defined patient information

Designed to record and track information, allowing for the investigation of specific clinical questions (NSQIP)


Large Volume Databases
Administrative
Clinical
- NIS
- CMS
- UHC
- NSQIP
- NCDB
- NCI
- SEER

Administrative databases

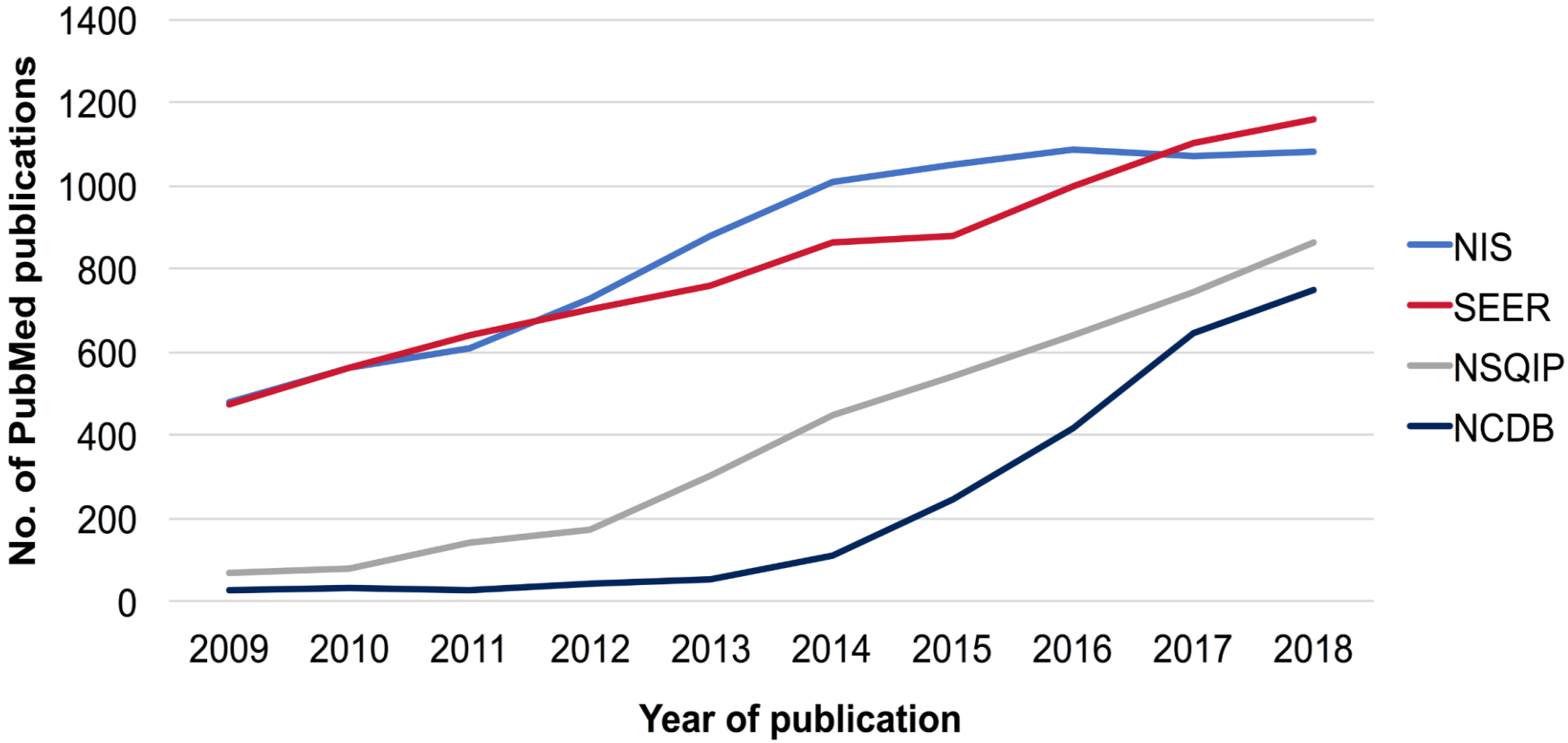
Registry	Acronym	Variables	Geography	Website
Healthcare Cost and Utilization Project Nationwide Inpatient Sample Kids Inpatient Database Nationwide ED Sample State Inpatient Database State Ambulatory Surgery Database	HCUP NIS KID NEDS SID SASD	Primary/secondary diagnoses Primary/secondary procedures Admission/ discharge status Patient demographics Provider/hospital characteristics Cost, LOS, insurance Inpatient mortality	Nationwide State State	http://www.ahrq.gov/data/hcup
University Health System Consortium	UHC	Diagnoses on admission Inpatient procedures Severity of index score Admission type Mortality, morbidity, LOS, readmission rates, ICU admission, discharge location Cost Provider/hospital characteristics	Nationwide	http://www.uhc.edu
MEDICARE Centers for Medicare and Medicaid Services	CMS	Inpatient, outpatient, skilled nursing facility services Physician services	Nationwide	http://www.resdac.org/
Medicaid Centers for Medicare and Medicaid Services	CMS	Eligibility basis Patient demographics Services provided Prescription drugs		http://www.resdac.org/

Abbreviations: LOS, length of stay; ICU, intensive care unit.

Clinical databases

Registry	Acronym	Variables	Geography	Website
The Surveillance, Epidemiology, and End Results Program National Cancer Institute	SEER NCI	Stage/date of diagnosis Primary disease site, therapy Mortality Demographics	17 cancer registries covering ~28% population	http://seer.cancer.gov/
National Cancer Database	NCDB	Patient/hospital characteristics Stage, tumor histology, treatment 6 secondary diagnoses	1450 hospitals	http://www.facs.org/cancer/ncdb/
Cancer Care Outcomes and Research Consortium	CanCORS	ICD oncology codes 6 secondary diagnoses Mortality, stage, comorbidities	5 regions 5 health care systems 15 VA hospitals	http://outcomes.cancer.gov/cancors/
National Surgical Quality Improvement Program American College of Surgeons Veterans Affairs	NSQIP NSQIPACS NSQIPVA	Preoperative risk factors Intraoperative data, Patient demographics Outcomes Procedures 30-Day morbidity/mortality	Participating hospitals nationwide	http://site.acsnsqip.org/
Automated Central Tumor Registry U.S. Department of Defense	ACTUR	Date of diagnosis, date of death Stage, tumor grade Patient demographics	U.S. Department of Defense	Available on request
National Trauma Data Bank	NTDB	Patient demographics Injuries Hospital demographics	National sample Level I/II trauma centers	http://www.facs.org/trauma/ntdb/index.html

Large volume databases have several benefits that have fueled their popularity among surgeon investigators



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Benefits

Capture **“Real World”** experience

Size – Allow investigation of rare diseases, procedures, and outcomes

Speed and cost – studies are quick and inexpensive

Inherent Limitations

Not specifically designed for research

Investigator does not determine what is measured, or how it is measured

LVD limitations

- Data sources

  ICD/CPT based information is influenced by reimbursement strategies
- Data quality
- Data completeness
- Scope of information included

  confounders and comorbidities

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Practice of Epidemiology

Evaluating the Impact of Database Heterogeneity on Observational Study Results

David Madigan*, Patrick B. Ryan, Martijn Schuemie, Paul E. Stang, J. Marc Overhage, Abraham G. Hartzema, Marc A. Suchard, William DuMouchel, and Jesse A. Berlin

Same question, different database, different results

Sometimes statistically significant in opposite directions

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Importance of Database Selection

- Key first step
- Determined by research question
  - *Can it be answered?*
- Databases are very heterogeneous
- NSQIP is comparatively rigorous

Assessing value to the evidence base

Contribution of any study to the evidence base should reflect the rigor with which it was designed, executed, and analyzed

RCT are generally rigorously designed, executed, and analyzed

RCT have two key bias minimizing components

(1) Treatments are assigned at random

(2) Pre-determined protocol

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	

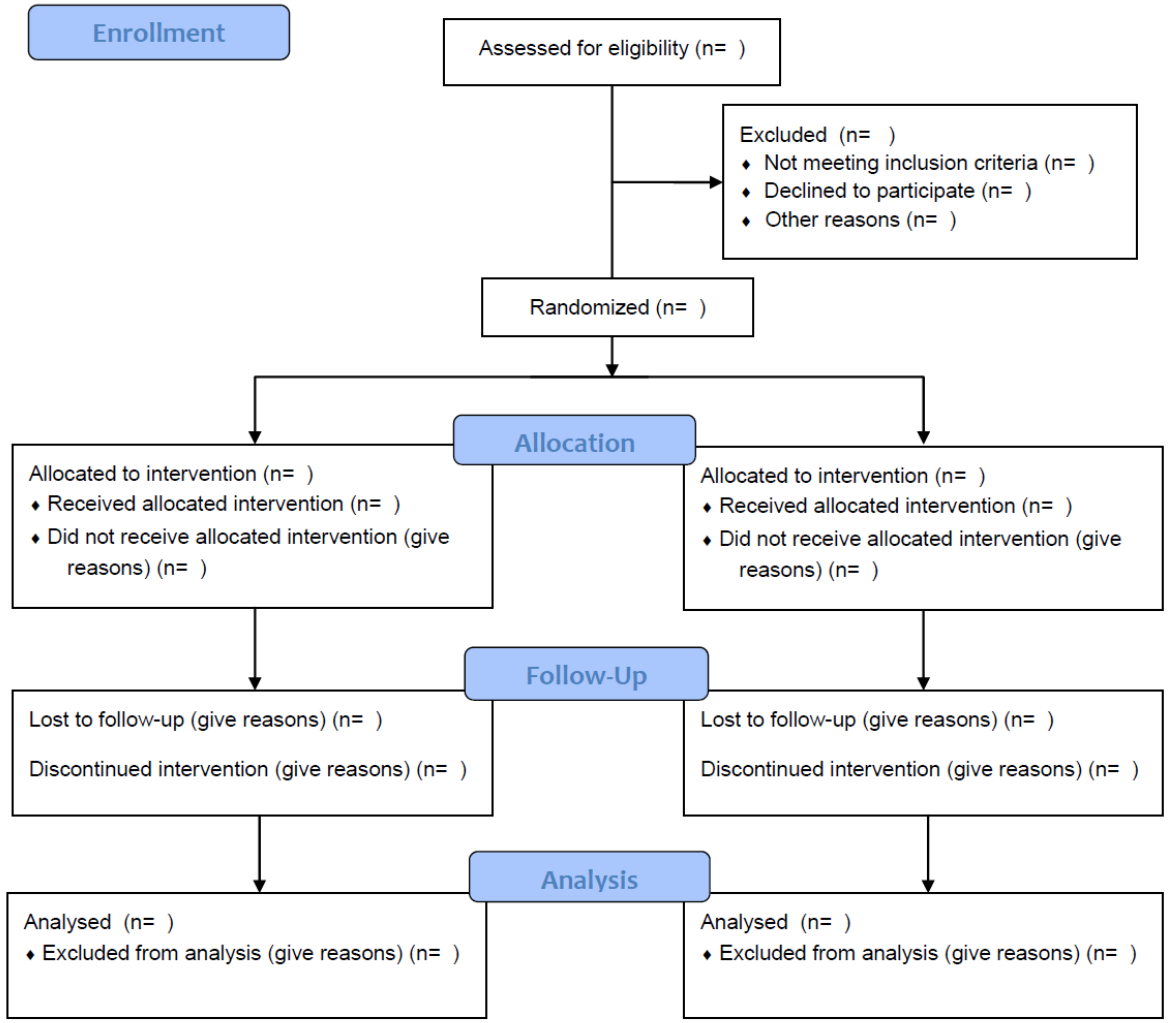
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



LVD and the evidence base

Contribution of research using LVD ("outcomes research") to evidence base is challenged by questions of rigor and bias

LVD studies should follow a pre-specified “protocol”

Surg Endosc (2011) 25:2254–2260
DOI 10.1007/s00464-010-1543-7

A review for clinical outcomes research: hypothesis generation, data strategy, and hypothesis-driven statistical analysis

David C. Chang · Mark A. Talamini

Statistical solutions to minimize bias

Borrowed from epidemiology

Not obviously adequate

Propensity ("balancing") scores to adjust for confounders

- *Epidemiological studies can determine confounders to measure*
- *Residual bias remains larger relative to effects in epidemiologic studies*

The touted benefits of using LVD (cheap, fast, “easy”, sample size) coupled with bias inducing limitations (inconsistent data, missing covariates) are a substantial threat to rigor

Bias

A systematic error in the design, recruitment, data collection or analysis that results in the erroneous estimation of a true effect

Omitted Confounder

Success	Procedure A	Procedure B
Yes	1600	2000
No	2400	2000
Success Rate	**40%**	**50%**

	Comorbidity Present		Comorbidity Absent	
Success	**Procedure A**	**Procedure B**	**Procedure A**	**Procedure B**
Yes	900	200	700	1800
No	2100	800	300	1200
Success Rate	**30%**	**20%**	**70%**	**60%**

Better outcomes with A in each stratum

Better outcomes in patients absent comorbidity

Patients with comorbidity more likely to receive A

The Statistical Research Group (SRG) was a classified WWII program assembled American statisticians in support of the war effort

Navy asked Abraham Wald to help determine how to reinforce Navy fighter jets to reduce losses from enemy fire

The Navy wanted Wald to figure out the best balance of armor in each often-hit location

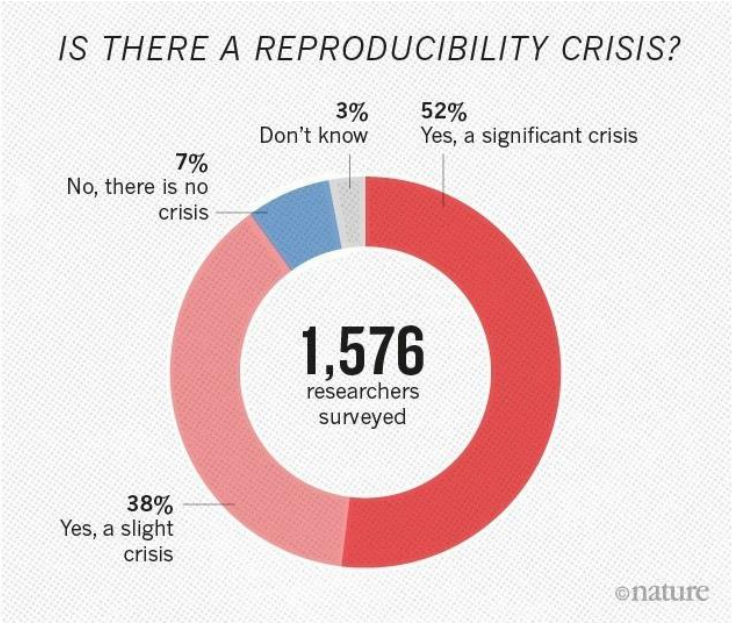
Plane Section	Bullet holes per square foot
Engine	1.11
Fuselage	1.73
Fuel System	1.55
Rest of plane	1.80

Wald: *Areas with fewer bullet holes ⍰ More Reinforcements*

Planes with more engine hits less likely to return

Survivor Bias !

Reproducibility and Transparency



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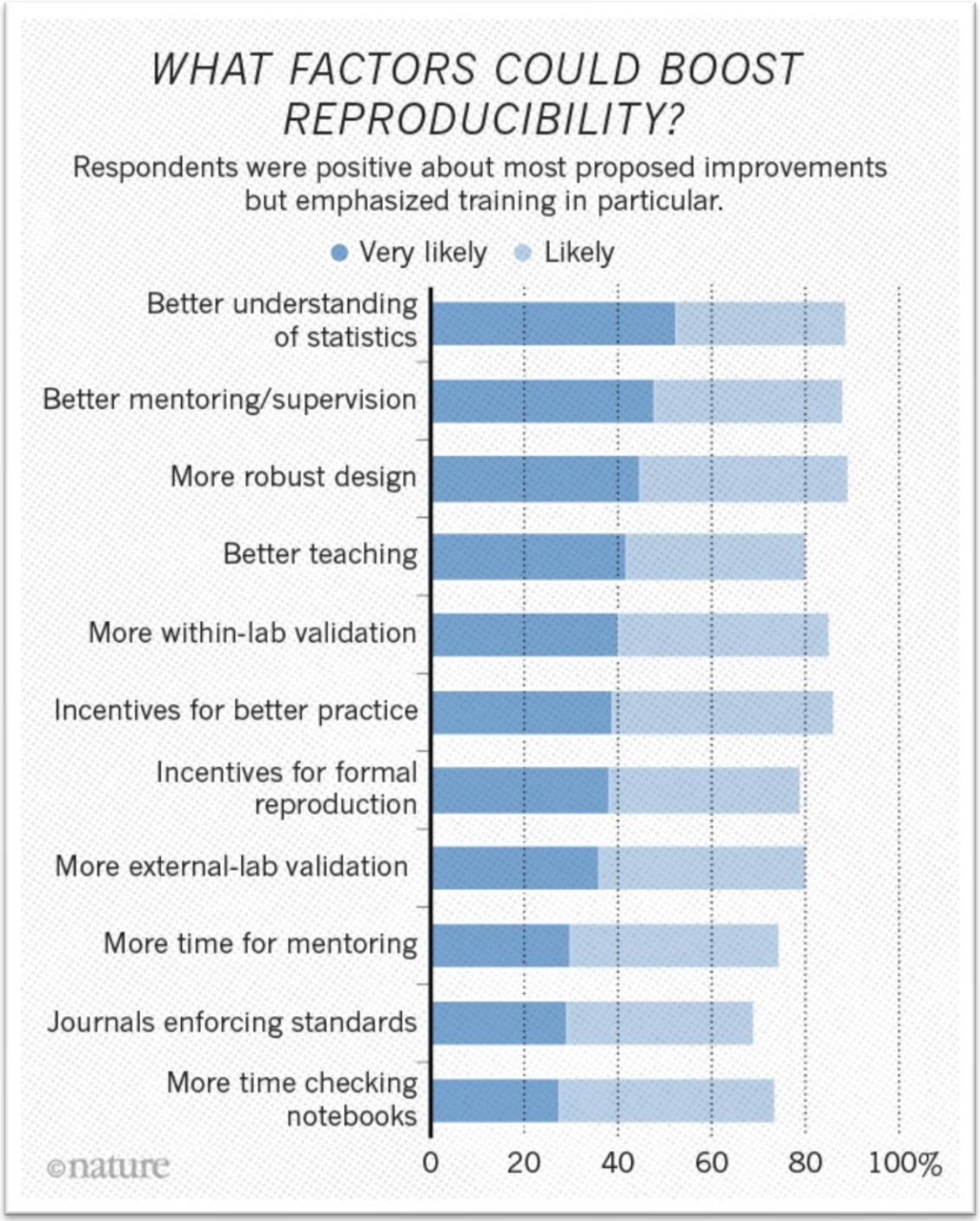
WHAT FACTORS COULD BOOST REPRODUCIBILITY?
Respondents were positive about most proposed improvements but emphasized training in particular.
Very likely
Likely
Better understanding of statistics
Better mentoring/supervision
More robust design
Better teaching
More within-lab validation
Incentives for better practice
Incentives for formal reproduction
More external-lab validation
More time for mentoring
Journals enforcing standards
More time checking notebooks
0
20
40
60
80
100%
©nature

Summary

RCT is gold standard

Use limited by ethical and practical concerns—but in these situations LVD analysis is also limited

Summary

Contributions of Surgical Outcome Studies

- Geographic variations
- Volumes
- Disparities (racial/economic/age-related)
- Time Trends
- Cost-effectiveness
- Surgical quality/risk adjustment

Summary

Variety of approaches to clinical research

"Traditional" prospective clinical trials, cohort studies, and case-control studies, and outcomes research (using LVD)

RCT is gold standard but use is limited

Complementary approaches – suited for different questions

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Key determinant of a study's value to EBM is the rigor with which it is designed, executed, and analyzed

Thank you