CLINICAL RESEARCH & MEDICAL AFFAIRS

EPIDEMIOLOGY AND BIOSTATISTICS

Faculdade de Ciências Médicas da Santa Casa
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Prof. Dr. Ruben Sciuto
Track Record

2009 – 2019	Biostatistician consultant and dirctor of the company **SCIUTO STAT CONSULTING**, São Paulo, Brazil. **http://www.sciutoestatisticamedica.com.br**
2014– 2019	Senior Medical Statistician Consultant in the **RIGHT CONCEPT ASSOCIADOS**, São Paulo, Brazil.
2006–2019	Statistical Consultant at **CLINICAL LABORATORY EMERGENCY** "Hospital de Clínicas", and the journal of the **URUGUAYAN SOCIETY OF CLINICAL PATHOLOGY**, Montevideo-Uruguay.
2007–2008	Professor of Biostatistics, **DEPARTMENT OF BIOSTATISTICS**, Faculty of Agronomy of Uruguay (UDELAR).
2003–2006	Statistical and Methodological Advisor, **DEPARTMENT OF CARDIOLOGY** at "Hospital de Clínicas“ and **DEPARTMENT OF PNEUMOLOGY** at “Maciel Hospital” of Montevideo-Uruguay
1997–2004	Professor of Medical Statistics, **DEPARTMENT OF QUANTITATIVE METHODS**, Faculty of Medicine of Uruguay (UDELAR).
2001	MD (Medical Doctor), PhD in General Medicine graduated from the Faculty of Medicine, University of the Republic (UDELAR) Montevideo - Uruguay.

Biostatistics applied to clinical research and health sciences

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STATISTICS ≠ MEDICAL STATISTICS

STATISTIC

BIOSTATISTIC

MEDICAL STATISTICS

MAPPING & STATISTICAL ORGANIZATION

1. DESCRIPTIVE STATISTICS

2. PROBABILITY & PROBABILITY DISTRIBUTIONS

3. INFERENTIAL STATISTICS

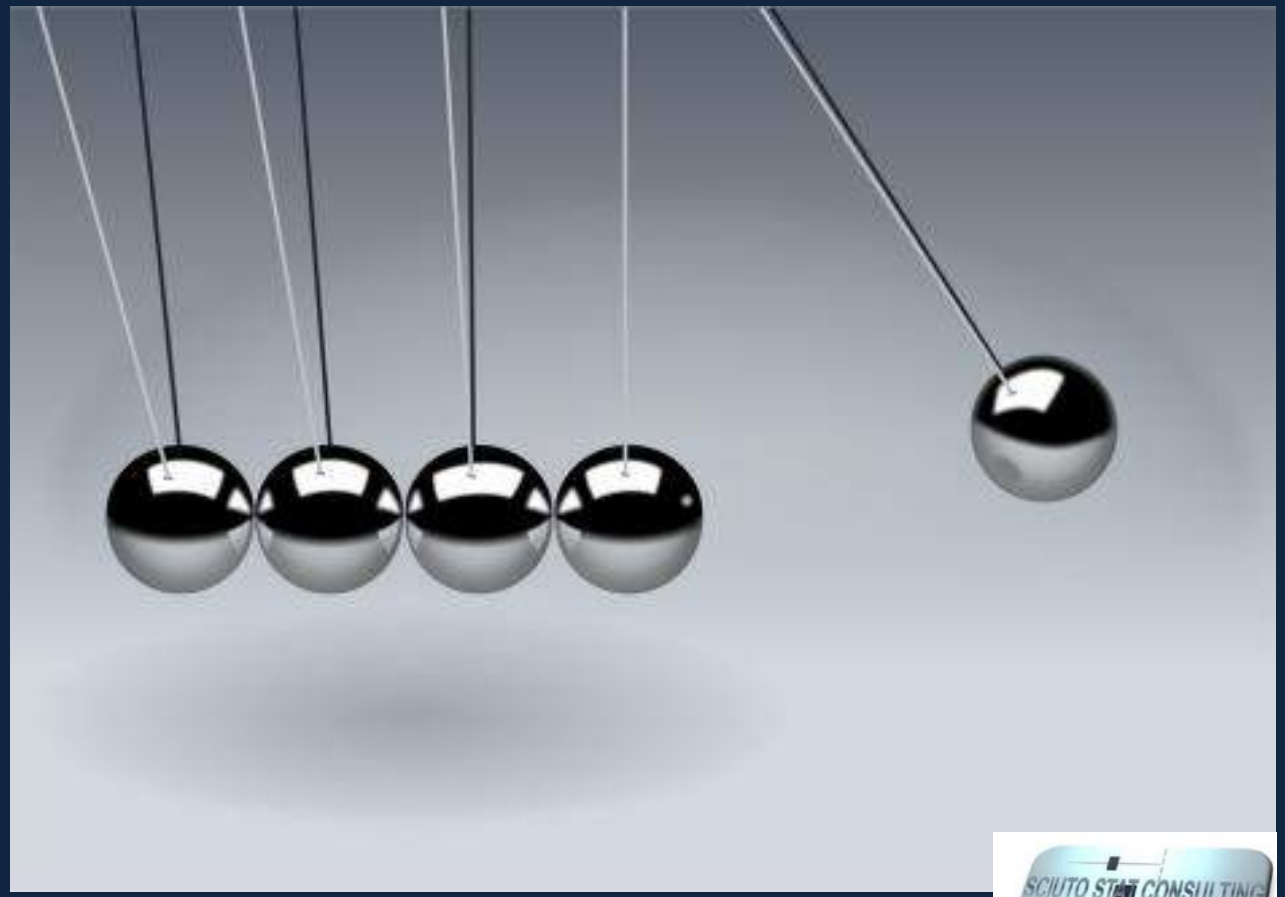
- STATISTICAL ESTIMATION THEORY
- STATISTICAL DECISION THEORY.
- STATISTICAL MODELS THEORY.

WHAT IS THE IMPORTANCE OF KNOWING THE MAIN STUDY DESIGNS AND STATISTICAL TESTS RELATED TO CLINICAL RESEARCH?

- Acquire knowledge to create clinical research (Clinical Research Engine).
- Appropriate bibliographic survey and adequate understanding of the scientific literature (evaluate, criticize and discuss).
- Apply the appropriate statistical tests and risk measures according to the type of study.
- Know the limitations of each type of study.
- Know the advantages and disadvantages of each type of study.

SCIENTIFIC EVIDENCE OF WHAT?

EVIDENCE OF THE CAUSATION OF A FACTOR (EXPOSURE) RELATED WITH A ENDPOINT



QUALITY OF SCIENTIFIC EVIDENCE

MINIMIZE

- ERRORS
- BIAS
- CONFOUNDERS

MINIMIZE:
ERRORS, BIAS AND CONFOUNDERS

➢ RANDOM ERROR

The measurements are almost always in subjects and there may be random variations.
To minimize random error it is necessary to calculate a suitable sample size.

➢ BIAS

Caused by systematic error: in the selection of patients, measurement of results (clinical scales, laboratory analyzes, etc.), statistical analysis of data, interpretation of results and other tendentious conducts in all clinical research.

➢ CONFOUNDERS

Factors that affect the interpretation of results. This is another variable (taken into account or not in the study), however it was not considered in the analyzes and may be affecting the true value or meaning of the "factor - outcome" relationship.

WHAT EXACTLY DO YOU INTEND TO DO?

PICO

P – who are the **patients** or what's the **problem**?
I – what is the **intervention** or **exposure**?
C – what is the **comparison** group?
O – what is the **outcome** or **endpoint**?

Population (P)
Interventions (I) or Exposures (E)
Outcomes (O)
Centre for Evidence Based Medicine, Oxford, UK www.cebm.net

WHAT EXACTLY DO YOU INTEND TO DO?

PATIENTS
- Disease or condition
- Stage, severity
- Demographic characteristics (age, gender, etc.)

INTERVENTION
- Type of intervention or exposure
- Dose, duration, timing, route, etc.

COMPARISON
- Risk or treatment
- Placebo or other active treatment

OUTCOME
- Frequency, risk, benefit, harm
- Dichotomous or continuous
- Type: mortality, morbidity, quality of life, etc.

ARE YOU GOING TO OBSERVE OR EXPERIMENT?

OBSERVATIONAL

Cross sectional, case series, case-control studies and cohort studies.

- identify participants
- observe and record characteristics
- look for associations

EXPERIMENTAL

Before and after studies, comparative trials (controlled or head to head), randomised trials .

- identify participants
- place in common context
- intervene
- observe/evaluate effects of intervention

LEVELS OF THE SCIENTIFIC EVIDENCE

WHAT DEFINES THE LEVEL OF THE SCIENTIFIC EVIDENCE OF A STUDY?

The main "sources of errors" , that define the level of evidence!

- **Related to study design aspects**

a) Different types of biases: information, selection, inclusion, etc.
b) Confounders.
c) Variability: biological, instrument, temporal, etc.
They are related to the **INTERNAL VALIDITY**: to measure properly what has to measure ...

- **Related to the statistical (inferential) aspects**

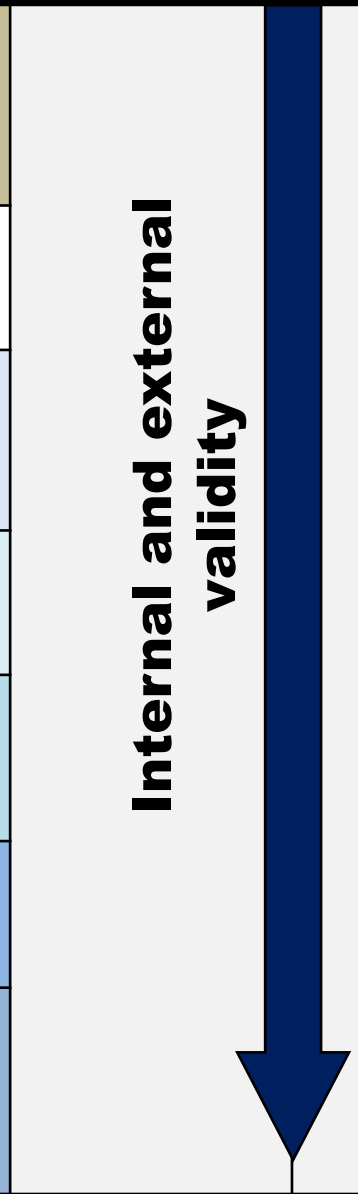
a) Power of study.
b) Level of significance of the study.
c) Use of appropriate tests and estimators.
d) Adequate samples size .
They are related to **EXTERNAL VALIDITY**: generalization of results to the population ...

CLINICAL RESEARCH DESIGN

No intervention		Intervention	
Observational		**Experimental**	
Comparison group		**Random Allocation**	
Yes	**No**	**Yes**	**No**
Analytical Study • Case-Control Study (*Outcome → Exposure*) • Cohort Study (*Exposure → Outcome*) • Cross Sectional Study (*Exposure and Outcome at the same time*)	**Descriptive Study** • Prevalence Study (Cross Sectional Study)	**Randomized Controlled Trial (RCT)**	**Non – Randomized Controlled Trial**

CLINICAL RESEARCH DESIGN

PRIMARY RESEARCH		SECONDARY RESEARCH
In vitro studies		Editorials
Animal studies		Quantitative reviews
Case reports and series		Systematics reviews
Retrospective studies		Pairwise meta-analysis
Prospective observacional studies		Network meta-analysis
Randomized clinical trials		Umbrella reviews *(tertiary research)



LEVELS OF SCIENTIFIC EVIDENCE

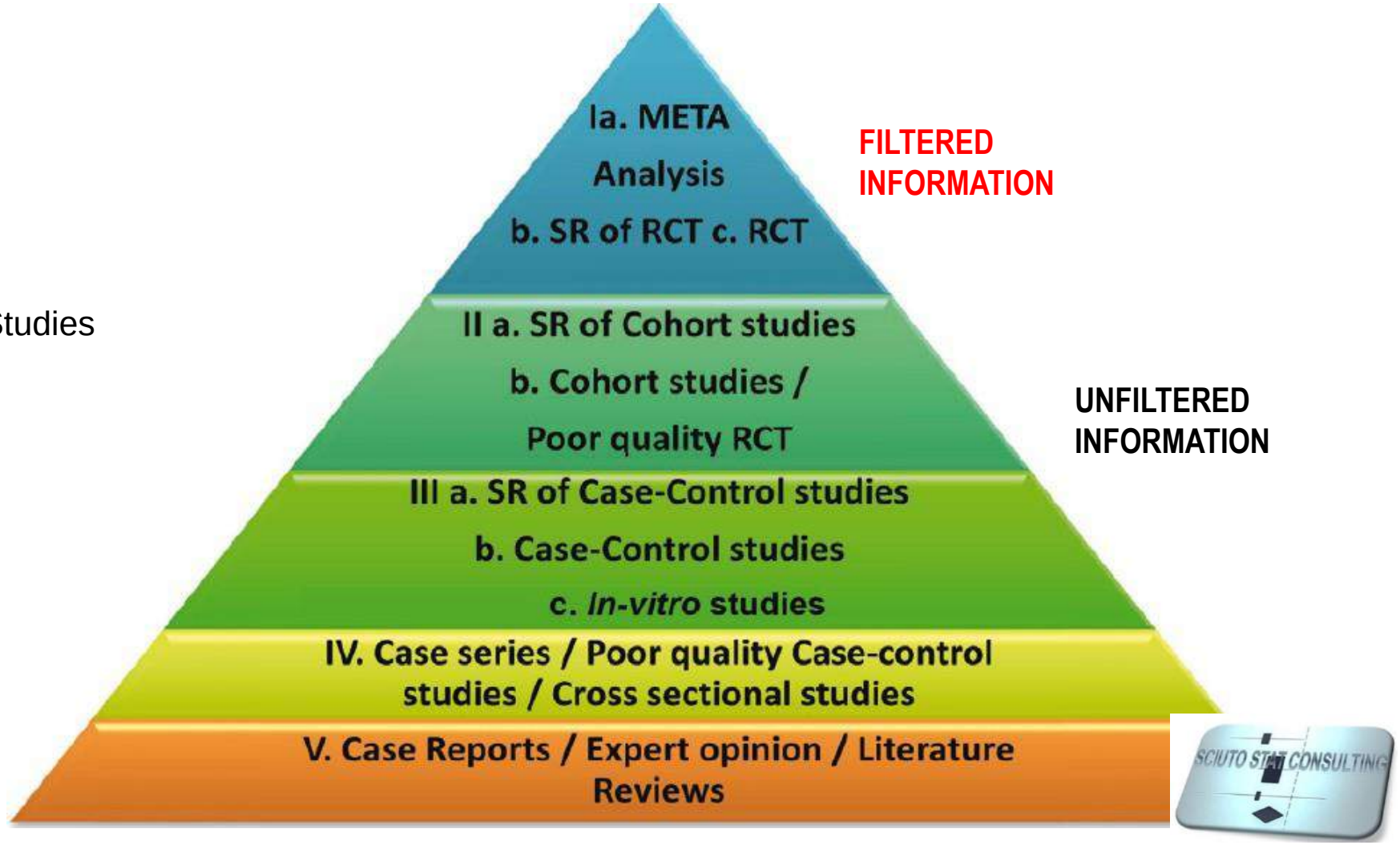
Level I
* Systematic review (SR) and Meta-Analysis of Randomized Controlled Trials (RCT)
* Randomized Controlled Trials

Level II
* Systematic review of Cohort Studies
* Cohort Studies
* Poor quality RCT

Level III
* Systematic review of Case-Control Studies
* Case-Control Studies
* In-vitro Studies

Level IV
* Case Series
* Cross-sectional studies
* Poor quality case control studies

Level V
* Case Reports
* Expert opinion/Literature review.



LEVELS OF SCIENTIFIC EVIDENCE

PRIMARY STUDIES

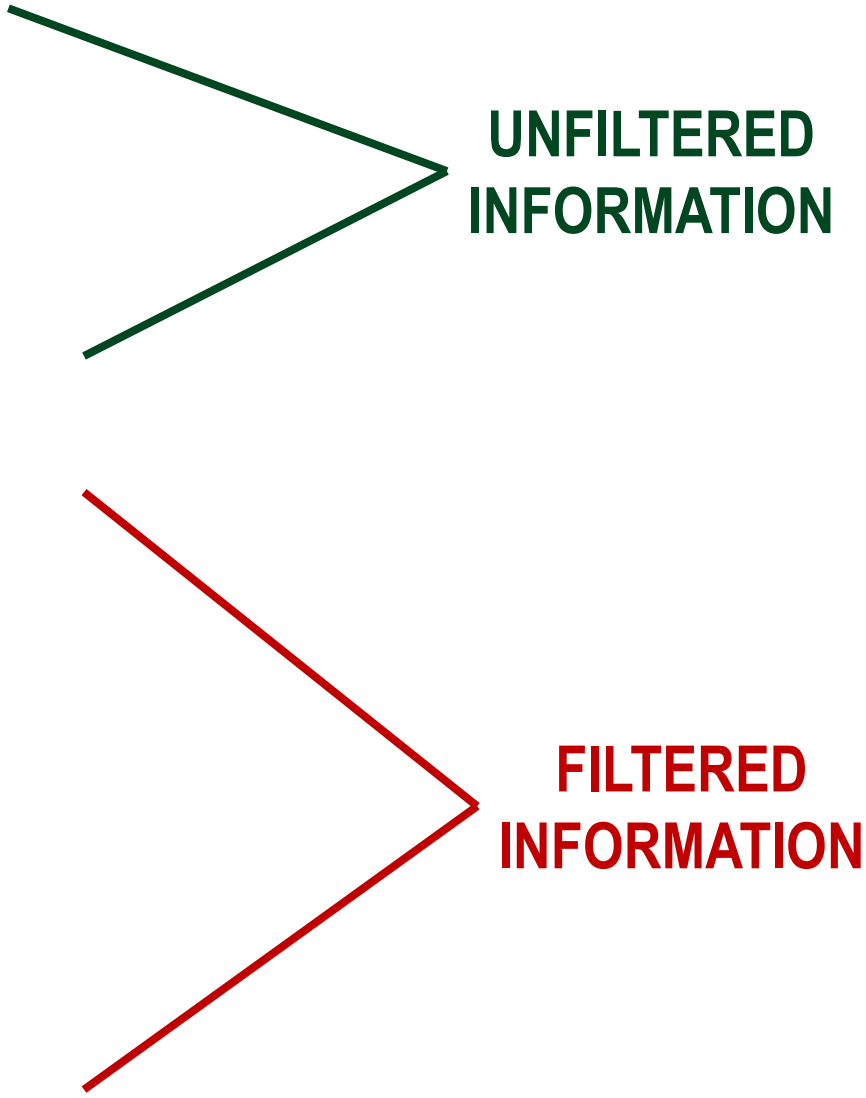
- Case Series
- Cross-sectional studies
- Case-control studies
- Cohort Studies
- Randomized Controlled Trials

SECONDARY STUDIES

- Narrative reviews
- Systematic reviews (SR)
- SR and pairwise meta-analysis
- SR and network meta-analysis

TERTIARY STUDIES

- Meta epidemiologic studies
- Overview of reviews
- Umbrella reviews

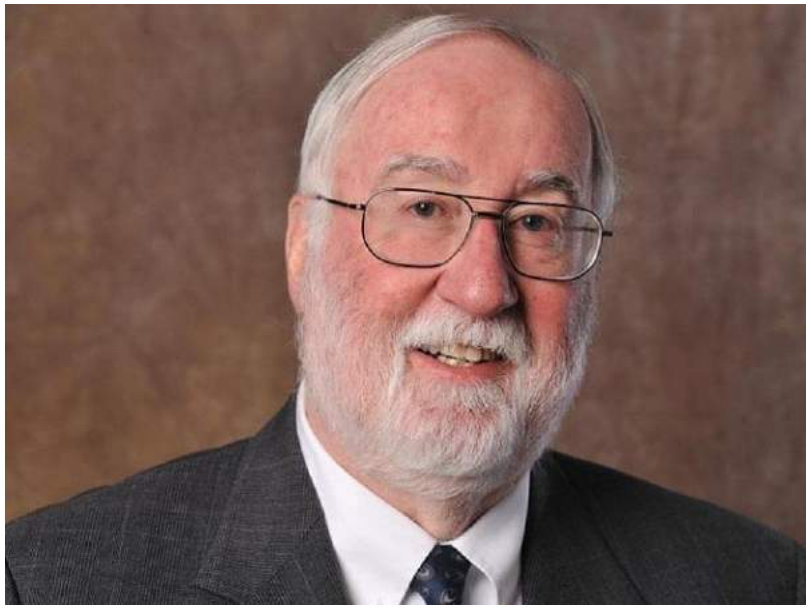


LEVELS OF SCIENTIFIC EVIDENCE

BIAS: is the difference between study result and truth

THE BEST EVIDENCE: is the evidence most likely to provide an unbiased view of the truth.

- Of course, we can never know the truth, but we can try to come as close as possible by performing and using **well-designed** and **well executed studies**.

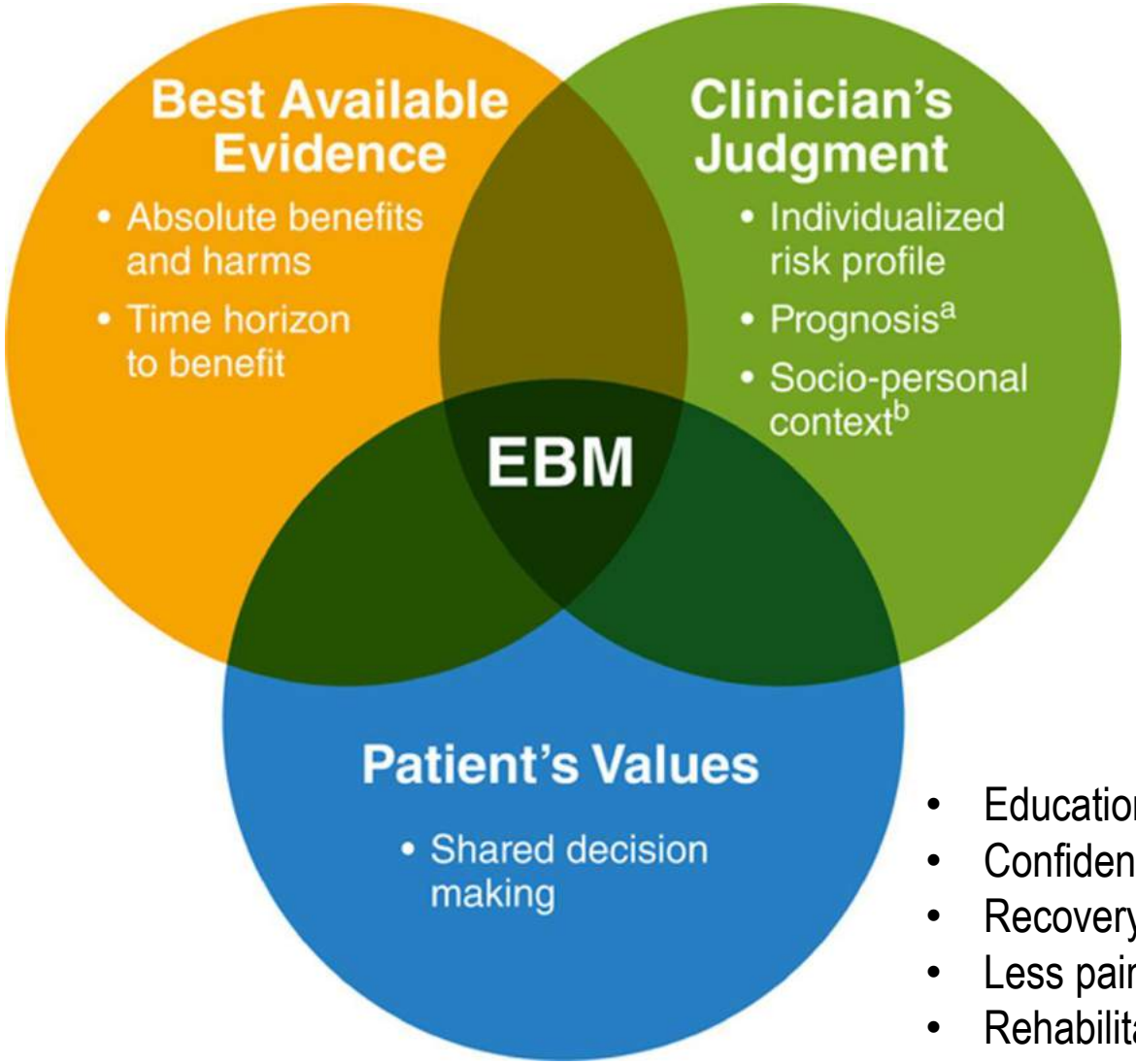


David Lawrence Sackett.
November 17, 1934, Chicago, Illinois, United States, May 13, 2015, Markdale, Ontario, Canada. was an American-Canadian medical doctor and a pioneer in evidence-based medicine.
He is known as the fathers of Evidence-Based Medicine.
In 1994, he moved to the University of Oxford in England to establish the International Centre for Evidence-Based Medicine.

LEVELS OF SCIENTIFIC EVIDENCE

The EBM triad

- Safety and efficacy evidence
- RCT
- Cohort studies
- Case-control studies



- Clinical expertise
- Follow-up
- Therapy
- Prediction
- Clinical knowledge

- Education
- Confidence
- Recovery
- Less pain
- Rehabilitation

The Oxford Centre for Evidence-Based Medicine

The **Centre for Evidence-Based Medicine** was established in Oxford in 1995 with the aim of promoting evidence-based health care to all offering effective and up-to-date decision-making in health care around the world.

It provides support and resources to doctors, clinicians, teachers and others interested in learning about Evidence Based Medicine (EBM).

LEVELS OF SCIENTIFIC EVIDENCE

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)

Level	Therapy/Prevention, Aetiology/Harm
1a	SR (with homogeneity) of **RCTs**
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	SR (with homogeneity) of **cohort studies**
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	"Outcomes" Research; Ecological studies
3a	SR (with homogeneity) of **case-control studies**
3b	Individual Case-Control Study
4	**Case-series** (and poor quality cohort and case-control studies)
5	**Expert opinion** without explicit critical appraisal, or based on physiology, bench research or "first principles"

What is **GRADE**?

- **GRADE** is a systematic and explicit approach to making judgements about quality of evidence and strength of recommendations.
- It was developed by the **Grading of Recommendations, Assessment, Development and Evaluations (GRADE)** Working Group, and it is now widely seen as the most effective method of linking evidence-quality evaluations to clinical recommendations.
- When placed alongside our existing intervention categorizations, **GRADE** gives clinicians a clear view of the evidence relating to key treatment interventions.

How does it work?

GRADE addresses many of the perceived shortcomings of existing models of evidence evaluation. Crucially, when using GRADE, we rate evidence not study by study, but across studies for specific clinical outcomes.

The **GRADE** approach specifically assesses:

Methodological flaws within the component studies
Consistency of results across different studies
Generalizability of research results to the wider patient base
How effective the treatments have been shown to be.

Treatment comparisons are given ***one of four GRADE scores*** reflecting the **quality of the evidence** — high-, moderate-, low-, or very low-quality evidence.

The final **GRADE** score

We use 4 categories of evidence quality based on the overall GRADE scores for each comparison: **high** (at least 4 points overall), **moderate** (3 points), **low** (2 points), and **very low** (one or less).

National Comprehensive Cancer Network

Your Best Resource in the Fight Against Cancer®

NCCN
Categories of Evidence and Consensus

- **Category 1**: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A**: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2B**: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- **Category 3**: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Table 1 Comparison of NCCN Categories of Evidence and Consensus and Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence

NCCN categories of evidence	Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of evidence		
	Recommendations	Evidence level	Description
Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate	A	1a	Systematic reviews (with homogeneity) of randomized controlled trials
		1b	Individual randomized controlled trials (with narrow confidence interval)
		1c	All or none randomized controlled trials (all patients die before the application of treatment, and some patients survive after treatment; or some patients die before the application of treatment and no patient dies after treatment)
Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate	B	2a	Systematic reviews (with homogeneity) of cohort studies
		2b	Individual cohort study or low quality randomized controlled trials (e.g., <80% follow-up)
Category 2B: based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate		3a	Systematic review (with homogeneity) of case-control studies
		3b	Individual case-control study
Category 3: based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate	C	4	Case-series (and poor quality cohort and case-control studies)
	D	5	Expert opinion or comment

STATISTICAL DIFFERENCE ≠ CLINICAL DIFFERENCE