EVIDENCE-BASED MEDICINE (EBM) Overview: Notes on Validity, Precision, & Contextualization of Results[1,2,3,4,5]

Loren Regier BSP BA © www.RxFiles.ca June 2025

Critical Appraisal of Drug Studies [6,7]

A) Is the study valid?

1. Were patients **randomized** to treatment (tx) groups & was allocation **concealed** (AC)? {Without concealment, 37% bias in favor of tx. Sealed, opaque envelopes or central registry used to attain AC[8,9]}
2. Was everyone (patients, physicians, investigators, assessors) **blinded** to tx? {Especially important for assessors of subjective outcomes e.g. pain.}
3. Was the study **controlled**? (e.g. RCT: inclusion of **placebo or active** control group/arm; in an "N of 1" trial, patient is their own control.)
4. Were treatment & control **groups similar at baseline** for prognostic factors related to outcome of interest? If not, were adjustments made?
5. Were **all patients accounted for** at end? {Missing patients addressed?}
6. Was data analyzed based on groups patients were initially randomized to? {Intention to treat or **ITT**; protects integrity of prognostic randomization; per protocol (**PP**) analysis also of interest for harms, non-inferiority RCTs.
7. Were **groups treated similarly** apart from the intervention studied?
8. How was the study **funded** (**role** of funder)? Was study stopped early?
9. Was study type, design & comparator drug & dose a good choice?

B) What are the study results?

1. What was the primary (1°) endpoint? What were the secondary (2°) endpoints? Were endpoints & subgroups pre-specified?[10] Avoid data mining!
2. What was the difference in outcomes? (Both benefits & harms.)
3. Were the differences statistically significant? …clinically significant? {What were the 95% confidence intervals (**CIs**) or p values? Does the CI 95 cross line of no effect?}
4. What are the absolute and relative risk reductions, or increases?
5. What is the number needed to treat (**NNT**) &/or harm (**NNH**)?

C) How does this study matter to my patients?

1. How **clinically relevant/important** are the outcomes?
2. Were the patients similar to those in my practice? (Generalizability) {Consider **inclusion & exclusion criteria**; very sick, old, young, drug interactions & complicated/co-morbid patients often excluded.}
3. Do treatment **benefits outweigh the harms, costs & impact on life**?

Study Types for Tx (from low to **high level** of evidence) [11]

- **Case-control study**: a retrospective observational study which selects patients a) with the outcome of interest (cases) & b) without that outcome (controls); attempts to find exposures linked to the outcome.
- **Cohort study**: an observational study in which 2 groups (cohorts) are observed over time for an outcome. One cohort has exposure to a condition/treatment that the other does not. {**Observational studies**: association does not prove causation! Allow for, or assess for, confounding!} Strength of association: RR: 1.01-1.5 *weak*; 1.51-3 *moderate*; >3 *strong*.[12]}
- **Randomized controlled trial** (**RCT**): a prospective study in which patients are randomized to treatment or control groups (equal/random chance at being assigned to any group). Groups are followed for the outcome of interest. (Good for efficacy; often limited for in safety outcomes.)
- **Crossover RCT**: a design in which each patient receives both treatments in two phases separated by a washout period. Each patient serves as own control, thus less variability in outcomes, & smaller sample size OK; period effects may limit findings
- **Systematic Review (SR)**: a systematic collection, review & presentation of available evidence addressing a clinical question using specific criteria & methods; may, or may not, include meta-analysis. e.g. *Cochrane*[13]*/Campbell*[14]*/CADTH Reviews*[36]

{**Meta-analysis (MA)**: the combining of studies meeting prespecified criteria, addressing a clinical question. Results are calculated from each study's data, then pooled. ↑ sample size & statistical power useful if single trial or subgroup analysis underpowered**. Assess appropriateness** of a) variables & outcomes; b) studies included; c) if study quality & heterogeneity accounted for.}

Evidence Pyramid: SR {MA >RCT >observational study >expert opinion}.[15] Observational studies useful to assess safety, generalization-different populations & insights into real world effect, especially when specific RCT not practical.[38]

Caution: Lots of low-quality RCTs not better than 1 good quality RCT! A low-quality SR, or a SR of low-quality trials, does not high-level evidence make. SR = a lens for understanding.[41]

GRADE: a systematic approach for making clinical practice recommendations in EBM - Link

Terms: Related To Validity

- **Risk of Bias**: design flaws leading to over/underestimation of tx effect e.g. recall bias, selection bias, publication bias; confounding factors esp observational studies {*Risk of Bias* should be distinguished from a) *Reporting*, & b) *Quality* assessment.[45]}
- **Blinding**: if investigators, patient etc. are unaware of who receives tx vs control, they are less likely to inappropriately report better results with tx.

{**CONSORT Statement**: a checklist of standards for standardized reporting of RCTs intended to reduce bias, Update 2022; & 2022 Checklist}

Study Results: Size Of The Treatment Effect [16,17,18,19]

- **Event rate** (**ER**): the number of people experiencing the event as a proportion of total number of people in the population or group
  -Experimental ER (**EER**): {# events in experimental group / total in exp. group}
  -Control group ER (**CER**): {# events in control group / total in control group}
- **Relative risk** (**RR**) or **risk ratio**: {EER/CER}
- **Relative risk reduction** (**RRR**): the RR subtracted from 1 {RRR=1–RR} [Whereas ARR varies with type of population treated, RRR is often more constant.]
- **Absolute risk reduction** (**ARR**): the arithmetic difference between the 2 event rates {CER–EER} [If ↑ risk: **ARI**= absolute risk increase]
- **Number needed to treat** (**NNT**): the number of people who would have to be treated with the studied intervention for the studied time period to see 1 extra benefit compared to the control. {**NNT**=100/ARR%}
- **Number needed to harm** (**NNH**): number of people who would have to be treated with the studied intervention for the studied time period for 1 extra person to experience an adverse outcome (ie an AE. {**NNH**=100/ARI%}
- **Odds ratio** (**OR**): = experimental event odds / control event odds; especially used in case-control studies where baseline risk is not known; also used in meta-analysis. When events are rare, the OR is similar to the RR; however, OR rate exaggerated relative to RR when events more common. {Link www.cebm.net: tool for converting OR to NNT[20]}
- **Point estimate**: the trial result used as best estimate of the true effect
- **Hazard ratio** (**HR**): like RR but more accurate; accounts for the time each participant was in the study before having *a 1st event* or withdrawing.

Study Results: Precision of Treatment Effect [21]

- **Confidence Interval** (**CI**): a 95% CI provides the range of values we are 95% certain overlap the true value. CI's indicate the precision of the estimate; where CI's are wide, they indicate less precise estimates of effect (an estimate of the worst & best case scenario of the outcome; related to p-value) {For ratios, a CI that includes "1" means possibility of no difference. For ARR, ARI, NNT, NNH, a CI that includes "zero" means possibility of no difference between tx. Non-significant results, *trends,* may provide clues re uncertainties & future research.}
- **Type 1 (or α) error**: *the false positive*; to find a difference when there is none. **p-value**: reflects type 1 error. A p <0.05 suggests a <1 in 20 probability that any difference is due to chance (statistically significant by convention). The smaller the **p-value**, the less likely that the result is due to chance.
- **Type 2 (or β) error**: *the false negative*; to conclude there is no difference when there really is a difference (e.g. if not enough patients enrolled)
- **Heterogeneity**: when studies within a meta-analysis have more variation than expected; may indicate its inappropriate to combine studies.[22] {***Q statistic***: measure of within-study variance; ***I²***: ratio of variability among studies to total variation.}

How do the results matter to me, my patients & society?

- **Clinical significance vs statistical significance**: some studies may detect extremely small statistically significant differences between groups; however magnitude of effect may be too small (e.g.high **NNT #**) to change practice. Evaluate both 1) the endpoint, & 2) the **NNT** or **NNH**. {e.g. small cognitive score improvement not noticeable to patient.[23,24]}
- **Composite endpoints**: combining endpoints can increase a study's power allowing for smaller or shorter trials. Outcomes should have **similar value**. Examination of individual outcomes can be important in interpretation as one endpoint may be the primary *driver*. {e.g. In **DREAM**, outcome of "diabetes diagnosis the driver **or** death" =example of unequal endpoints.[25]}
- **Surrogate endpoints**: an endpoint meant to reflect / be correlated with another endpoint (e.g. BP/LDL/A1c for CV events; CD4 cell count for HIV mortality). Clinical outcomes are more important since surrogate endpoints **assume** correlation with an outcome which may, or may not always be true.[26] {eg. lower A1c target <6% **ACCORD**: but ↑ death; doxazosin ↓ BP **ALLHAT** but ↑ HF/stroke; & clofibrate **WHO-CLOF** ↓ LDL but ↑ death.}
- **Other considerations**: What uncertainties remain, & how should they be weighed (e.g. legitimate vs illegitimate uncertainty[39])? Has the drug been studied well enough to detect rare serious adverse events (SAE)? What duration is studied & what are the potential benefits/harms over a longer term of exposure? Is real-world experience consistent with clinical trial data? Any insights for interpretation from subgroup analysis (see ICEMAN tool[40])? What are the cost considerations? Any evidence of data-dredging?[42] How benefits & harms are described e.g. RR vs **NNT** will also affect decisions.[27]
- **What *patient specific* &/or *societal* values need to be considered?**

Heads Up! Know what the numbers are telling you.

⇨ *You "double" your chance of winning a lottery if you buy a 2nd ticket; however your chance of winning is impacted more by whether 2 tickets or 2 million tickets are sold!*

- ***Beware of the Relatives***
  - Benefits are often given as **relative** numbers, whereas harms are often given as **absolute** numbers. This tends to exaggerate benefits & minimize the harms. ⇨ Look for **NNT** & **NNH**.
    {e.g. **VIOXX** monograph 2004[CPS]: reported ~50% ↓ in GI complications with Vioxx 50mg/day vs naproxen 500mg BID & a thrombotic event rate of 1.8% (Vioxx) vs 0.6% (naproxen). Actual GI complication reductions 0.59% vs 1.37% (ARR=0.78; **NNT≈129**); whereas thrombotic risk worse (**NNH≈83**). **VIGOR**}
    {e.g. Oral contraceptives: risk of DVT in a younger, non-smoking ♀ may be ↑300% but absolute risk is <1.5/10,000 /yr, & lower than risk in pregnancy}
- ***Non-Equivalent Durations & Risk/Benefit Perception***
  - Benefits are often given for total duration of trial which may be several years, whereas harms may be reported as per year.
    {e.g. **UKPDS-33**: benefits listed over **10 yrs**; risk of hypoglycemia **per yr**.[28]}
- ***Analysis: Pooling Together or Dividing Out***
  - Discussing the multiple benefits of a composite endpoint while only sorting out individual harms may minimize risk perception.
    {e.g. **In WHI**, risk of just breast ca with HRT was **8/10,000 pt-years**; yet risk of any harm (DVT, CHD, stroke, PE & breast cancer) was **1/66 over 5.2yrs**.[29] }

Calculations Example: 1 yr trial	**RRR**	**ARR**	**NNT**	**NNH**: if 60% of patients in tx group experienced *headaches* compared with 27% in control group (ARI=33%)
◆200 patients in Control group ◆200 patients in Treatment (tx) group ◆Deaths: Control grp: 40. **CER**=40/200=0.2 tx grp: 30. **EER**=30/200=0.15	= (0.20 - 0.15)/0.20 X 100 = 25% {risk of event is ↓ by 25%}	20% - 15% = 5% {absolute risk of event is reduced by 5%}	= 100/5% = **20 / yr**	**NNH** = 100/33% = **3 / yr**
Vs placebo: for every **20** persons treated for 1yr, there is 1 less *death*; & for every **3** treated there will be 1 extra *headache*.				

A few NNT / NNH of interest (NOTE that duration matters for NNT interpretation)	**NNT**
↓ mortality with simvastatin 20-40mg/day over 5.4yr vs placebo in patients with CHD **4S**; see link to statin trials cht	**30** / 5.4yr
↓ mortality with metformin 2550mg/day over 10.7 years vs non-intensive tx in obese T2DM patients **UKPDS-34**; see link	**14** / 10 yr
↓ CV death/MI/stroke; clopidogrel 75mg/day + ASA vs ASA alone in ACS pt (↑ bleeding: **NNH=99**) **CURE**	**48** / 9mo
↓ neuropathic pain by ≥50% vs placebo: TCA ~75mg/day, gabapentinoids, SNRI duloxetine 60mg/day; (short-term) [37]	**4, 7, 8**

What makes for a good NNT? *It all depends!!!* NNTs will vary greatly with variations in baseline population risk, duration of tx, & type & number of endpoints included in composite. Values & preferences also impact interpretation.

Evidence-Based Medicine

Acknowledgements: Written/updated by Loren D Regier. Thanks to our reviewers: Alex Crawley, Brent Jensen, G Michael Allen MD, CCFP, Associate Professor, Director of EBM, Dept of Fam Med, U of A. Michael Allen MD, Associate Professor, Director Evidence-based Programs, Dalhousie University CME, Pam Maclean-Veysey, Drug Eval Unit, Halifax. Derek Jorgenson, PharmD, U of S. Darcy Lamb, C of Pharmacy, U of S. David Blackburn, C of Pharmacy, U of S. G. Turcotte MD, FM/EBM teaching, Gatineau, Quebec.
Disclosures: No conflicts of interest are reported by Loren Regier.
Disclaimer: RxFiles Academic Detailing is part of the College of Pharmacy and Nutrition at the University of Saskatchewan. The content of this work represents the research, experience and opinions of the authors and not those of the University of Saskatchewan. Neither the authors nor the University of Saskatchewan nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the materials will imply acknowledgment of this disclaimer and release any responsibility of the University of Saskatchewan, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources.

💻 EBM Online Extras

Table 1. Assessing Guidelines.

Guidelines provide guidance based on evidence, clinical experience and someone's values and preferences. When evaluating guidelines, you may ask:

Evidence	• How current is the evidence? Has level/strength of evidence (evidence quality) been assessed for recommendations? (Readers may have more confidence if multiple high quality trials.) • What outcomes are evaluated? Are they patient-orientated or surrogate outcomes? • Has evidence been allowed to inform pre-existing assumptions, biases, and beliefs? • Is the evidence applicable to your patient(s)?
Clinical Experience / Consensus	• Is expert opinion, and extent of agreement acknowledged?
Conflicts of Interest	• Are conflicts of interest disclosed? Conflicts may be financial or non-financial. • Was the guideline methodology transparent and rigorous to inform objectively on best available evidence?
Values	• In what way are values and preferences included? • Whose values are included: patient? Society? Payer? Professional?
Overall Assessment	• Look for transparency, evidence ratings, peer review, conflicts of interest. • Do the guidelines allow for, and enable, shared decision making with patients?

see analysis at www.cmaj.ca/content/193/2/E49

If the guidelines don't apply, don't apply them! Almost all guidelines contain a chapter/disclaimer noting that any recommendations must be assessed and individualized for the patient in front of you. Recommendations are often intended to apply to a majority of patients, but may not be suitable for the patient in front of you. If so, document the reason for your decision. See also *The Value, Role & Limitation of Clinical Practice Guidelines*, published online at RxFiles, June 2015.

Table 2. Useful EBM Resources.

- Evidence Alerts (McMaster): www.evidencealerts.com
- EBM Focus (DynaMed): www.ebsco.com/clinical-decisions/dynamed-solutions/about/ebm-focus
- Centre for Evidence-Based Medicine (CEBM-Oxford): www.cebm.ox.ac.uk
  Critical Appraisal Tools (CEBM): https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools
  - Critical appraisal worksheets to help appraise the reliability, importance and applicability of clinical evidence
  - Covers: systematic reviews, diagnostics, prognosis, randomized controlled trials, qualitative studies
  - Includes "**PICO**" critical appraisal worksheet
    - **P**atients
    - **I**ntervention
    - **C**omparator
    - **O**utcomes
- RxFiles Critical Appraisal – RCT – Alternate Worksheet Tool (Links to a) pdf version; b) word version
- PEER Evidence (Alberta College of Family Physicians): https://peerevidence.ca; U of A, EBM Workshops
- Therapeutics Initiative (University of British Columbia): www.ti.ubc.ca. Wisconsin Appraisal mcw EBM
- CADTH Guide to Searching the Grey Literature: www.cadth.ca/grey-matters-practical-tool-searching-health-related-grey-literature
- Knowledge Translation Clinical Significance Calculator (Dalhousie): contact to see if available
- Z Score Calculator for Statistical Significance www.socscistatistics.com/tests/ztest/default2.aspx
- Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN):[40] www.iceman.help/overview
- BMJ Talk Evidence Podcast: www.bmj.com/podcasts/talkevidence
- The NNT: www.thennt.com
- Essential Evidence Plus (Wiley); including InfoPOEMS: www.essentialevidenceplus.com
- Users' Guide to the Medical Literature – Text – 3rd Ed. http://thepafp.org/website/wp-content/uploads/2017/05/Users-Guides-to-the-Medical-Literature-3rd-ed-2016.pdf
- Top POEMs (Patient-Oriented Evidence that Matters) – annually from American Family Physician
- Therapeutics Education Collaboration: Medication Mythbusters – Best Science (BS) Medicine Podcast
- Duke University – Evidence Based Practice: Home – PICO, Study Design, Search, Appraise, Calculate Results, Teach

Related RxFiles Presentations/Discussions/Seminars, Articles:

- Ways Drug Trials, and Our Own Assumptions, May Fool Us
- Evidence, Opinion & the Art of Using Science for Better Patient Care
- Drug Advertisements - What not to miss, that might be missing!
- RxFiles – Getting Evidence Into Practice with Academic Detailing
- The Value, Role & Limitation of Clinical Practice Guidelines - Link
- Critical Appraisal - Trial Summary Template; …Template Word version

Table 3. RxFiles Selected RCT/Trial Summaries

more available online at RxFiles.ca/Trials

Anemia: Trials Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Anemia-Key-Trials.pdf

Asthma: Asthma Landmark Trials: Treatment of "Mild" or Intermittent Adult & Adolescent Asthma 2021;
Asthma Trials/SR Overview/Summary 2006

Novel-START: https://www.rxfiles.ca/RxFiles/uploads/documents/members/ts-NovelStart.pdf 2021
PRACTICAL: https://www.rxfiles.ca/RxFiles/uploads/documents/members/ts-PRACTICAL.pdf 2021
SYGMA-1: https://www.rxfiles.ca/RxFiles/uploads/documents/members/ts-SYGMA1.pdf 2021
SYGMZ-2: https://www.rxfiles.ca/RxFiles/uploads/documents/members/ts-SYGMA2.pdf 2021

CKD-Prevention

FIDELITY Pooled Analysis – Finerenone for CV and Kidney Outcomes in CKD {FIGARO-DKD, FIDELEO-DKD} 2025
FLOW – Semaglutide vs Placebo (Coming soon)
CONFIDENCE 2025 – Simultaneious Finerenone + Empaglifozin vs Either Drug Alone - UACR & Safety Outcomes

Dementia: CATIE-AD: http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-CATIE-AD-trial-summary.pdf

Diabetes: Landmark Trials Summary: Glucose
Landmark Trials Summary: NON-Glucose
ACCORD-ADVANCE Comparison: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-A1C-ACCORD-vs-ADVANCE-COMPARISON.pdf
ACCORD-BP & LIPID: http://www.rxfiles.ca/rxfiles/uploads/documents/ACCORD-BP-Lipid-Trial-Overview.pdf
ACCORD: Glucose http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf
ADVANCE: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-ADVANCE-trial.pdf
AVANDIA & CV risk – Meta-analysis: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Avandia-CV-Meta-Comments.pdf
DREAM: http://www.rxfiles.ca/rxfiles/uploads/documents/Dream-QandA.pdf
ELIXA: Lixisenatide : http://www.rxfiles.ca/rxfiles/uploads/documents/Lixisenatide-ELIXA%20Trial%20Summary.pdf 2016
EMPA-REG: http://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf 2016
LEADER: Liraglutide: http://www.rxfiles.ca/rxfiles/uploads/documents/Leader-Liraglutide%20VICTOZA%20and%20Cardiovascular%20Outcomes%20in%20Type%202%20Diabetes.pdf 2016
RECORD:http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-RECORD-Trial-Summary.pdf
SAVOR-TIMI 53: http://www.rxfiles.ca/rxfiles/uploads/documents/SAVOR-TIMI-53-Saxagliptin-CV-Outcomes-Trial-Summary.pdf
TECOS: Sitagliptin CV outcomes: http://www.rxfiles.ca/rxfiles/uploads/documents/TECOS-Trial-Summary.pdf 2016

Hypertension: Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/HTNLandmarkHypertensionTrials.pdf
ACCOMPLISH: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-Accomplish.pdf
ALLHAT: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-Update-2003-Final.pdf
ANBP2: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-ANBP2.pdf
ASCOT-BPLA: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-ASCOT.pdf
SPRINT: http://www.rxfiles.ca/rxfiles/uploads/documents/SPRINT-BP-Trial-Overview.pdf 2015
Trial Summary table - abridged: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-HTN-trial-summary.pdf

HF: CHARM: http://www.rxfiles.ca/rxfiles/uploads/documents/CHARM-Comments.pdf
DAPA-HF: Dapagliflozin versus Placebo in Patients with Heart Failure & Reduced EF
DELIVER: Dapagliflozin 10mg versus Placebo in Patients with Heart Failure With Mildly Reduced or Preserved Ejection Fraction
EMPEROR: -Preserved 2021 ; -Reduced 2020
FINEARTS-HF: Finerenone versus Placebo in Patients with Mildly Reduced or Preserved Ejection Fraction 2024
PARADIGM-HF: http://www.rxfiles.ca/rxfiles/uploads/documents/PARADIGM-HF-Trial-Sacubitril.pdf 2015
VICTORIA: Vericiguat versus Placebo in Patients with Heart Failure & Reduced EF 2020

Hirsutism: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Hirsutism%20Trial%20Summary.pdf

Infectious Disease

Hoberman et al – 5 day vs 10 day Antimicrobial Treatment for Acute Otitis Media (AOM) in Young Children. 2024
Papi et al – RSV Prefusion F Protein (RSVPreF3; AREXVY) Vaccine in Older Adults 2024

HRT/MHT: WHI: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT Post-WHI-2002-Header.pdf
WHI & Age: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-Age-and-the-WHI.pdf ;
WHI & Extras/Perspectives on NNTs, NNHs: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-WHI-Extras-Perspectives.pdf
Efficacy and Safety of Menopause Hormone Therapy (MHT): Trial Evidence Summary 2023

Lipid: Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid agents-major trials.pdf
& Q&A 2004: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Update-Oct04.pdf
AIM-HIGH: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-AIM-HIGH-nicotinic-acid-Niaspan-trial.pdf
ASCOT-LLA: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-ASCOT.pdf
CARDS: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-CARDS.pdf
ENHANCE: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-ENHANCE trial overview.pdf
FOURIER: https://www.rxfiles.ca/RxFiles/uploads/documents/members/ts-FOURIER.pdf
FIELD Substudy: http://www.rxfiles.ca/rxfiles/uploads/documents/FIELD-Sub-Analysis-Women-Trial-Summary.pdf 2015
IDEAL: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-IDEAL.pdf
IMPROVE-IT: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-IMPROVE-IT-Trial-Summary-QandA.pdf 2014
JUPITER: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-Jupiter-trial-overview.pdf
LODESTAR: LODESTAR Trial Summary - treat to target vs fire and forget | www.RxFiles.ca 2024
PROVE-IT: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Prove-It.pdf
REDUCE-IT: https://www.rxfiles.ca/RxFiles/uploads/documents/members/ts-REDUCE-IT.pdf 2023
REPRIEVE: Pitavastatin LIVALO to prevent CV disease in HIV 2024
SHARP: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-Sharp-CKD-trial.pdf
SPARCL: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-SPARCL.pdf

Thrombotic (antithrombotics: ASA, clopidogrel, anticoagulants: warfarin) :
ACTIVE-A & ACTIVE-W trials http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf
Antithrombotics Summary Chart:: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf
ARISTOTLE: Apixaban vs warfarin in A Fib: http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE-AF-Apixaban.pdf
CHARISMA: http://www.rxfiles.ca/rxfiles/uploads/documents/Charisma-QandA.pdf
Clopidogrel-PPI drug interaction: http://www.rxfiles.ca/rxfiles/uploads/documents/Clopidogrel-PPI-interaction-QandA.pdf
DAPT: 12 vs 30months http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT-Trial-12vs30months.pdf
MATCH: Clopidogrel PLAVIX + ASA ASPIRIN vs Clopidogrel PLAVIX in high-risk Patients with recent stroke or recent TIA
PCI-Clarity: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CLARITY%20Trial%20Summary.pdf 2016
PCI-CURE: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CURE%20Trial%20Summary.pdf 2016
PEGASUS-TIMI 54: Ticagrelor vs PI, prior-MI: http://www.rxfiles.ca/rxfiles/uploads/documents/PEGASUS%20Trial%20Summary.pdf 2016
PIONEER AF-PCI: Rivaroxaban + P2Y12 Inhibitor or Rivaroxaban + DAPT vs. Warfarin + DAPT in Patients with Atrial Fibrillation & PCI
PLATO: Ticagrelor vs clopidogrel ACS: http://www.rxfiles.ca/rxfiles/uploads/documents/PLATO%20Trial%20Summary.pdf 2016
RE-LY: Dabigatran vs warfarin in Atrial Fibrillation http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf
ROCKET-AF: Rivaroxaban vs warfarin in A Fib: http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf
TRITON-TIMI 38: Prasugrel vs clopidogrel, ACS: http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf 2016

MISC.:
Catie-AD: Atypical Antipsychotics in Patients with Alzheimer's http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-CATIE-AD-trial-summary.pdf
FLAME: *Indacaterol+Glycopyrronium vs Salmeterol+Fluticasone for COPD:*http://www.rxfiles.ca/rxfiles/uploads/documents/FLAME-Trial-Summary.pdf 2016
Meloxicam: SELECT, MELISSA; *celecoxib* CLASS, *rofecoxib* VIGOR,: http://www.rxfiles.ca/rxfiles/uploads/documents/QandA-Meloxicam-2.pdf
OAB: Darifenacin-Oxybutynin Memory Trial : http://www.rxfiles.ca/rxfiles/uploads/documents/UI-Darifenacin-Kay-Trial-QandA.pdf
PALLAS: Dronedarone in High-Risk Permanent Atrial Fibrillation
RACE-II: https://www.rxfiles.ca/RxFiles/uploads/documents/RACE-II-trial.pdf
SELECT: Semaglutide versus Placebo in Patients with Obesity without Diabetes 2024
SENIOR: http://www.rxfiles.ca/rxfiles/uploads/documents/Senior-Trial-Oxybutynin-Solifenacin-Elderly-Cognitive-Impairment.pdf
Vitamin D: Effect of High-Dose Vitamin D on Bone Density and Bone Strength 2020
WARFASA: http://www.rxfiles.ca/rxfiles/uploads/documents/Aspirin-warfarin-trial-summary-WarfASA.pdf

Pandemic: COVID-19 2020-2022
EPIC-HR: Paxlovid in patients unvaccinated high-risk patients with COVID-19
Other COVID-19 RCT Summaries: COMET-ICE (sotrovimab tx) , PROVENT (Evusheld prevention, TACKLE (Evusheld tx), PINETREE (remdesivir tx)

Search Terms

EBM	226
Evidence Based Medicine	226
NNH	226
NNT	226
Precision	226
Validity	226

References for EBM (Evidence Based Medicine) Overview:

[1] Sackett D, Straus S, Richardson WS, Rosenberg, Haynes R. Evidence-Based Medicine: how to practice and teach EBM. Churchill Livinstone. 2000.

[2] Dawes M, Davies P, Gray A, Mant J, Seers K, Snowball. Evidence-based Practice; a primer for health care professionals. Elsevier, 2nd edition 2005.

[3] Allen J. Pharmacist's Letter / Prescriber's Letter. Applying Study Results to Patient Care. June 2005, 21;1-14.

[4] Jadad A, Enkin M. Randomized Controlled Trials: Questions, Answers and Musings 2nd edition. Blackwell Publishing 2007; BMJ Books

[5] Edited by: Geyman J, Deyo R, Ramsey S. Evidence-Based Clinical Practice: Concepts and Approaches. Butterworth Heinemann 2000.

[6] Centre for Evidence Based Medicine (CEBM) Oxford: EBM Tools accessed online 31Jul08 at: http://www.cebm.net/index.aspx?o=1157

[7] Centre for Evidence Based Medicine, University Health Network, Toronto. Critical Appraisal tools; accessed online 31Jul08: http://www.cebm.utoronto.ca/teach/materials/caworksheets.htm

[8] Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995 Feb 1;273(5):408-12. {Compared with trials in which authors reported adequately concealed treatment allocation, trials in which concealment was either inadequate or unclear (did not report or incompletely reported a concealment approach) yielded larger estimates of treatment effects (P < .001). Odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials (adjusted for other aspects of quality). Trials in which participants had been excluded after randomization did not yield larger estimates of effects, but that lack of association may be due to incomplete reporting. Trials that were not double-blind also yielded larger estimates of effects (P = .01), with odds ratios being exaggerated by 17%.}

[9] Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998 Aug 22;352(9128):609-13. {FINDINGS: The quality of trials was low. Masked assessments provided significantly higher scores than unmasked assessments (mean 2.74 [SD 1.10] vs 2.55 [1.20]). Low-quality trials (score < or = 2), compared with high-quality trials (score > 2), were associated with an increased estimate of benefit of 34% (ratio of odds ratios [ROR] 0.66 [95% CI 0.52-0.83]). Trials that used inadequate allocation concealment, compared with those that used adequate methods, were also associated with an increased estimate of benefit (37%; ROR=0.63 [0.45-0.88]). The average treatment benefit was 39% (odds ratio [OR] 0.61 [0.57-0.65]) for all trials, 52% (OR 0.48 [0.43-0.54]) for low-quality trials, and 29% (OR 0.71 [0.65-0.77]) for high-quality trials. Use of all the trial scores as quality weights reduced the effects to 35% (OR 0.65 [0.59-0.71]) and resulted in the least statistical heterogeneity. INTERPRETATION: Studies of low methodological quality in which the estimate of quality is incorporated into the meta-analyses can alter the interpretation of the benefit of intervention, whether a scale or component approach is used in the assessment of trial quality.}

[10] Fletcher J. Subgroup analyses: how to avoid being misled. BMJ. 2007 Jul 14;335(7610):96-7.

[11] Centre for Evidence Based Medicine (CEBM) Oxford: EBM Tools accessed online 31Jul08 at: http://www.cebm.net/index.aspx?o=1039

[12] Oleckno WA. Essential Epidemiology Principles and Applications. Long Grove IL: Waveland Press Inc, 2002. (page 108)

[13] http://www.cochrane.org/ ; http://www.cfp.ca/cgi/content/full/55/11/1155?etoc

[14] http://www.campbellcollaboration.org/ ; http://www.campbellcollaboration.org/library.php

[15] Centre for Evidence Based Medicine (CEBM) Oxford: EBM Tools accessed online 31Jul08 at: http://www.cebm.net/index.aspx?o=1025

[16] Barratt A, Wyer PC, Hatala R, McGinn T, Dans AL, Keitz S, Moyer V, For GG; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ. 2004 Aug 17;171(4):353-8.

[17] Bandolier; Number Needed to Treat. Accessed online 31Jul08 at: http://www.medicine.ox.ac.uk/bandolier/band59/NNT1.html

[18] Finlay A. McAlister. The "number needed to treat" turns 20 — and continues to be used and misused. CMAJ 2008; 179: 549-553. http://www.cmaj.ca/cgi/content/full/179/6/549

[19] James P McCormack. NNT misses the mark on baseline risks. Electronic Letter, CMAJ online. (17 September 2008) http://www.cmaj.ca/cgi/eletters/179/6/549#20357

[20] Centre for Evidence Based Medicine (CEBM) Oxford: NNT calculator tool. Accessed online 31Jul08 at http://www.cebm.net/index.aspx?o=1044 .

[21] Montori VM, Kleinbart J, Newman TB, Keitz S, Wyer PC, Moyer V, Guyatt G; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 2. Measures of precision (confidence intervals). CMAJ. 2004 Sep 14;171(6):611-5.

[22] Hatala R, Keitz S, Wyer P, Guyatt G; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results. CMAJ. 2005 Mar 1;172(5):661-5.

[23] Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. 2005 Aug 6;331(7512):321-7. http://www.bmj.com/cgi/reprint/331/7512/321 {A systematic review by Kaduszkiewicz and colleagues (p 321) included 22 double blind randomised controlled trials with the follow-up ranging from six weeks to three years, but the trials scored poorly on a predefined checklist of criteria of methodological quality. Further, the outcomes measuring cognition did show beneficial effects of cholinesterase inhibitors, but these effects were minimal (ranging from 1.5 points to 3.9 points on a 70 point Alzheimer's disease assessment scale).}

[24] Regier L. RxFiles Trial Summary: Darifenacin (ENABLEX) vs Oxybutynin ER extended release (DITROPAN XL) vs Placebo: Effects On Memory / Cognitive Impairment. Accessed at: http://www.rxfiles.ca/rxfiles/uploads/documents/UI-Darifenacin-Kay-Trial-QandA.pdf

[25] Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. BMJ. 2007 Apr 28;334(7599):882-4.

[26] Montori VM. Treat the Target or Treat the Patient. Aust Prescr 2011;34:94-5. Accessed online Aug 2, 2011 http://www.australianprescriber.com/magazine/34/4/94/5.

[27] Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing treatments: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):848-56. Summary for patients in: Ann Intern Med. 2007 Jun 19;146(12):I50.

[28] Anonymous. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and the risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

[29] Regier L. HRT in Light of the WHI – Data in Perspective. Sept 2002. Available online at: **http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-WHI-Extras-Perspectives.pdf**
[30] Ross JS, Mulvey GK, Hines EM, et al. Trial publication after **registration** in ClinicalTrials.Gov: A cross-sectional analysis. PLoS Med 2009; DOI:10.1371/journal.pmed.1000144.
[31] Mathieu S, Boutron I, Moher D, et al. Comparison of registered and published **primary outcomes** in randomized controlled trials. JAMA 2009; 302: 977-984.
[32] McNutt Robert A.; Livingston Edward H. Evidence-Based Medicine Requires Appropriate **Clinical Context**.JAMA. 2010;303(5):454-455.
[33]Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. BMJ. 2018 Dec 10;363:k4245.
[34]Laffin LJ, Besser SA, Alenghat FJ. A data-zone scoring system to assess the generalizability of clinical trial results to individual patients. Eur J Prev Cardiol.2018:2047487318815967.
[35]Senn SJ, Lewis RJ. Treatment Effects in Multicenter Randomized Clinical Trials. JAMA. 2019 Mar 1.
[36] CADTH: https://www.cadth.ca/
[37] Falk J, Thomas B, Kirkwood J, Korownyk CS, Lindblad AJ, Ton J, et al. **PEER systematic review of randomized controlled trials: Management of chronic neuropathic pain** in primary care. Can Fam Physician. 2021 May;67(5):e130-e140.. Accessed online 21May21 at: https://www.cfp.ca/content/67/5/e130.long
[38] Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. N Engl J Med. 2017 Aug 3;377(5):465-475.
[39] Djulbegovic B. Ethics of **uncertainty**. Patient Educ Couns. 2021 Nov;104(11):2628-2634. doi: 10.1016/j.pec.2021.07.025. Epub 2021 Jul 15. PMID: 34312034. Accessed online, 15Nov2021.
[40] *Schandelmaier S, Briel M, Varadhan R, Sauerbrei W, Devasenapathy N, Hayward RA, Gagnier J, Borenstein M, VanderHeijden GJMG, Dahabreh I, Schmid CH, Ioannidis JPA, Walsh M, Thabane L, Guyatt GH. Development of a new Instrument to assess the Credibility of Effect Modification ANalyses (**ICEMAN**) in randomized controlled trials and meta-analyses. CMAJ. 2020 192(32):E901-E906*
[41] *Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid.* Evid Based Med. *2016;21(4):125-127. doi:10.1136/ebmed-2016-110401*
42. Erasmus A, Holman B, Ioannidis JP. Data-dredging bias. BMJ Evidence-Based Medicine. 2022 Aug 1;27(4):209-11.
43. Re-Use Old Drugs [for COVID] Quickly, While They Still Work! EBSCO. EBM Focus - Volume 17, Issue 29. Available from https://www.ebsco.com/clinical-decisions/dynamed-solutions/about/ebm-focus/re-use-old-drugs-covid-quickly-while-they
44. Schmidt S. Context matters! What is really tested in an RCT?. BMJ Evidence-Based Medicine. 2023 Jun 1;28(3):187-8.
45. Garegnani LI. **Bias**, **quality** and **reporting** in health research: differences **and tools for appraisal**. BMJ Evid Based Med. 2023 Nov 22;28(6):407-409. Accessed online Dec 2023.

Additional References:

Alahdab F, Murad MH. **Evidence maps**: a tool to guide research agenda setting. BMJ Evid Based Med. 2019 Dec;24(6):209-211.
Aubin D, Hebert M, Eurich D. The importance of measuring the impact of **patient-oriented research**. CMAJ. 2019 Aug 6;191(31):E860-E864.
Bibens M, Vassar M, Wayant C. **Use of a meta-research team** to facilitate evidence-based medicine to the next generation. BMJ Evid Based Med. 2019 Dec;24(6):205-206.
Brassey J, Price C, Edwards J, et al. Developing a fully automated **evidence synthesis tool** for identifying, assessing and collating the evidence. BMJ Evid Based Med. 2019 Aug 29.
Brown JP, Hunnicutt JN, Ali MS, et al. Quantifying possible bias in clinical and epidemiological studies with **quantitative bias analysis**: common approaches and limitations. BMJ. 2024 Apr 2;385:e076365.
Chu B, Liu M, Leas EC, et al**. Effect size reporting** among prominent health journals: a case study of odds ratios. BMJ Evidence- Based Medicine Epub ahead of print: Aug 2021. doi:10.1136/bmjebm-2020-111569. Accessed 04 Aug 2021 online at https://ebm.bmj.com/content/ebmed/early/2020/12/10/bmjebm-2020-111569.full.pdf
Colunga-Lozano LE, Foroutan F, Rayner D, et al. **Clinical judgment** shows similar and sometimes superior discrimination **compared to prognostic clinical prediction models**. A systematic review. J Clin Epidemiol. 2023 Oct 28:S0895-4356(23)00276-7.
Dal-Ré R. **Analysis of retracted articles on medicines administered to human**s. Br J Clin Pharmacol. 2019 Jun 24.
Frank O, Tam CM, Rhee J. Is it time to stop using **statistical significance**? Aust Prescr. 2021 Feb;44(1):16-18. doi: 10.18773/austprescr.2020.074. Epub 2021 Feb 1. PMID: 33664545; PMCID: PMC7900272. Accessed online 04 Aug 2021 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7900272/
Ghannad M, Yang B, Leeflang M, Aldcroft A, Bossuyt PM, Schroter S, Boutron I. A randomized trial of an editorial **intervention to reduce spin** in the abstract's conclusion of manuscripts showed no significant effect. J Clin Epidemiol. 2021 Feb;130:69-77. doi: 10.1016/j.jclinepi.2020.10.014. Epub 2020 Oct 21. PMID: 33096222. {Related: An unsuccessful initiative to reduce 'spin' in biomedical literature. Drug Ther Bull. 2021 Dec;59(12):182. doi: 10.1136/dtb.2021.000059. Epub 2021 Nov 12. PMID: 34772742.}
Goupil B, Balusson F, Naudet F, et al. Association between **gifts from pharmaceutical companies** to French general practitioners and their drug prescribing patterns in 2016: retrospective study using the French Transparency in Healthcare and National Health Data System databases. BMJ. 2019 Nov 5;367:l6015.
Herrera-Perez D, Haslam A, Crain T, et al. A comprehensive review of **randomized clinical trials** in three medical journals reveals 396 medical reversals. Elife. 2019 Jun 11;8.
Howick J, Koletsi D, Ioannidis JPA, et al. Most **healthcare interventions tested in Cochrane Reviews are not effective** according to high quality evidence: a systematic review and meta-analysis. J Clin Epidemiol. 2022 Apr 18;148:160-169.
Ioannidis JPA. Options for publishing **research without any P-values**. Eur Heart J. 2019 Aug 14;40(31):2555-2556.
Ito C, Hashimoto A, Uemura K, Oba K. **Misleading Reporting (Spin) in Noninferiority Randomized Clinical Trials** in Oncology With Statistically Not Significant Results: A Systematic Review. JAMA Netw Open. 2021 Dec 1;4(12):e2135765.
Johansson M, Guyatt G, Montori V. **Guidelines should consider clinicians' time needed to treat**. BMJ. 2023 Jan 3;380:e072953.
John LK, Loewenstein G, Marder A, Callaham ML. Effect of **revealing authors' conflicts of interests** in peer review: randomized controlled trial. BMJ. 2019 Nov 6;367:l5896.
Kaul S, Butler J. **Stopping Trials Early for Benefit**: Insights From Recent Pivotal Trials in Chronic Kidney Disease. J Am Coll Cardiol. 2024 Sep 24;84(13):1268-1271.
Khan MS, Lateef N, Siddiqi TJ, et al. Level and Prevalence of **Spin in Published Cardiovascular Randomized Clinical Trial Reports** With Statistically Nonsignificant Primary Outcomes: A Systematic Review. JAMA Netw Open. 2019 May 3;2(5):e192622.
Messerli FH, Bangalore S, Messerli AW. **Meta-Analysis in the Mirror** of its Quotations: Science, Scepticism, Scorn, and Sarcasm. Eur Heart J. 2019 Oct 21;40(40):3290-3291.

Mostofsky E, Dunn JA, Hernández-Díaz S, Mittleman MA. Patient and Physician **Preferences for Reporting Research Findings**. Fam Med. 2019 Jun;51(6):502-508.
Murray SB, Heathers JA, Schauer RM, et al. Postpublication Metrics of Randomized Clinical Trials With and Without Null Findings. JAMA. 2019 May 14;321(18):1825-1826.
Niforatos JD, Weaver M, Johansen ME. Assessment of **Publication Trends of Systematic Reviews and Randomized Clinical Trials**, 1995 to 2017. JAMA Intern Med. 2019 Jul 29.
Nissen SE, Reed GW. Can we trust **observational data for clinical decision-making**? Eur Heart J. 2018 Dec 27.
Norton EC, Dowd BE, Maciejewski ML. Marginal Effects-Quantifying the Effect of Changes in Risk Factors in Logistic Regression Models. JAMA. 2019 Mar 8.
Park JJH, Detry MA, Murthy S, Guyatt G, Mills EJ. How to Use and Interpret the Results of **a Platform Trial:** Users' Guide to the Medical Literature. JAMA. 2022 Jan 4;327(1):67-74.
Phillips R, Cornelius V. **Future directions of research into harms** in randomised controlled trials. BMJ. 2023 Apr 24;381:p926.
Reynolds-Vaughn V, Riddle J, Brown J, et al. Evaluation of **Spin in the Abstracts of Emergency Medicine Randomized Controlled Trials**. Ann Emerg Med. 2019 May 14.
Sanders GD, Maciejewski ML, Basu A. Overview of Cost-effectiveness Analysis. JAMA. 2019 Mar 11.
Sterne JAC, Savović J, Page MJ, et al. RoB 2: a **revised tool for assessing risk of bias** in randomised trials. BMJ. 2019 Aug 28;366:l4898.
Tang B, Sandarage R, Chai J, et al. A systematic review of **evidence-based practices for clinical education and health care delivery** in the clinical teaching unit. CMAJ. 2022 Feb 14;194(6):E186-E194
Thynne TRJ, Gabb GM. Limitations of randomized controlled trials as evidence of drug safety. Australian Prescriber Aug 2023.
Trinquart L, Erlinger AL, Petersen JM, et al. Applying the E-value to Assess the Robustness of Epidemiologic Fields of Inquiry to Unmeasured Confounding. Am J Epidemiol. 2019 Mar 15.
Wieseler B, Neyt M, Kaiser T, et al. **Replacing RCTs with real world data** for regulatory decision making: a self-fulfilling prophecy? BMJ. 2023 Mar 2;380:e073100.
Wilson FP. Free yourself from **study fragility and *P*values**. Medscape. Sept 25, 2019. Accessed online 21 Oct 2019 at https://www.medscape.com/viewarticle/918733.
Yao L, Ahmed MM, Guyatt GH, et al**. Discordant and inappropriate discordant recommendations** in consensus and evidence based guidelines: empirical analysis. BMJ. 2021 Nov 25;375:e066045.
Mike Allan and James McCormack. Opinion: Surefire tricks to get the most out of your vitamin supplements. https://vancouversun.com/opinion/op-ed/opinion-surefire-tricks-to-get-the-most-out-of-your-vitamin-supplements