

Critical Appraisal of Drug Studies ^{6,7}

A) Is the study valid?

- 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}
- Was everyone (patients, physicians, investigators, assessors) **blinded** to tx? (Especially important for assessors of subjective outcomes eg. Pain.)
- Was the study **controlled**? (e.g. inclusion of placebo or active control group/arm; in an "N of 1" trial, patient is own control.)
- Were treatment & control **groups similar** in prognostic factors for outcome of interest at beginning of study? If not, were adjustments made?
- Were **all patients accounted for** at end? (Missing patients addressed?)
- Was data analyzed based on groups patients were initially randomized to? (Intent to treat or **ITT**; protects integrity of prognostic randomization; per protocol (PP) analysis may also be of interest (e.g. non-inferiority trials)
- Were patient **groups treated similarly** except for study intervention?
- How was the study **funded** (role of funder)? Was study stopped early?
- Was active comparator drug & dose a good choice?

C) What are the study results?

- What was the primary (1^o) endpoint? What were the secondary (2^o) endpoints? Were endpoints & subgroups pre-specified?¹⁰ Avoid data mining!
- What was the difference between treatments? (Benefits & Harms)
- Were the differences **statistically significant**? **Clinically significant**? (What were the 95% confidence intervals (CIs) or p values? Does the CI cross line of no effect?)
- What are the **absolute** and **relative** risk reductions or increases?
- What is the number needed to treat (NNT) or harm (NNH)?

D) Does this study matter to my patients?

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

Types of Studies (from low to high level of evidence) ¹¹

- Case-control study**: a retrospective observational study which selects patients with the outcome of interest (cases) & patients without that outcome (controls); attempts to find exposures linked to the outcome.
- Cohort study**: an observational study in which two groups (cohorts) are observed over time for an outcome of interest. One cohort has exposure to a condition or treatment that the other does not. (Observational studies: association does not prove causation! Strength of association: RR: 1.01-1.5 *weak*; 1.51-3 *moderate*; >3 *strong*.¹²)
- Crossover study**: 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 required; period effects may limit findings.
- Randomized controlled trial (RCT)**: a prospective study in which patients are randomized to treatment or control groups (equal chance at being assigned to any group). Groups are followed for outcome of interest.
- Systematic Review (SR)**: a systematic collection, review & presentation of available studies addressing a clinical question using specific criteria & methods; may include meta-analysis. e.g. *Cochrane*¹³/*Campbell*¹⁴ *Reviews*
- Meta-analysis**: the combining of studies meeting prespecified criteria & addressing a clinical question. Results are calculated from the data of each study. Data is then pooled. ↑ sample size & statistical power useful if individual trials underpowered or subgroup analysis.

[Level of evidence: SR > RCT > observational study > expert opinion.¹⁵

Caution: Lots of low quality RCTs may not be better than 1 good quality RCT!
A low quality SR, or a SR of low quality trials does not constitute high-level evidence.]

Terms: Related To Validity

- Bias**: design flaws leading to over/underestimation of treatment effect e.g. recall bias, selection bias, publication bias; confounding factors esp observational studies
- Blinding**: if investigators, patient etc are unaware of who receives tx vs control, they are less likely to inappropriately report better results with tx.

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 patients who would have to be treated with the studied intervention for the studied time period for 1 of them to benefit. {NNT= 100 / ARR%}
- Number needed to harm (NNH)**: number of patients who would have to be treated with the studied intervention per studied time period for 1 extra person to experience the adverse event. {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 NNT²⁰)
- 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 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 that overlaps the true value. CI's indicates the precision of the estimate; where CI's are wide, they indicate less precise estimates of effect (just an estimate of the worst & best case scenario of the outcome)
{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 eg. *trends* may provide clues for 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 inappropriate to combine studies.²² (**Q statistic**: measure of within-study variance; **I²**: ratio of variability among studies to total variation.)

Calculations Example: 1 yr trial

- 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

RRR	ARR
= (0.20 - 0.15)/0.20 X 100 = 25% {risk of event is reduced by 25%}	20% - 15% = 5% {absolute risk of event is reduced by 5%}

NNT	NNH
= 100 / 5% = 20	if 60% of patients in Tx group experienced <i>headaches</i> compared with 27% in control group (ARI=33%) NNH= 100 / 33% = 3

For every 20 patients treated for 1yr, there is 1 less *death*; & for every 3 patients treated there will be 1 extra *headache*.

A few NNTs / NNHs of interest

↓ mortality with simvastatin 20-40mg/day over 5.4yrs vs placebo in patients with CHD ⁴⁵	NNT	30 / 5.4yrs
↓ mortality with metformin 2550mg/day over 10 years vs non-intensive in obese T2DM patients ^{UKPDS-34}	NNT	14 / 10 yrs
↓ CV death/MI/stroke; clopidogrel 75mg/day + ASA vs ASA alone in ACS pts (↑ bleeding; NNH=99) ^{CURE}	NNT	48 / 9mo
↓ pain by ≥50% with TCAs (e.g. amitriptyline 100mg/day) vs placebo in neuropathic pain (short term trials)	NNT	2

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. The value of the endpoint also varies from patient to patient.

Do the study results matter to me & my patients?

- Clinical significance vs statistical significance**: some studies may detect extremely small statistically significant differences between groups; however magnitude of effect (e.g. NNT) may be too small 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 (eg. 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? Has drug been studied in enough patients to detect serious rare adverse events? What duration of intervention is studied & what are the potential benefits & risks over a longer term of exposure? Does real-world experience appear to be consistent with clinical trial data? Cost? How benefits & risks are described will also affect decisions.²⁷
- What patient specific and 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 more related to 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 NNTs & NNHs.**
{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 complications reductions 0.59% vs 1.37% (ARR=0.78; NNT=129); whereas thrombotic risk was worse (NNH=83).}
{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 are often given per year.
{e.g. *UKPDS-33*: aggressive glucose control benefit on microvascular endpoints given per **10 years**; risks of hypoglycemia were given per year.²⁸}
- Analysis: Pooling Together or Dividing Out**
- Discussing the multiple benefits of a composite endpoint while individually sorting out risks 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}

Other Online EBM Resources/Links:



EBM Portal **Links** (SK): http://web.mac.com/malees/Primary_Care_Portal/EBM.html; Evidence Updates service: <http://plus.mcmaster.ca/EvidenceUpdates/Default.asp>

General: U of T: <http://www.cebm.utoronto.ca/>; Oxford: <http://www.cebm.net/?o=1011>; McMasters: How to teach evidence based clinical practice – **Links:** <http://hsl.mcmaster.ca/ebcp/>. Dynamed: www.ebscohost.com/dynamed/
User's Guide: UoFA, Centre for Health Evidence: <http://www.cche.net/usersguides/main.asp>; UBC: <http://www.ti.ubc.ca/>; Grey Literature Searching: <http://www.cadth.ca/index.php/en/cadth/products/grey-matters>
SchHARR Intro to Evidence Based Practice (Sheffield, UK) <http://www.shef.ac.uk/scharr/ir/netting/>; BMJ – Clinical Evidence **Links:** http://clinicalevidence.bmj.com/cweb/resources/useful_links.jsp; NNTs <http://www.thennt.com/>
Clinical significance CALCULATORS: UBC: <http://spph.ubc.ca/sites/healthcare/files/calcl/clinsig.html>; Wisconsin: <http://intsmain.is.mcw.edu/clincalc/bayes.html>. Essential Evidence Plus: <http://www.essentialevidenceplus.com/>
Dalhousie **Katie** Clinical Significance Calculator: <http://ktcalc.cme.dal.ca/site/login.php> Z-score: <http://www.socscistatistics.com/pvalues/normaldistribution.aspx> Teaching EBM Videos: McMaster Guyatt: http://ebm.mcmaster.ca/materials_videos.htm

RxFiles – Select Trial Summaries (more available online at www.RxFiles.ca)

Anemia: Trials Summary: <http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Anemia-Key-Trials.pdf>
Dementia: CATIE-AD: <http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-CATIE-AD-trial-summary.pdf>
Diabetes: Landmark Trials Summary: Glucose: <http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf>
Landmark Trials Summary: NON-Glucose: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-DIABETES-Landmark-Trials-Non-Glucose.pdf>
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>
PARADIGM-HF: <http://www.rxfiles.ca/rxfiles/uploads/documents/PARADIGM-HF-Trial-Sacubitril.pdf> 2015
Hirsutism: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/Hirsutism%20Trial%20Summary.pdf>
HRT: 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>

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>
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>
PROVE-IT: <http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Prove-It.pdf>
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>
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 P, prior-MI: <http://www.rxfiles.ca/rxfiles/uploads/documents/PEGASUS%20Trial%20Summary.pdf> 2016
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>
SENIOR: <http://www.rxfiles.ca/rxfiles/uploads/documents/Senior-Trial-Oxybutynin-Soifenacin-Elderly-Cognitive-Impairment.pdf>
WARFASA: <http://www.rxfiles.ca/rxfiles/uploads/documents/Aspirin-warfarin-trial-summary-WarfASA.pdf>

RxFiles: Evidence Based Medicine (EBM) Overview - References

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