L6-Evidence based medicine 1&2

Objectives:

- Identify the principles of evidence based health practice
- Justify why EBM is important with historical background
- Explain how to practice EBM by 5 steps approach
- Explain Step 1- PICO formulation
- Explain benefits of asking focused questions
- Search skills and available resources
- Revised the terms of PICO question.
- Identify available resources for EBM (primary and secondary)
- Identify the hierarchy of major study designs
- Explain how to select scientific literature that is relevant to a clinical question.
- Show in live practice some useful on-line resources to practice EBM.

Randomised Control Trials:

- Understand why randomised controlled trials produce the most reliable evidence for questions about effectiveness
- Understand the important elements of trial design to minimise bias
- Have critically appraised a randomised controlled trial

For more examples and information check Dr. Nada's slides.

What is Evidence-Based Medicine?

"The integration of individual clinical expertise with the best available clinical evidence from systematic research." David L Sackett, W Scott Richardson, William Rosenberg, R Brian Haynes *Evidence Based Medicine--How to Practice and Teach EBM*, 1996

Uses of "EBM":

- **Use of empirically-verified treatments in the care of patients**
- **Incorporation of research results into the process of care**
- **Ability to critically appraise research results**

What is EBM (3 E's) ?

- Clinical Expertise, Best research Evidence, Patient's values & Expectations. (Sackett, et al 1996)

The evidence, by itself, does not make the decision, but it can help support the patient care process. The full integration of these three components into clinical decisions enhances the opportunity for optimal clinical outcomes and quality of life. The practice of EBP is usually triggered by patient encounters which generate questions about the effects of therapy, the utility of diagnostic tests, the prognosis of diseases, and/or the etiology of disorders.

- # IMPORTANCE:

1. Our daily need for valid information about diagnosis, prognosis, therapy and prevention (up to 5 times per in-patient and twice for every 3 out-patients).
2. The inadequacy of traditional sources for this information because they are out-of-date (textbooks), frequently wrong (experts), ineffective (didactic continuing medical education) or too overwhelming in their volume and too variable in their validity for practical clinical use (medical journals).
3. The disparity between our diagnostic skills and clinical judgment, which increase with experience, and our up-to-date knowledge and clinical performance, which decline.
4. Our inability to afford more than a few seconds per patient for finding and assimilating this evidence, or to set aside more than half an hour per week for general reading and study.

- # WHAT HAVE BEEN DONE?

- The development of strategies for **efficiently tracking down and appraising evidence**.
- The creation of **systematic reviews and concise summaries** of the effects of health care (the cochrane collaboration).
- The creation of evidence-based journals of secondary publication (that publish the 2% of clinical articles that **are both valid and of immediate clinical use**).
- The creation of information systems for bringing the foregoing to us in seconds.
- The identification and application of effective strategies for life-long learning.

• Steps of EBM: 5 A's

ASK
- ASK the question
- Construct a well built clinical question derived from the case

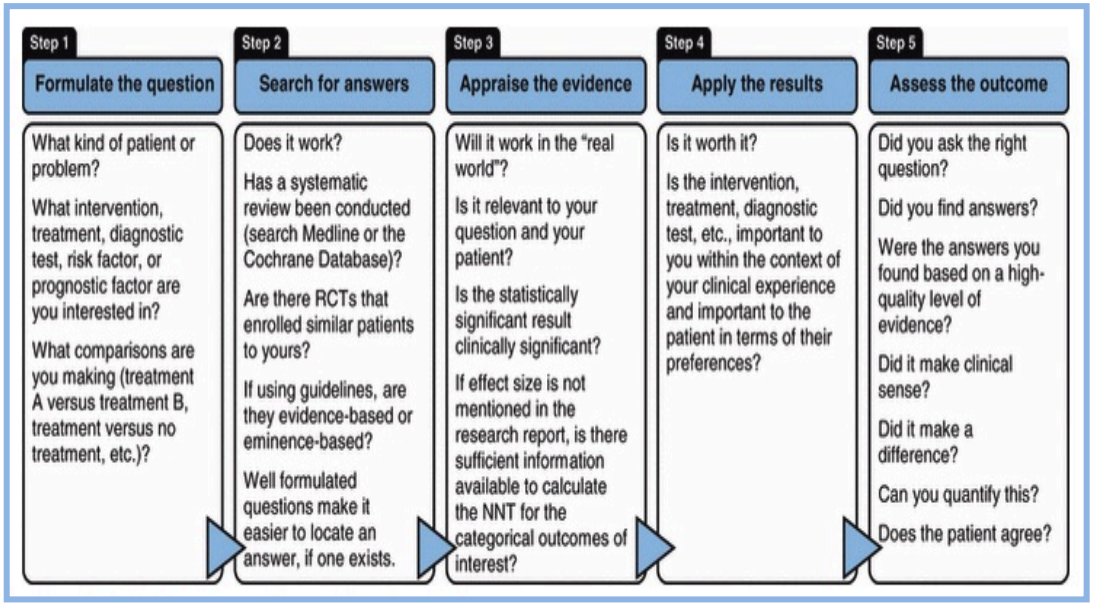
Access
- ACQUIRE the evidence
- Select the appropriate resource(s) and conduct a search

Appraise
- APPRAISE the evidence
- Appraise that evidence for its validity (closeness to the truth) and applicability (usefulness in clinical practice

Apply
- talk with the patient
- Return to the patient -- integrate that evidence with clinical expertise, patient preferences and apply it to practice

ASSESS
- ASSESS the patient.
- Start with the patient -- a clinical problem or question arises from the care of the patient

Self evaluation: Evaluate your performance with this patient



(Citrome, & Ketter, 2009)

- # The Process of Creating an Effective EBM Question:

  Add **specifications** to your question using a PICO table to further refine it.

- ## PICO (M):

  - ✓ **Patient/Problem.** What types of patients and pathologies do you want to study or exclude from the study?
  - ✓ **Intervention.** What variations of the treatments o interventions do you want to consider or exclude?
  - ✓ **Comparison/Control.**
  - ✓ **Outcome/Effects.** What specific outcomes or complications are the most important to measure and evaluate?
  - ✓ **Methodology**

	1	2	3	4
	Patient or Problem	**Intervention** (a cause, prognostic factor, treatment, etc)	**Comparison Intervention** (if necessary)	**Outcomes**
Tips for Building	Starting with your patient, ask "How would I describe a group of patients similar to mine?" Balance precision with brevity.	Ask "Which main intervention am I considering?" Be specific	Ask "What is the main alternative to compare with the intervention?" Again, be specific	Ask "What can I hope to accomplish?", or "What could this exposure really affect?" Again, be specific
Example	"In patients with heart failure from dilated cardiomyopathy who are in sinus rhythm..."	"...would adding anticoagulation with warfarin to standard heart failure therapy..."	:...when compared with standard therapy alone..."	"...lead to lower mortality or morbidity from thromboembolism. Is this enough to be worth the increased risk of bleeding?"

• Formulating Answerable Clinical Questions:

- Every time we see a patient, we need new information about some element of the diagnosis, prognosis or management.
- Because our time to try to find this information is often limited, we need to be very efficient in our searching.
- To achieve this efficiency, we need to become skilled at formulating clinical questions.

• Background and Foreground Questions:

- Add **specifications** to your question using a PICO table to further refine it.

Foreground Questions	Background Questions
These patient-centered problematic questions, involve interpretation and consideration of the risks vs. benefits for a patient or group of like patients.	general questions about a clinical problem or a disease process, e.g. "What is the overall best approach to trauma?
Complex clinical questions are best answered by **going to the primary or pre-assessed studies in the literature.** This can be approached efficiently and effectively if you start by first systematically clarifying the question (**PICO M),** understanding what type of clinical question it is and what type of study design is appropriate before searching the literature. Using the PICO acronym will help you organize your query into a searchable foreground question.	best answered by **going to an excellent review article or respected evidenced-based textbook**. When in need of an overview on clinical presentation of a disease, standard therapies, diagnostic tools, etc., consult a textbook

PICO (M)

Question Categories: Identify the question type to consider appropriate studies and data sets.

-Diagnosis -Diagnostic Test -Harm/Etiology
-Prognosis -Prevention/Therapy

Cases:

Case 1:

A 2-year-old boy presents in an outpatient clinic with fever and severe pain in his right ear. He has a history of recurrent ear infections, and his mother expresses a concern that he has been on the antibiotic amoxicillin for the past few weeks. She is worried about the consequences of the long-term antibiotic use. She is also concerned about the outcome associated with recurrent ear infections. She wants to know if the prescribed amoxicillin is effective, or it can be substituted with another antibiotic because of its side effects such as frequent diarrhea.

Answers:

Background Questions: "What is otitis media?" or "How does amoxicillin work?"

Foreground Questions:

1- In children suffering from otitis media, will cefuroxime result in the improvement of symptoms and reduction in developing resistance?

2- Does treatment with amoxicillin increase the risk of developing resistance in children suffering from otitis media?

3- Does surgical procedure has better outcome for the treatment of otitis media in children after repeated antibiotic therapy?

P: In children with acute otitis media
I: cefuroxime
C: as compared to amoxicillin
O: effective in reducing the duration of symptoms.

Case 2:

After careful consideration of the clinical manifestations, you suspect that your patient has acute cholecystitis. In order to confirm a Dx you plan to order a test. You know that cholescintigraphy /HIDA (radionuclide) scan has been shown to have the highest sensitivity and specificity.However,the attending tells you to order an ultrasound because "**it is the best first test**." Seeking further evidence you decide to consult the literature and then frame the question.

Answers:

"In patients with suspected acute cholecystitis, without previous gallbladder disease ,is ultrasound a better first test than cholescintigraphy or hida / radionuclide scan?"

A Question of Diagnostic Test.

[**A background question would be:**

"**What is the differential diagnosis for acute upper right quadrant pain**?"]

P: Acute Cholecystitis
I: Ultrasound
C: Cholescintigraphy Hida Radionuclide scan
O: sensitivity and specificity
M: Prospective study RCT Meta-analysis.

Cases:

Case 3:

As a resident you have just seen a 58-year old patient with type 2 diabetes with normal blood pressure. You consider treating this patient with ACE inhibitors because the attending said treatment could delay progression to diabetic nephropathy. **What is the Clinical Question?**

Answers:

P: DM elderly

I: ACE inhibitors

C: Placebo

O: Delay progression.

Case 4:

In children with asthma, are inhaled corticosteroids more likely to result in growth delay than standard therapy with beta-agonists?

Answers:

A PubMed search strategy might look like this:

inhaled corticosteroids AND asthma AND growth delay

Limits Activated: All Child: 0-18 years

P: children with asthma
I: inhaled corticosteroids
C: beta-agonists
O: growth delay.

Case 5:

The patient is a 65 year old male with a long history of type 2 diabetes and obesity. Otherwise his medical history is unremarkable. He does not smoke. He had knee surgery 10 years ago but otherwise has had no other major medical problems. Over the years he has tried numerous diets and exercise programs to reduce his weight but has not been very successful. His granddaughter just started high school and he wants to see her graduate and go on to college. He understands that his diabetes puts him at a high risk for heart disease and is frustrated that he cannot lose the necessary weight. His neighbor told him about a colleague at work who had his stomach stapled and as a result not only lost over 100 lbs. but also "cured" his diabetes. He wants to know if this procedure really works.

Clinical question:

In patients with type 2 diabetes and obesity, is bariatric surgery more effective than standard medical therapy at increasing the probability of remission of diabetes?

It is a **therapy question** and the best evidence would be a **randomized controlled trial (RCT)**. If we found numerous RCTs, then we might want to look for a **systematic review**

P: obese, DM type 2, male, elderly.
I: stomach stapling (gastric bypass surgery)
C: standard medical care
O: remission of DM; weight loss; mortality

Test 1:

You admit a 75 year old man with a stroke (left sided weakness) who is having trouble ambulating, feeding, bathing and dressing himself. He has hypertension but it is well controlled with a diuretic. He is otherwise well and now that he is medically stable you decide after discussion with him to transfer him to a stroke unit. His family asks to see you because they are concerned about this transfer. They live very close to the acute care hospital and wonder why he can't stay on the general medical ward where he currently is. You arrange to meet with him and his family to discuss their concerns. In the meantime, you decide to review the evidence for the use of stroke units.

P: 75 year old man with a stroke and residual weakness.

I: Admission to a stroke unit.

C: general care

O: Functional status .

Question: In an elderly man with a stroke, does admission to a stroke unit decrease the risk of death and dependency?

Test 2:

You see a 70 year old man in your outpatient clinic 3 months after he was discharged from your service with an ischemic stroke. He is in sinus rhythm, has mild residual left-sided weakness but is otherwise well. His only medication is ASA and he has no allergies. He recently saw an article on the BMJ website describing the risk of seizure after a stroke and is concerned that this will happen to him.

P: 70 year old man.

I: stroke.

C: -

O: seizure.

Question: In a 70 year old man does a history of stroke increase his risk for seizure?

Test 3:

You admit a 75 year old woman with community-acquired pneumonia. She responds nicely to appropriate antibiotics but her hemoglobin remains at 100 g/l with an MCV of 80. Her peripheral blood smear shows hypochromia, she is otherwise well and is on no incriminating medications. You contact her family physician and find out that her Hgb was 105 g/l 6 months ago. She has never been investigated for anaemia. A ferritin has been ordered and comes back at 10 mmol/l. You admit to yourself that you're unsure how to interpret a ferritin result and aren't sure how precise and accurate it is.

P: Elderly woman with anemia.
I: Ferritin.
C:-
O: Iron deficiency anemia
M: case- control study.
Question: In an elderly woman with hypochromic, microcytic anemia, can a low ferritin diagnose iron deficiency anemia?

Test 4:

You see a 50 year old man who asks for a repeat prescription of sotalol which he has been taking for extrasystoles for several years. He has a remote history of an MI. You haven't seen him previously and are concerned about the proarrhythmic properties of sotalol given what is known about other antiarrhythmics.

P: Man with extrasystoles.
I: Sotalo .
C: Placebo.
O: Death .
Question: : In a man with extrasystoles and a remote history of MI, does treatment with sotalol increase his risk of death?

USEFULNESS OF MEDICAL INFORMATION:

- DISEASE ORIENTED EVIDENCE THAT MATTERS (DOES):
- PATIENT ORIENTED EVIDENCE THAT MATTERS (POEMS):

e.g.: Quality of life , complication? Improvement of symptoms.

(DOES) >> (POEM)

Drug A lowers cholesterol	Drug A decreases cardiovascular mortality/morbidity	Decreases overall mortality
PSA screening detects prostate cancer most of the time and at an early stage	PSA screening decreases mortality	PSA screening improves quality of life
Corticosteroid use decreases neutrophil chemotaxis in patients with asthma	Corticosteroid use decreases admissions, length of hospital stay, and symptoms of acute asthma	Corticosteroid use decreases asthma-related mortality
Tight control of type 1 diabetes mellitus can keep fasting blood glucose <140mg/dl	Tight control of type 1 diabetes can decrease microvascular complications	Tight control of type 1 diabetes can decrease mortality and improve quality of life

Type of Question:

- Two additional elements of the well-built clinical question are *the type of question* and *the type of study*.
- This information can be helpful in focusing the question and determining the most appropriate type of evidence or study.

The type of question is important and can help lead you to the best study design:

Most common type of questions:	Type of study:
Diagnosis how to select and interpret diagnostic tests	prospective, blind comparison to a gold standard or cross-sectional
Therapy how to select treatments that do more good than harm and that are worth the efforts and costs of using them	randomized controlled trial > cohort study
Prognosis how to estimate the patient's likely clinical course over time (based on factors other than the intervention) and anticipate likely complications of disease	cohort study > case control > case series
Harm/Etiology how to identify causes for disease (including iatrogenic forms)	cohort > case control > case series

Complete a PICO Table:

- The question should be structured using criteria such as PICO which breaks down an individual question into components which may ***directly translate into keywords*** that inform the design and literature search of any study.
- Using a criterion also ensures that any publications resulting from your project will be found during a literature search on the same subject.

Conclusions:

- The PICO framework is invaluable for helping you **refine your EBM question**.
- The more focused your study question is, the higher the likelihood that you will be able to find a meaningful answer to it.

Table 1. Possible Solutions to Barriers to Answering Clinical Questions

Barrier	*Possible solutions*
Attitude	Value your own questions and write them down as they occur
	Respond positively when colleagues ask questions
	Create a "question-and-answer club" where you and your colleagues share the best available evidence to answer recent clinical questions
Environment	Make computers available where you practice, or carry a tablet computer, PDA, or smartphone
	Plan adequate time every week or month to review recent literature
Lack of computer skills	Attend computer boot camps at AAFP national meetings
	Buy a PDA or smartphone and practice using it
	Take classes at a local college or read books that teach basic computer skills
	Practice searching for answers to become more proficient
Lack of resources	Subscribe to relevant evidence-based information sources
	Create a Web portal that has links to commonly used information sources (see http://www.google.com/ig or http://www.myhq.com)
	Keep a computer, PDA, or smartphone handy while seeing patients or while on rounds
Lack of time	Carry a PDA or smartphone for rapid access to information
	Make sure computers are available wherever you see patients

AAFP = American Academy of Family Physicians; PDA = personal digital assistant.

Information from references 1 and 2.

How to Find Answers to Clinical Questions. *Am Fam Physician.* 2009;79(4):293-296.

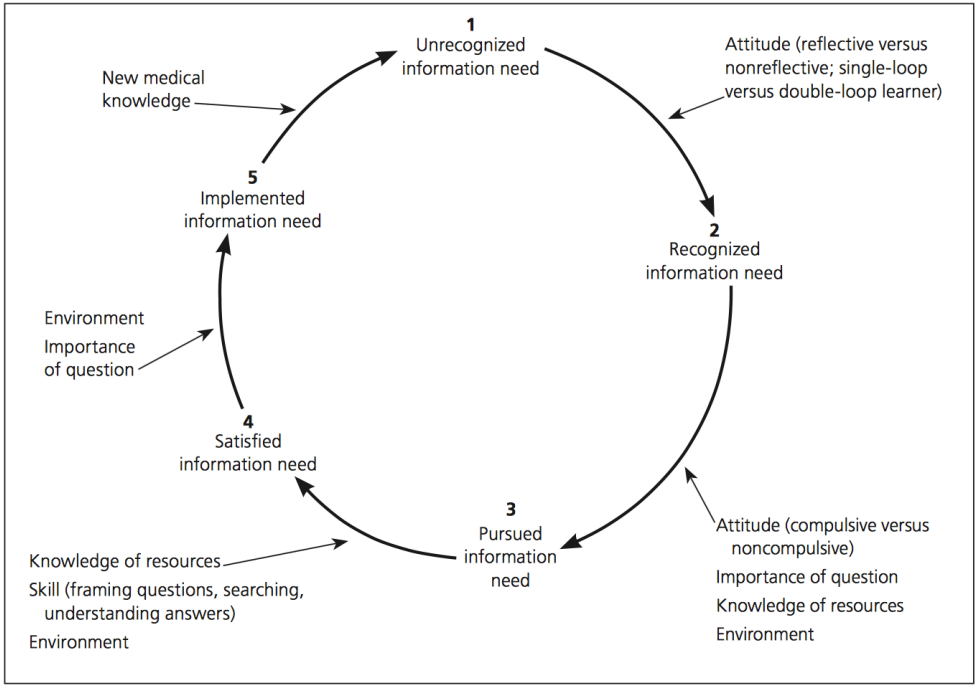


Figure 1. The process of asking and answering clinical questions and relevant barriers.

Reprinted with permission from Ebell M. Information at the point of care: answering clinical questions. J Am Board Fam Pract. *1999;12(3):229.*

- **Examples popular Search Engines:**

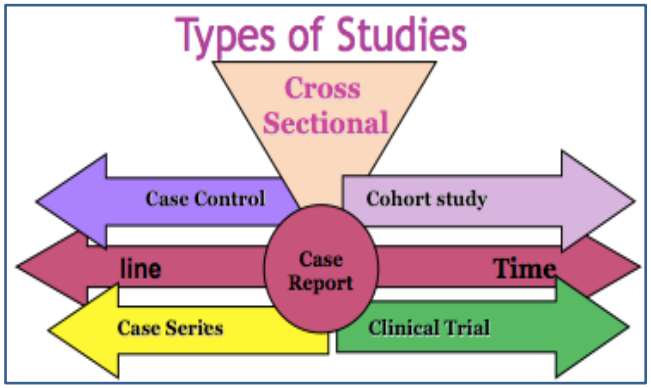
- **Search for the Best Evidence:**
  - ✓ Community/professional standards.
  - ✓ **Systematic reviews.**
  - ✓ Original results.
  - ✓ Review articles ✖

- **What are the Sources of Good Evidence?**

1. The Cochrane Library **(http://www.thecochranelibrary.com)** An online library of **published systematic reviews of evidence.**
2. Database of Abstracts of Reviews of Effects (DARE) **http://www.crd.york.ac.uk/crdweb** This is a database of **abstracts**, quality assured by the DARE team, of systematic reviews of evidence.
3. Trip Database **http://www.tripdatabase.com** A medical search engine with emphasis on evidence based medicine & clinical guidelines and queries.
4. NICE Evidence Services **https://www.evidence.nhs.uk** Part of the National Institute for Health and Care Excellence (NICE), this is an online library of evidence of effectiveness and uncertainty.
5. NHS Choices **http://www.nhs.uk/Pages/HomePage.aspx** Aimed at the **general public**, this is an online library of summaries of evidence plus information about the NHS and services available.
6. PubMed Health **https://www.ncbi.nlm.nih.gov/pubmedhealth** PubMed Health provides information for consumers and clinicians on prevention and treatment of diseases and conditions.

“Best Available Clinical Evidence”:

- **Therapy**
  Double-blind, placebo-controlled, randomized clinical trial.
- **Diagnosis**
  Independent, blind comparison with a reference standard.
- **Prognosis**
  Representative and well-defined prospective cohort of patients at a similar point in the course of disease.



Levels of Evidences:

(I-1) **a well done systematic review of 2 or more RCTs**

(I-2) **a RCT**

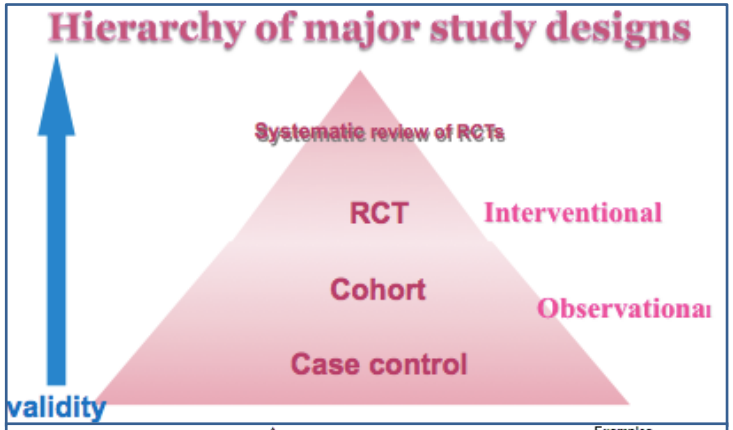
(II-1) a cohort study

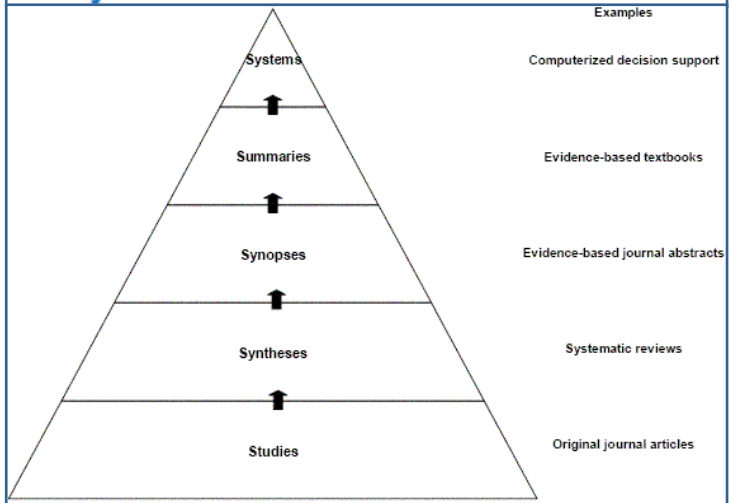
(II-2) a case-control study

(II-3) a dramatic uncontrolled experiment

(III) respected authorities, expert committees, etc..

(IV) ...someone once told me....





Types of Epidemiological Studies:

- **Observational:**
  - ✓ Case Reports, Case series.
  - ✓ Cross – Sectional.
  - ✓ Case- Control.
  - ✓ Cohort.
- **Interventional:**
  - ✓ **Clinical Trials**

Resources:

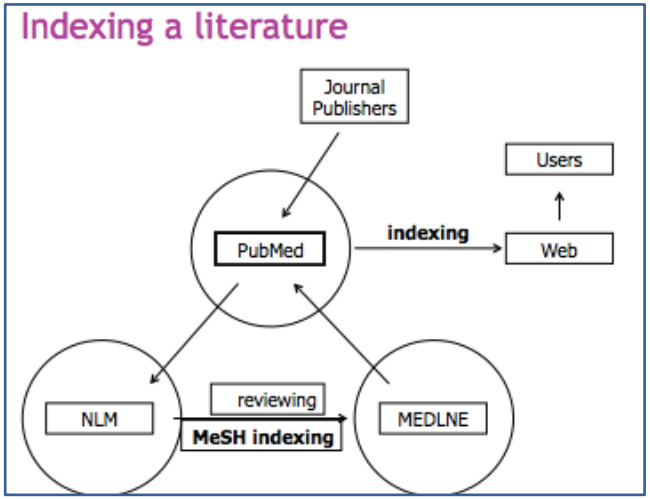
- **Secondary sources: already apprised**
  - ✓ **Guidelines**: UK National Library for Health, NICE, SIGN; US National Guidelines Clearinghouse; Canadian Medical Association; New Zealand Guidelines Group.
  - ✓ **Evidence-Based Summaries**: Bandolier, Clinical Evidence
  - ✓ **Structured Abstracts**: EBM Online, ACP Journal Club
  - ✓ **Systematic Reviews**: Cochrane Library To search several of the databases simultaneously you can use: www.tripdatabase.com
- **Primary Sources:** Use methodological filters to target the right type of study. For instance, PubMED filters for: therapy, diagnosis, prognosis or etiology. **(needs critical appraisal)**

More databases…

- **Google Scholar.**

Key points:

- It is important when searching for evidence that search terms are referred back to your original **PICO question**.
- The process of finding evidence therefore follow three key steps; Identify terms to fit PICO question,
- Look **for secondary sources then Search for primary sources.**



What is PubMed?

- **PubMed** is a database developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (**NLM**) available on the Web.
- **NLM** is the worlds largest medical library
- **MEDLINE** is a database of indexes (with citations and abstracts)
- **PubMed** provides access to MEDLINE
- **PubMed** database is more current and comprehensive than **MEDLINE** (it includes citations even prior to their indexing with **MEDLINE**).

Why PubMed ?

Over 20 million citations for biomedical literature from app. 5500 selected journals from over 70 countries.

- **Source:**
  - MEDLINE (NLM database)
  - Life science journals
  - Online books
- **Fields:**
  - Medicine
  - Nursing
  - Dentistry
  - Veterinary medicine
  - Health care system
  - Preclinical sciences

MeSH(The Medical Subject Headings) :

- Similar to **key words** on other systems
- Used for indexing journal articles for MEDLINE
- Arranged in **hierarchy, from more general to more specific**
- Used by researchers.
- Mesh tutorial

What is a Boolean Operator?

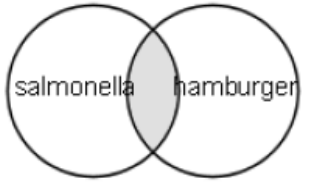
Boolean Operators are simple words (AND, OR, NOT or AND NOT) used as conjunctions to combine or exclude keywords in a search, resulting in more focused and productive results. This should save time and effort by eliminating inappropriate hits that must be scanned before discarding.

- **AND—requires both terms to be in each item returned. If one term is contained in the document and the other is not, the item is not included in the resulting list. (Narrows the search)**

example:

Salmonella AND Hamburger:

- Salmonella - 69432
- Hamburger - 2703
- Salmonella AND Hamburger **– 14**

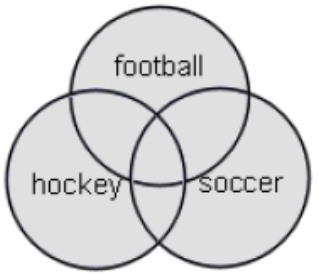


- **OR—either term (or both) will be in the returned document. (Broadens the search)**

example:

Football OR Hockey OR Soccer:

- Football - 3948
- Hockey - 1466
- Soccer - 3137
- **Total - 7538**

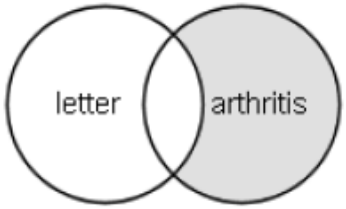


- NOT or AND NOT (dependent upon the coding of the database's search engine)—the first term is searched, then any records containing the term after the operators are subtracted from the results. (Be careful with use as the attempt to narrow the search may be too exclusive and eliminate good records). If you need to search the word not, that can usually be done by placing double quotes (<< >>) around it.

Example:

Arthritis NOT Letter:

- Arthritis - 185375
- Letter - 686049
- Arthritis “excluding” letter **- 176352**



Critical appraisal:

- **is the process of carefully and systematically examining research to judge its trustworthiness, and its value and relevance in a particular context.**
- It is an essential skill for evidence-based practice because it allows public health professionals and clinicians to find and use research evidence reliably and efficiently to inform their decision-making.

WHY APPRAISE THE EVIDENCE?

Where an article is published, or who wrote it should not be an indication of its trustworthiness and relevance. Using critical appraisal skills and tools enables users of research evidence to reach their own judgments.

APPRAISING THE EVIDENCE:

1. Is the study valid?

Decide whether studies have been undertaken in a way that makes their findings reliable.

The first step is to decide whether the study was unbiased by **evaluating its methodological quality.** Different criteria for validity of articles are used for different types of questions on: treatment, diagnosis, prognosis and economic evaluation. Depending on the validity of an article we can classify it within a scale of levels of evidence and degrees of recommendation.

2. What are the results?

Make sense of the results.

If we decide that the study is valid, we can go on to look at the results. At this step we consider whether the study's results are clinically important. For example, did the experimental group show a significantly better outcome compared with the control group? We also consider how much uncertainty there is about the results, as expressed in the form of p values, confidence intervals and sensitivity analysis.

3. Are the results useful?

Know what these results mean in the context of the decision that needs to be made.

Once you have decided that your evidence is valid and important, you need to think about how it applies to your question. It is likely, for example, that your patient or population may have different characteristics to those in the study. Critical appraisal skills provides a framework within which to consider these issues in an explicit, transparent way.

Structure of an article:

1. Title: Not always a good indication of the content of the article

2. Abstract: Sometimes unclear.

What should be in it: a summary of the the research question, key methods, results and conclusions of the study.

3. Introduction: **Should contain the research question (PICO) or hypotheses tested**

4. Background / review of literature: Research questions occur in the context of an already-formed body of knowledge. The background should address this context, help set the rationale for the study, and explain why the questions being asked are relevant.

5. Methodology: **Should describe exactly how the research was carried out:**

- Sample: characteristics, selection, number, non-response

- Measures: description of tests / questionnaires (validated?), data, outcome measures

- Procedure: study design (qualitative, quantitative, controlled?)

6. Results: Should tell the reader what the findings were. All outcome measures must be reported and confidence intervals for effect sizes should be presented.

7. Discussion:

-Interpretation of the results / relation to theory.

-Comparison with the results of other studies.

-Weaknesses / limitations of the study.

-Implications.

-Recommendations.

Clarification:

Now let's say that the same patient has heard from a friend that there is a vitamin that will help prevent migraines. What study design could answer the question of whether there is a vitamin that is useful in preventing migraine headaches in this patient?

Study Methods to Answer This Question:

- Epidemiology: Patients taking a vitamin are less likely to have migraines
- Pharmacology: Drug x affects cerebral vasculature in rat brain isolates
- Case report: "It worked on one patient"
- Case-series: "It worked on a bunch of patients"
- **Randomized controlled trial**: 1/2 get drug, 1/2 placebo. No one knows who 'til the end who took what

There are various ways that a study could be designed to answer this question. One study might be that a bunch of patients that take vitamins regularly are less likely to report migraine headaches (an epidemiologic approach). Another study might be that a certain drug or a vitamin had an effect on the cerebral vasculature in rat brain isolates (a pharmacologic approach). Another study might be a case report where someone gave a particular vitamin to a patient with migraines and the migraines stopped. Perhaps someone gave a vitamin to a whole bunch of patients with migraine headaches and all of them reported that their headaches improved (Case series).The last approach would be a randomized control trial where half of the patients were given a particular drug and half of them get placebo and no one knows who got what until the end of the study and the outcomes were evaluated.

What's A Paper on Therapy?

Randomised Control Trials: Clinical Trial Compares:

- INTERVENTION

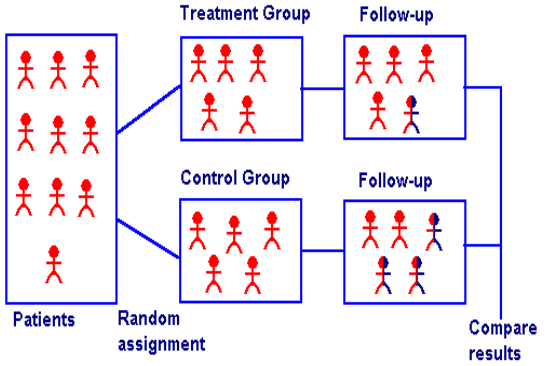
- ✓ Drug (New)
- ✓ Structured exercise program (e.g. osteoporosis)
- ✓ Surgical procedure

-CONTROL:

- ✓ Placebo, old drug or old intervention
- ✓ Usual regular advise given (osteoporosis)
- ✓ Another surgical procedure / No surgery

Process of RCTs:

- ✓ Preparation: Randomization, Computer generated list
- ✓ Eligibility assessment (Inclusion/exclusion)
- ✓ Consent
- ✓ Allocation to study arms (Concealment)
- ✓ Baseline assessment
- ✓ Initiation of intervention (Blind)
- ✓ Follow-up
- ✓ Outcome assessment
- ✓ Data analysis



Appraise the Evidence:

- ✓ Assess **validity**? Correctness (likely to be true)
- ✓ What are the **results**? Clinically important
- ✓ Can we **apply** the results to our patient? Applicable in and useful for my patients

VALIDITY

- **Internal validity:** How well was the study done? Do the results reflect the *truth*?
- **External validity:** can I apply these results to MY patients? (=applicability)

when we consider validity, we really need to look at two types of validity. Internal validity is, basically, how well methodologically was the study performed. In other words, was the study design rigorous enough so that we can be confident that the researchers found what they think they found? We're asking how well do the results reflect the truth of what actually happens in the world.

External validity asks the results found in the study apply to people not included in the study. In other words, can I apply these results to my patients? We need to determine the generalizability of the study to the population of patients we see. Rarely do we have a study that includes all types of patients and there are usually many types of exclusion and inclusion criteria that frequently do not apply to our patients. It's important for us to determine whether or not these results really have a probability of similarly affecting our particular patients.

1. **Randomization.**
2. **Concealment.**
3. **Blindness.**
4. **Follow up complete.**
5. **Intention to treat.**
6. **Similar groups at start.**
7. **Both groups treated equally.**

Are the results of this single preventive or therapeutic trial valid?

1.Was the assignment of patients to treatments **randomised?**	
2.Was the randomisation list **concealed**?	
3.Was follow-up of patients sufficiently **long and complete?**	
4.Were all patients **analysed** in the groups to which they were randomised?	
5.Were patients and clinicians kept **"blind"** to treatment?	
6.Were the groups **treated equally**, apart from the experimental treatment?	
7.Were the groups **similar at the start** of the trial?	

1.Randomization:

- Randomisation = similar groups at baseline
- **Equal (50%) chance to be in either group**
- How was it randomized?
- Was randomization concealed?
  - selection - allocation

2.Concealment: إخفاء هوية المريض

Was allocation assignment "concealed"?

Did investigators know to which group the potential subject would be assigned **before** enrolling them?

The gold standard for a therapeutic trial is no longer simply just the concept of randomization, but is also whether or not allocation assignment was concealed from the enrolling investigator ("concealed allocation). It has only been in the last 5 to 8 years that allocation concealment has been discussed or even mentioned in the medical literature. This is a very difficult concept for many and our goal in discussing it now is not for participants to fully understand it, but to grasp its importance. The definition of concealed allocation: Did the investigators know to which group a potential subject would be assigned before they were actually enrolled in this study?

Importance of concealed allocation:

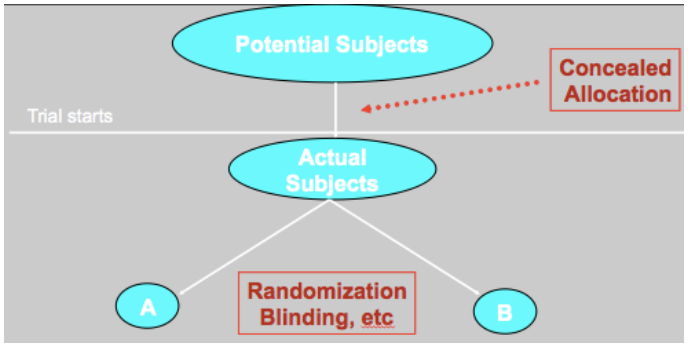
Trials with unconcealed allocation consistently overestimate benefit **by ~40%**

Ensuring Allocation Concealment:

- **Central computer randomization (BEST – most valid technique)**
- **Envelopes, etc (DOUBTFUL)**
- **Date of birth, alternate days, etc (NOT RANDOMIZED)**

Conducting a Study: This is a schematic of the difference between randomization and blindness and concealed allocation.

- **Concealed allocation** occurs **before** the trial even starts.
- **Randomization and blinding** occur **after** the study subjects are enrolled.



Selection bias: Reduced by:

- ✓ centralised randomisation
- ✓ on-site computer system with group assignments in a locked file
- ✓ sequentially numbered, sealed, opaque envelopes
- ✗ Not: alternation, dates of birth, day of week.

3.Blindness:

Was study "double-blinded"?

- ✓ Did the ***patients*** know to which group they were assigned?
- ✓ Did the ***treating*** physician know?
- ✓ Did ***investigators*** assessing outcomes know("triple-blinding"(when all three don't know the group assignment) – up to 7 levels!)?

- Judicial assessor blind + allocation concealment = surgery RCTs.

Measurement Bias - minimizing differential error:

- Blinding – **Who?**
  - ✓ Participants?
  - ✓ Investigators?
  - ✓ Outcome assessors?
  - ✓ Analysts?
- Most important to use "blinded" outcome assessors when outcome is not objective!
- Papers should report WHO was blinded and HOW it was done.

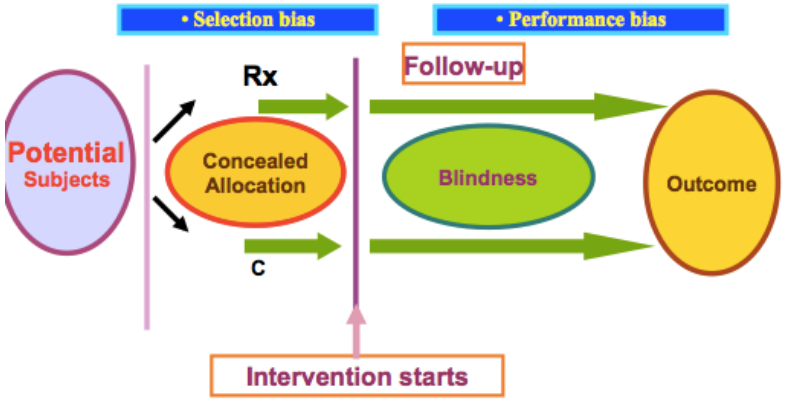
- ❖ If patient knows: Placebo effect Those who are on effective treatment perform better than those who receive Placebo.
- ❖ If Physician knows: Overestimate Treatment effect (More care, Co-intervention).

How RCTs differ from other design:

Two balanced groups:

- **Start Balanced:** All prognostic factors are equally distributed at the start (Concealed Randomization)
- **Run Balanced:** All prognostic factors are maintained balanced throughout the study (Blindness and the 3C)
- **End Balanced:** All prognostic factors are maintained balanced at the end of the study (ITT)

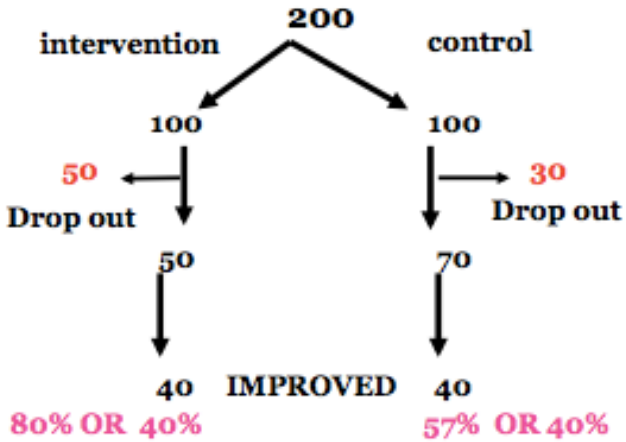
Intervention

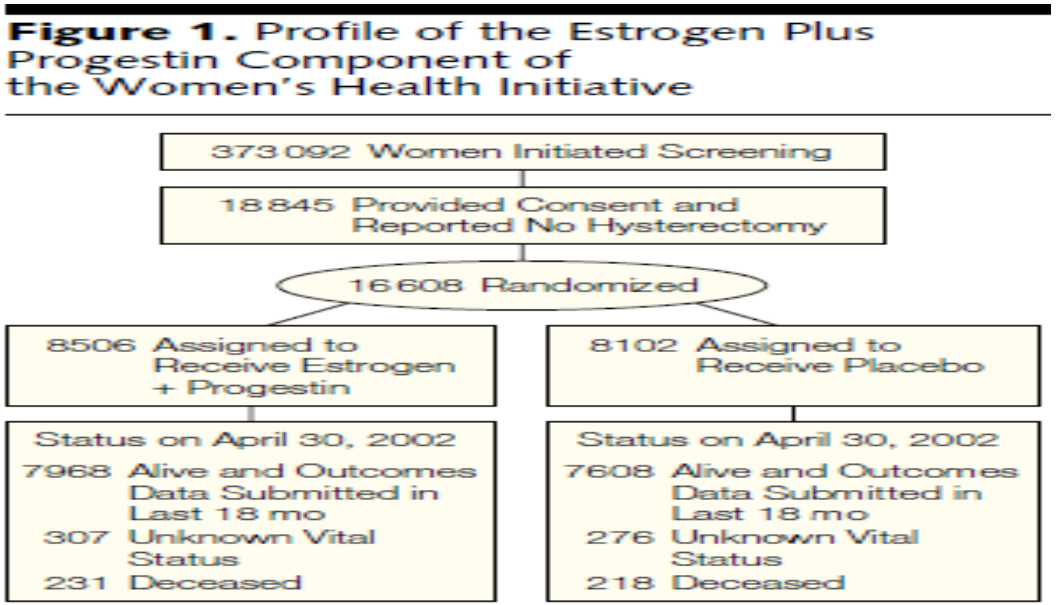


4. Intention to treat (ITT):

All patients analyzed in the groups to which they were allocated**. (drop out group should be included in the analysis)**

Intervention: Experimental Event Rate=
40/100= 40 ٪(drop out group included)
40/50= 80 ٪(40% over estimated without drop out group)
^That's what drugs' companies do
Control: Control Event Rate =
40/100= 40%
40/70= 57% (17% over estimated)





5. Follow up:

- duration of study.
- drop out **< 20%.**

Was follow-up of patients sufficiently long and complete?

Losses-to-follow-up: How many is too many?

"5-and-20 rule of thumb"

5% probably leads to little bias.

>20% poses serious threats to validity.

6. Similar groups at start.

Were the groups similar at the start of the trial?

7. Both groups treated equally.

Were the groups treated equally, apart from the experimental treatment?

RESULTS: Magnitude (treatment effect) IMPORTANT!

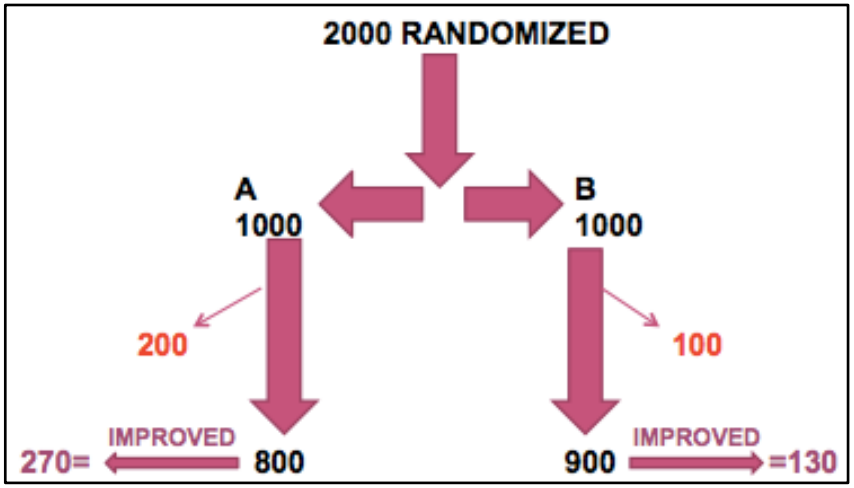
1. Number Needed to Treat (NNT):

Number of persons who would have to receive an intervention for 1 to benefit.

NNT=1/ARR. آشخاص عشان واحد يتشافى 10أو أقل كويسه لاني احتاج اعالج 10اذا كان الناتج

Experimental Event Rate=270/800 = 33%= 0.33
Control Event Rate = 130/900=14 %=0.14
Absolute RR= 0.33-0.14= 0.19
Number needed to treat =1/0.19= 5.2=6

EER=270/1000=27%=0.27
CER=130/1000= 13%=0.13
ARR=0.27-0.13=0.14
NNT=1/0.14=7



2. NUMBER NEED TO HARM (NNH)

WHAEN THE OUTCOME IS UNFAVOURABLE.

3. Magnitude (treatment effect):

- Absolute effects **(ARR & NNT)**
- Relative effects **(RR, RRR)**

4. Precision:

- **P value.**
- **Confidence interval?**

The range within which the likelihood of a true value is expected to be within a given degree of certainty , usually evaluated at 95% CI.

Result Tabulation:

- EER = Experimental Event Rate (a/a+b)
- CER = Control Event Rate (c/c+d)

	Event + Ve	Event - Ve	Total
Experimental	a	b	a+b
Control	c	d	c+d

- EER-A (Risk A) = 20/100 = 20% (0.2)
- CER-B (Risk B) = 40/100 = 40% (0.4)

	Bleeding Present	Bleeding Absent	Total
Drug A	20	80	100
Drug B	40	60	100

Calculations:

- ARR = CER - EER
- NNT = 1 / ARR
- RR = EER/CER (Risk A/Risk B)
- RRR = 1- RR

Answers:

- ✓ ARR = CER – EER = 0.4 – 0.2 = 0.2 (20%)
- ✓ NNT = 1 / ARR = 1/0.2 = 5
- ✓ RR = EER/CER = 0.2/0.4 = 0.5
- ✓ RRR = 1- RR = 1- 0.5= 0.5 (50%)

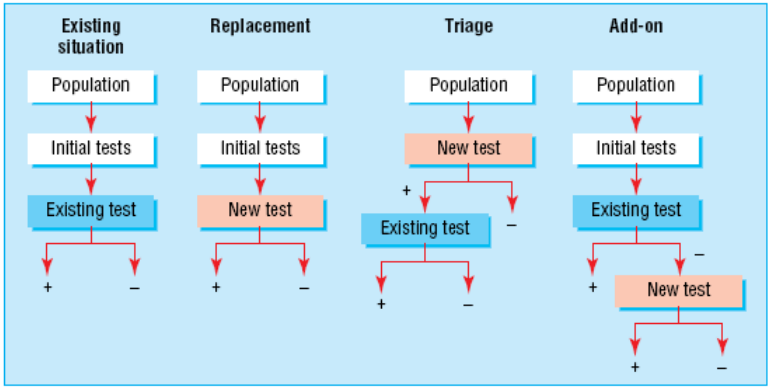
APPLICABILITY:

- ✓ CAN I APPLY THESE VALID, IMPORTANT RESULTS TO MY PATIENT?
- ✓ Do these results apply to my patient?
  - IS OUR PATIENT SO DIFFERENT?
  - IS THE TREATMENT FEASIBLE?
  - POTENTIAL BENEFITS AND HARMS
- ✓ Are my patient's values and preferences satisfied by the intervention offered?

Evaluating Research about Diagnostic Tests

Roles of a new test:

- **Replacement – new replaces old**
  E.g., CT colonography for barium enema
- **Triage – new determines need for old**
  E.g., B-natriuretic peptide for echocardiography
- **Add-on – new combined with old**
  ECG and myocardial perfusion scan



Roles of tests and positions in existing diagnostic pathways

Appraising a diagnostic test study using a critical appraisal checklist:

Defining the clinical question: PICO or PIRT

Patient/Problem: How would I describe a group of patients similar to mine?
Index test: Which test am I considering?
Comparator… or …Reference Standard: What is the best reference (gold) standard to diagnose the target condition?
Outcome….or….Target condition : Which condition do I want to rule in or rule out?

Patient-Initiated Treatment of Uncomplicated Recurrent Urinary Tract Infections in Young Women

Kalpana Gupta, MD, MPH; Thomas M. Hooton, MD; Pacita L. Roberts, MS; and Walter E. Stamm, MD

Background: Recurrent urinary tract infections (UTIs) are a common outpatient problem, resulting in frequent office visits and often requiring the use of prophylactic antimicrobial agents. Patient-initiated treatment of recurrent UTIs may decrease antimicrobial use and improve patient convenience.

Objective: To determine the safety and feasibility of patient-initiated treatment of recurrent UTIs.

Design: Uncontrolled, prospective clinical trial.

Setting: University-based primary health care clinic.

Participants: Women at least 18 years of age with a history of recurrent UTIs and no recent pregnancy, hypertension, diabetes, or renal disease.

Intervention: After self-diagnosing UTI on the basis of symptoms, participating women initiated therapy with ofloxacin or levofloxacin.

Measurements: Accuracy of self-diagnosis determined by evidence of a definite (culture-positive) or probable (sterile pyuria and no alternative diagnosis) UTI on pretherapy urinalysis and culture. Women with a self-diagnosis of UTI that was not microbiologically confirmed were evaluated for alternative diagnoses. Post-therapy interviews and urine cultures were used to assess clinical and microbiological cure rates, adverse events, and patient satisfaction.

Results: 88 of 172 women self-diagnosed a total of 172 UTIs. Laboratory evaluation showed a uropathogen in 144 cases (84%), sterile pyuria in 19 cases (11%), and no pyuria or bacteriuria in 9 cases (5%). Clinical and microbiological cures occurred in 92% and 96%, respectively, of culture-confirmed episodes. No serious adverse events occurred.

Conclusion: Adherent women can accurately self-diagnose and self-treat recurrent UTIs.

Ann Intern Med. 2001;135:9-16. www.annals.org
For author affiliations, current addresses, and contributions, see end of text.
See related article on pp 41-50 and editorial comment on pp 51-52.

Reference standard

Accuracy

Series of patients

Index test

Appraising a diagnostic test study using a critical appraisal checklist:

1. VALIDITY: Is the study valid?

❑ Screening:

✓ **Was there a clear question for the study to address?**
- the population, test, setting, and outcome
- This information can usually be found in the abstract or the introduction to the study

✓ **Is there comparison with an appropriate (gold) reference standard for diagnosing the disorder under assessment?**
- ***The reference standard comparison should be the best available indicator of the target disorder.***
- As the answer is yes to both of our initial screening questions, we should continue with our analysis of the diagnostic test study

❑ Population:

✓ **Did the study include people with all the common presentations of the target disorder? For example, symptoms of early manifestations as well as people with more severe symptoms, and/or people with other disorders that are commonly confused with the target disorder when diagnosing?**

❑ Blinding:

✓ **Were the people assessing the results of the index diagnostic test blinded to the results of the reference standard?**

❑ Testing:

✓ **Was the reference standard applied regardless of the index test result?**

✓ **Was the diagnostic test validated in a second independent group of patients?**

❑ Methods:

✓ **Were the methods of the diagnostic test described in sufficient detail? Consider if descriptions of the following are included:**
- Rationale for the ref standard.
- Technical specifications or references for running the index test and reference standard (e.g., including enough information that the tests could be replicated).
- Methods for calculating or comparing measures of diagnostic accuracy and statistical uncertainty (95% CI).

Now that we have established that the study is valid, we should consider the results

Appraising a diagnostic test study using a critical appraisal checklist:

2. RESULTS:

- ✓ **Do the results include information about people who satisfied inclusion criteria for the study but did not receive the diagnostic index or reference standard test?**
- ✓ **Do the results include how indeterminate results, missing results, and outliers of the index test were handled?**
- ✓ **Do the results include criteria for defining the severity of the target disorder?**
- ✓ **Do the results include cross tabulation of the index test results by the reference standard results? Or enough information to generate this table?**

Yes, the study includes sensitivity, specificity, and positive and negative predictive values for all of the comparisons made, and the calculations used. Using these results, you could if needed generate the cross tabulation table, for example below:

- e.g: Site 1, *Chlamydia* Rapid Test with self collected vaginal swab specimens versus polymerase chain reaction

	Reference Standard			
Index test		Positive	Negative	Total
	Positive	47	7	54
	Negative	9	600	609
	Total	56	607	663

Do the results include estimates of diagnostic test accuracy and statistical uncertainty (95% CI)?

Yes the study includes 95% CI for all comparisons made. For example:

Table 1 | Unresolved performance of *Chlamydia* Rapid Test with self collected vaginal swab specimens versus polymerase chain reaction. Values are percentages (numbers) (95% confidence intervals)

Site	Sensitivity	Specificity	Positive predictive value	Negative predictive value
1 (n=663)	83.9 (47/56) (74.3 to 93.5)	98.8 (600/607) (98.0 to 99.7)	87.0 (47/54) (78.1 to 96.0)	98.5 (600/609) (97.6 to 99.5)
2 (n=385)	80.6 (29/36) (67.6 to 93.5)	98.0 (342/349) (96.5 to 99.5)	80.6 (29/36) (67.6 to 93.5)	98.0 (342/349) (96.5 to 99.5)
3 (n=301)	83.3 (15/18) (66.1 to 100)	99.6 (282/283) (99.0 to 100)	93.8 (15/16) (81.9 to 100)	98.9 (282/285) (97.8 to 100)
Total (n=1349)	82.7 (91/110) (75.7 to 89.8)	98.8 (1224/1239) (98.2 to 99.4)	85.8 (91/106) (79.2 to 92.5)	98.5 (1224/1243) (97.8 to 99.2)

No significant difference in *Chlamydia* Rapid Test performance was apparent among three sites (P=0.278, κ statistics).

2 by 2 table:

- IF only a test had perfect discrimination…

True positive, True negative.

• Sensitivity:

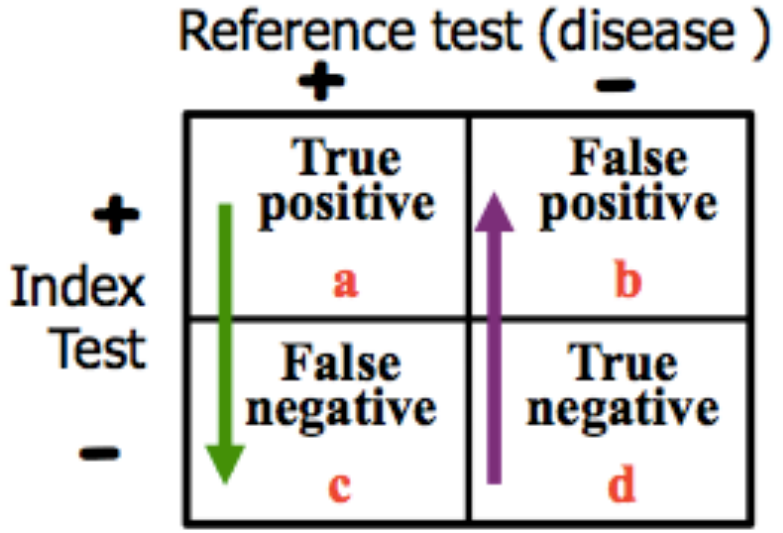
Proportion of people <u>with</u> the disease who have a <u>positive</u> test.

Sensitivity = a / a + c

• Specificity:

Proportion of people <u>without</u> the disease who have a negative test.

Specificity = d / b + d



For Example:

Sensitivity is useful to me
'The new chlamydia test was **positive in 47 out of 56** women with chlamydia (**sensitivity =83.9%**)'

Specificity seems a bit confusing
'The new chlamydia test was negative **in 600 of the 607** women who did not have chlamydia **(specificity = 98.8%**)'

So…**false positive rate** is sometimes easier
False positive rate = 1 – specificity So a specificity of 98.8% means that the new test is wrong (or falsely positive) in 1.2% of women

	Reference Standard		
Index test	Positive	Negative	Total
Positive	47	7	54
Negative	9	600	609
Total	56	607	663

- **True positive rate (= Sensitivity)**
- **False positive rate (= 1 – Specificity)**

SnNOUT:

Highly <u>sensitive</u> tests = good for screening Or SnNOUT Highly sensitive test, negative result rules out.

Sensitivity = a / a + c

SpPIN :

Highly specific tests = good for ruling in Or SpPIN Highly specific test, positive result rules in.

Specificity = d / b + d

3. APPLICABILITY:

- ✓ Does this diagnostic test apply to your specific patient?
- ✓ Is your patient similar to the people in the study in terms of clinical and demographic characteristics?
- ✓ Is the diagnostic test available, and if so, does it reflect current practice?
- ✓ Will the test result change the way the patient is managed?

Appraisal of a cohort:

1. Did the study address a clearly focused issue?
2. Was the cohort / panel recruited in an acceptable way? (selection bias)
3. Was the cohort/ panel representative of a defined population?
4. Was a control group used? Should one have been used?
5. Are objective and validated measurement methods used and were they similar in the different groups? (misclassification bias)
6. Was the follow up of cases/subjects long enough?
7. Could there be confounding?
8. Is the size of effect practically relevant?
9. Are the conclusions applicable?

Conclusion:

- Different types of question require different study designs.
- Does the study address a clearly focused question?
- Did the study use valid methods to address this question?
- Are the valid results of this study important?
- Are these valid, important results applicable to my patient or population?

Critical Appraisal (Meta-analysis/Systematic reviews Guidelines)

Narrative reviews:

- Usually written by **experts** in the field.
- Use **informal and subjective methods** to collect and interpret information.
- Usually **narrative summaries of the evidence.**
- Do not confuse with narrative systematic reviews, which describes the type of synthesis of data.

What is a systematic review?

A review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review.

Key elements of a systematic review:

Structured, systematic process involving several steps :

1) Formulate the question
2) Plan the review
3) Comprehensive search
4) Unbiased selection and abstraction process
5) Critical appraisal of data
6) Synthesis of data (may include meta-analysis)
7) Interpretation of results

* All steps described explicitly in the review

The Cochrane Collaboration:

International non-profit organisation that prepares, maintains, and disseminates systematic up-to-date reviews of health care interventions

Tools for critical appraisal:

- CASP: Critical Appraisal Skills Programme Checklists
- Critically Appraised Topics: generic systematic reviews (ACP Journal club)
- SIGN: Scottish Intercollegiate Guidelines Network
- GATE Frame

THE COCHRANE COLLABORATION®

Appraisal of a systematic review: 10 questions

- ❑ Clearly-focused question
- ❑ The right type of study included
- ❑ Identifying all relevant studies
- ❑ Assessment of quality of studies
- ❑ Reasonable to combine studies
- ❑ What were the results
- ❑ Preciseness of results
- ❑ Application of results to local population
- ❑ Consideration of all outcomes
- ❑ Policy or practice change as a result of evidence

Step 1 – Are the results of the review valid?

- Question – what is the PICO (etc.) **(Title, abstract, introduction)**
  - ❑ **What question (PICO) did the systematic review address?**
  - ❑ Is question clearly stated early on?
  - ❑ Treatment/exposure described?
  - ❑ Comparator/control described?
  - ❑ Outcome(s) described?
- Finding – comprehensive? **(method)**

1. Is it unlikely that important, relevant studies were missed? *Look for*

- ❑ Which bibliographic databases were used? More than 1?
- ❑ Search terms used (text and MeSH)?
- ❑ Search for unpublished as well as published studies?
- ❑ Search for non-English studies?

2. Is finding all published studies enough?

- Negative studies less likely to be published than 'Positive' ones
- How does this happen?
- Positive studies SUBMITTED 2.5x more often than negative.

3. Were the criteria used to select articles for inclusion appropriate? Look for

- ❑ Inclusion/exclusion criteria a priori?
- ❑ Are eligibility criteria related to PICO?
- ❑ Types of studies?

Step 1 – Are the results of the review valid?

- Appraise – did they select good ones? **(Methods, Results)**

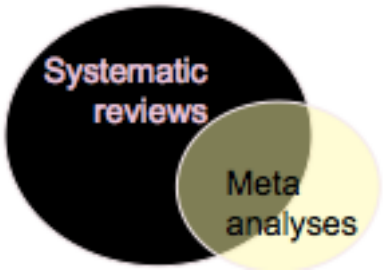
1. Were the included studies sufficiently valid for the type of question? *Look for*

- ❑ Criteria for quality assessment defined?
- ❑ Appropriate for the question?
- ❑ Were the assessment results provided?

- Synthesise – numerically/appropriate?

1. Were the results similar from study to study? *Consider whether*

- The results of all the included studies are clearly displayed
- The results are combined (meta-analysis): *Are studies sufficiently similar*
- The reasons for any variations in results are discussed



Meta-analysis:

= calculated "best guess" of the true effect size

- The statistical combination of the results gives a pooled, weighted average of the primary results
- It weights the effect size (result) of each study in relation to sample size of the study
- Optional part of SR

FOREST PLOTS:

A.Which is the smallest study?

Wider CI = smaller sample size

A.Which is the largest study?

B.How many are statistically Significant?

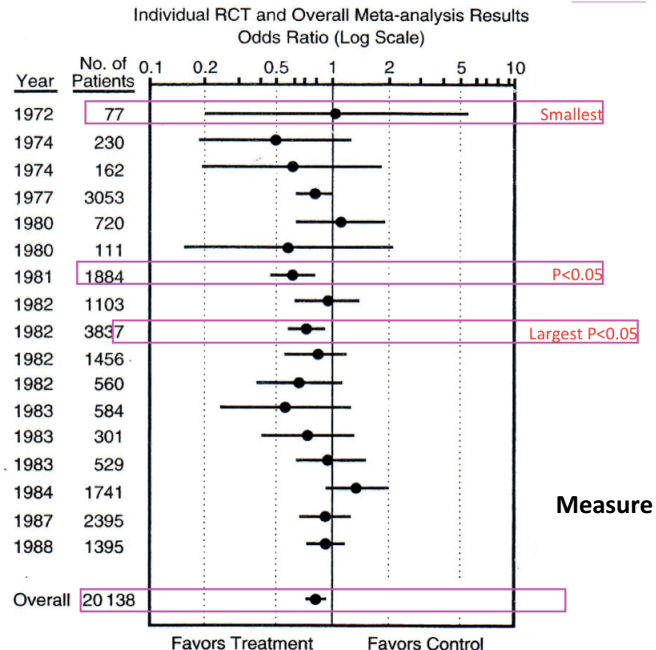
Any study cross the line of no effect is not significant .

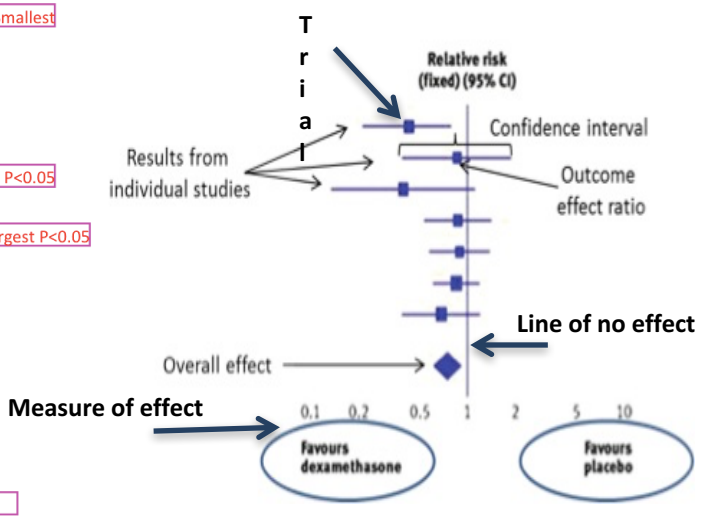
D.Is treatment better than control?

yes

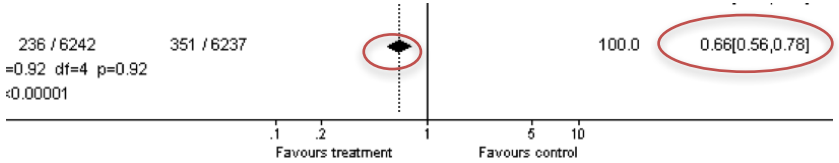
E. How much better?

[How to Interpret a Forest Plot]





FOREST PLOTS:



Effect size =

1 – 0.66 = 0.34

0.34 x 100 = 34%

There is a **34% reduced risk** of mortality in the treatment compared to the control group

The overall effect is represented by the diamond at the bottom (labelled 'Total') and represents the combined or pooled ratio. The ends of the diamond represent the 95% CI. Here we can see that treatment reduces mortality by 34%

Heterogeneity:

"The quality or state of being diverse in character or content"

- **Clinical heterogeneity**

Variability in the participants, interventions and/or outcomes studied.

- **Methodological heterogeneity**

Variability in study deign and risk of bias.

- **Statistical heterogeneity**

The observed intervention effects being more different from each other than we would expect due to random error (chance) alone.

High heterogeneity = appropriate to pool data?

Are the results similar across studies? 3 tests:

1. **'Eyeball' test – do they look they same?**
2. **Formal tests**
   a) **Proportion of variation not due to chance (I2)**
   Variation between tests, now preferred estimate
   - 0% to 40%: might not be important;
   - 30% to 60%: may represent moderate heterogeneity;
   - 50% to 90%: may represent substantial heterogeneity;
   - 75% to 100%: considerable heterogeneity

   b) **Test of 'Null hypothesis' of no variation (p-value)**
   - **Cochrane Chi-square: p<0.10 = heterogeneity**

Step 2 – What were the results?

- What these are (numerically if appropriate)
- How were the results presented/expressed (risk ratio, odds ratio, etc.)
- If you are clear about the review's 'bottom line' results (conclusion)

Step 3 – Can I apply these results to my case?

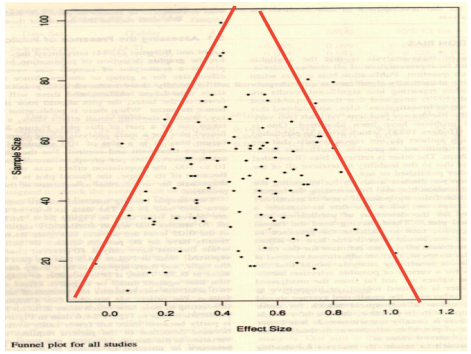
Is my patient so different to those in the study that the results cannot apply?

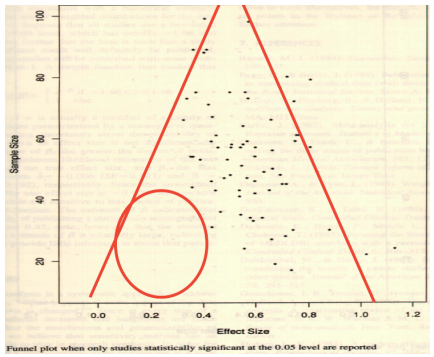
'Clinical pearls':

- Don't forget to ask "Is it worth continuing?"
- Look for 'key' references: Cochrane Risk of Bias, GRADE, PRISMA
- I2 >50%: adequate statistical heterogeneity to suggest looking deeper into clinical, methodological heterogeneity reported
- Would your patient meet the inclusion criteria of trials/studies in the review?

Publication bias:

- Occurs when publication of research results depends on their nature and direction
- Often happens because smaller (n and effect size) studies not submitted/rejected, selective reporting, selective citation (of +ve results)
- **Funnel plots** help identify if there is a bias:
  - Treatment effect vs. study size
  - Smaller the study = wider the effects
  - Largest studies will be near the average (truth), small studies will spread on both sides = symmetric funnel
  - Asymetric funnel indicates publication bias – but not all the time (e.g. heterogeneity)
  - Interpretation difficult if only a few studies in meta-analysis





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