8. Systemic reviews and meta-analysis

a. Understand the purpose of a systematic review
   - Comprehensive summary, critical appraisal, and synthesis of available evidence from primary studies that meet predefined eligibility criteria to address a specific clinical question.
   - Includes a systematic search to identify all relevant studies, a transparent approach to appraise studies for inclusion, assessment of the validity of the findings in the included studies, and discussion of discrepancies between the studies, the impact of bias, and applicability of the findings.

b. Understand the advantages of adding a meta-analysis to a systematic review
   - Statistical method that quantitatively combines the results from several primary studies
   - Provides a single overall quantitative estimate of the net benefit or harm of an intervention
   - Useful when there are several similar clinical trials with or without consistent outcomes, or when there are smaller to medium-sized trials with inconclusive results.

c. Interpret the results of a meta-analysis
   Data is usually displayed in the form of a Forest Plot:
   - Graphic representation of the effect sizes (magnitude and direction of treatment effect) and confidence intervals for each study
   - Shows the calculated estimate of the overall effect size of all included studies and corresponding overall confidence interval
   - Illustrates the extent to which results from individual studies vary (heterogeneity)

[Forest Plot Image]

   Study or subgroup  | Treatment n/N | Control n/N | Risk Ratio (95% CI)
   ------------------|--------------|-------------|----------------------
   Gamsu 1989        | 15/131       | 22/137      | 0.71 [0.39-1.31]     
   Garito 1992       | 12/36        | 12/41       | 1.14 [0.59-2.21]     
   Kari 1994         | 5/55         | 6/64        | 0.82 [0.25-2.61]     
   Liggins 1972a     | 100/601      | 122/617     | 0.91 [0.72-1.15]     
   Parsons 1988      | 0/23         | 1/22        | 0.32 [0.01-7.45]     
   Qublan 2001       | 21/72        | 41/67       | 0.48 [0.32-0.72]     
   Schutte 1980      | 6/65         | 12/58       | 0.45 [0.18-1.11]     
   Tausch 1979       | 10/56        | 12/71       | 1.06 [0.49-2.27]     
   Subtotal (95% CI) | 1813         | 1814        | 0.77 [0.67-0.89]     

   Combined result

   Study result:
   size reflects # participants
   Study 95% confidence interval
   Line of no effect
   Combined 95% confidence interval

   Combined result


d. Identify the limitations of a systematic review
- Publication bias favors inclusion of studies reporting significant outcomes
- Routine inclusion of unpublished data may lead to incorporation of data of lesser quality
- Does not overcome problems that were inherent in the design and execution of the primary studies
- Inclusion and exclusion criteria may be subject to bias

e. Identify the limitations of a meta-analysis
   - Similar to limitations of systematic review
   - Should only be performed when studies are similar with respect to population, outcome and intervention

B. Principles of Epidemiology and Clinical Research Design

1. Study types
   a. Distinguish between Phase I, II, III, and IV clinical trials

   Phase I:
   - Assesses the safety of a drug or device
   - Usually includes a small number (20-100) of healthy volunteers
   - Designed to determine how the drug is absorbed, metabolized, and excreted.
   - Investigates side effects that occur as dosage levels are increased.

   Phase II:
   - Gather preliminary data on efficacy; continued safety evaluation
   - Typically includes several hundred patients with the disease/condition for which the drug was developed
   - In most, participants are randomized between test group, which receives the study drug, and control group, which receives a placebo or different drug

   Phase III:
   - Designed to determine whether study drug offers treatment benefit compared to standard of care in specific population
   - Includes 300-3000 participants with disease for which the drug was developed
   - Large scale, multicenter, randomized, blinded, placebo-controlled trial

   Phase IV:
   - Occur after drug or device has been approved by the FDA for marketing
   - Gather additional information about safety (including any rare or long-term adverse effects), efficacy, or optimal use of the drug

b. Recognize a retrospective study
   - Looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study
   - Data are generated from historical data and recall

c. Understand the strengths and limitations of retrospective studies

   Strengths:
   - Relatively inexpensive and may be completed relatively quickly
   - Well-suited for studying rare outcomes

   Limitations:
   - Identification of representative controls may be challenging
   - Subject to recall bias
Limited ability to obtain additional historical information if not collected during initial encounters

d. Recognize a case series
   - Description of clinical data from a well-defined group of individuals without reference to a comparison group

e. Understand the strengths and limitations of case series
   Strengths:
   - Useful in forming hypotheses, planning natural history studies, and describing clinical experience
   - Easy and inexpensive to do in clinical settings
   - May be the first indication that a rare adverse event might be associated with a therapy or procedure
   Limitations:
   - Selection of cases or study patients may be biased, making generalization of results difficult

f. Recognize a cross-sectional study
   - Collect data about health-related characteristics and exposure status of a population at a single point in time
   - Typically employs a complex sampling design to ensure that the selected respondents are representative of the whole population

g. Understand the strengths and limitations of cross-sectional studies
   Strengths:
   - Cases are more representative of general population (unlike case series)
   - Can examine a wide variety of exposures and outcomes simultaneously
   Limitations:
   - Typically unsuitable for rare diseases or for diseases of short duration
   - More expensive and time-consuming in general than are case–control studies
   - Subject to nonparticipation bias
   - Cannot address the temporal relationship between measured factors and development of disease for identification of potential causal factors

h. Recognize a case-control study
   - Retrospective study that looks for possible associations between the disease of interest and one or more hypothesized risk factors

i. Understand the strengths and limitations of case-control studies
   Strengths:
   - Relatively inexpensive and may be completed relatively quickly
   - Well-suited for studying rare outcomes
   Limitations:
   - Cannot estimate incidence or prevalence
   - Identification of representative controls may be challenging
   - Subject to recall bias
- Limited ability to obtain additional historical information if not collected during initial encounters

j. Recognize a longitudinal study
- Involves repeated observations of the same variables in a cohort of subjects over long periods of time

k. Understand the strengths and limitations of longitudinal studies
Strengths:
- Provides information about natural history of disease and direct estimates of incidence and relative risk
- Establishes the temporal relationship between exposure and disease
- Well-suited for studying rare exposures

Limitations:
- Long duration and high expense; rare diseases require extraordinarily large sample sizes
- Susceptible to bias by differential loss to follow-up
- Observational in nature

l. Recognize a cohort study
- Subjects are selected for a particular exposure along with a comparable group of nonexposed “controls,” and both groups are followed forward in time to determine numbers of disease events in exposed and unexposed subjects.
- May be prospective or retrospective, using historical data when access is available to good records of large population samples

m. Understand the strengths and limitations of cohort studies
- See section k above

n. Recognize a randomized-controlled study
- Subjects are assigned to two or more interventions at the beginning of the study. One group of patients is often assigned to a placebo (placebo control) but a randomized trial can involve two active therapies (active control).
- Treatment effect is determined by evaluating subjects after defined period of time for differences in quantifiable outcome measures between experimental and control groups.

o. Understand the strengths and limitations of randomized-controlled studies
Strengths:
- Strongest evidence of the clinical efficacy of an intervention in the clinical setting
- May be used to establish causality

Limitations:
- Expensive and time consuming
- Placebo control may not be possible due to ethical considerations

p. Recognize a before-after study
- Observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not. The study gauges the effects of the event or intervention.
q. Understand the strengths and limitations of before-after studies
Strengths:
- Most common type of study used to assess process improvement and patient safety initiatives
- Useful for demonstrating the immediate impacts of short-term programs
Limitations:
- Less useful for evaluating longer term interventions, as more circumstances can arise over time that may obscure the effects of an intervention.

r. Recognize a crossover study
- Each study participant receives all treatments that are being investigated during different treatment periods. The order in which a study participant receives the treatments is randomized.
- Treatment periods are usually separated by a washout period. Outcomes are examined during and/or after each treatment period

s. Understand the strengths and limitations of crossover studies
Strengths:
- Significantly removes between-subject variability, as each subject acts as his/her own control
- Requires fewer patients than a parallel study for an equal number of treatment comparisons
- Useful for studying conditions with relapsing/remitting or episodic symptoms
Limitations:
- No guarantee that washout periods will completely control for carryover effects
- Requires longer period of enrollment
- Ethical concerns about keeping patients off treatment during washout period
- Less useful for unstable or progressive conditions, because added variability due to change in disease will be introduced over the course of the study.

t. Recognize an open-label study
- Type of clinical trial in which both the researchers and participants know which treatment is being administered
- Contrasts with single blind and double blind experimental designs, where participants +/- researchers are not aware of what treatment they are receiving

u. Understand the strengths and limitations of open-label studies
- May be unavoidable under some circumstances, such as comparing the effectiveness of a medication to intensive physical therapy sessions.
- Lack of blinding introduces bias

v. Recognize a post-hoc analysis
- Looking at the data after a study has concluded for patterns that were not specified a priori

w. Understand the strengths and limitations of post-hoc analyses
- Risk of making a false discovery with multiple comparisons can be greatly inflated even if the error rate is well-controlled at the level of the individual test. It
is often impossible to discern from published results how many tests were conducted to arrive at a conclusion.

x. Recognize a subgroup analysis
- Used to check for consistency of treatment effect across different demographic or disease-severity subgroups of patients in a clinical trial.

y. Understand the strengths and limitations of subgroup analyses
- Type I error: more likely to find statistically significant difference by chance alone with larger number of subgroups tested
- Lower statistical power
- Should be considered exploratory and hypothesis-generating rather than definitive

2. Bias and confounding
a. Understand how bias affects the validity of results
Bias occurs when a systematic error in the design, recruitment, data collection or analysis that results in a mistaken estimation of the true effect of the exposure and the outcome.
Different types of bias include:
- Nonresponse/withdrawal bias: occurs when subjects identified for inclusion fail to provide data or participate in the study and are clinically different from those who participate
- Selection bias: selection of nonrepresentative population due to convenience
- Information bias: includes response and recall bias

b. Understand how confounding affects the validity of results
Confounding occurs when the effect or association between an exposure and outcome is distorted by the presence of another variable, which is independently associated with both the outcome of interest and the exposure.
- Positive confounding occurs when the observed association is biased away from the null
- Negative confounding occurs when the observed association is biased toward the null

c. Identify common strategies in study design to avoid or reduce bias
Randomization, blinding, consecutive recruiting, using objective data (rather than self-reported data) whenever possible. Prospective study design allows for more chance to control for bias than retrospective design.

d. Identify common strategies in study design to avoid or reduce confounding
Restriction, stratification and matching based on known confounding variables, multivariable regression analysis

e. Understand how study results may differ between distinct sub-populations (effect modification)
Effect modification occurs when a variable differentially (positively and negatively) modifies the observed effect of a risk factor on disease status. The effect is real, but the magnitude of the effect is different for different groups of individuals
3. Causation
   a. Understand the difference between association and causation
      - An observed statistical association between a risk factor and a disease does not necessarily mean that the risk factor causes the disease.
      - Experimental studies and clinical trials are required to establish causation, whereas observational studies can only show an association between a risk factor and a disease.
   b. Identify factors that strengthen causal inference in observational studies:
      - Temporal sequence: exposure must precede outcome
      - Dose response: changes in disease rates should follow from corresponding changes in exposure
      - Repetition in a different population and consistency with other studies
      - Biologic plausibility: agrees with current knowledge of disease mechanism or can be explained by potential biological mechanism

4. Incidence and prevalence
   a. Distinguish disease incidence from disease prevalence
      - Prevalence: number of individuals with a given disease at a given point in time divided by the population at risk at that point in time; reflects the burden of disease in a population and is proportional to disease incidence and duration
      - Incidence: number of new events that have occurred in a specific time interval divided by the population at risk at the beginning of the time interval; reflects the risk of developing a disease

5. Screening
   a. Understand factors that affect the rationale for screening for a condition or disease
      Major objective of screening is to reduce morbidity or mortality from a disease by early detection, when treatment may be more successful
      - Prevalence: fraction of individuals in a population that have a disease (reflects probability that a subject selected at random has the disease)
      - Accuracy = TP + TN = Prevalence x Sensitivity + (1 – Prevalence) x Specificity
      - Risks of screening test and confirmatory testing should be balanced against test accuracy and benefit of early diagnosis and intervention
      - Utility of screening depends on the presence of presymptomatic state at time of testing

6. Decision analysis
   a. Understand the strengths and limitations of decision analyses
      - Allows users to apply evidence-based medicine to make informed and objective clinical decisions when faced with complex situations
      - Most useful in clinical decisions where there is uncertainty regarding appropriate clinical strategy and when a meaningful tradeoff of advantages and disadvantages is present in the clinical problem
   b. Interpret a decision analysis
- Decision Tree: illustrates all plausible relationships, alternatives and outcomes involved with a given decision.
- Associated with each step in the decision tree are literature-derived probability and outcome values

![Decision Tree Diagram]

7. Cost-benefit, cost-effectiveness, and outcomes
   a. Differentiate cost-benefit from cost-effectiveness analysis
   - Cost-benefit analysis: places a monetary value to health outcomes
   - Cost-effectiveness analysis: measures the relative value of an intervention as the additional cost to achieve an incremental health benefit, such as dollars to prevent a case of cancer; measures monetary and health benefits separately
   b. Understand how quality-adjusted life years are used in cost analyses
   - QALY is a unit of health, which reflect both prolongation of life and quality of life associated with the additional years; it is used in cost-utility analysis
   c. Understand the multiple perspectives that influence interpretation of cost-benefit and cost-effectiveness analyses:
   - Individual patients may consider the out-of-pocket cost or co-payment for a medication or procedure and number or work-days missed
   - Health payers may consider costs of providing and paying for an intervention
   - Society perspective considers everyone affected by an intervention and the health benefits and harms that flow from it, even when these occur in individuals who are not the intended recipients of the intervention.

8. Sensitivity analysis
   a. Understand the strengths and limitations of sensitivity analysis
   - Used to estimate the impact of unmeasured confounders on causal associations
   - May also be used to assess the sensitivity of study findings to changes in exposure and outcome definitions, and to other assumptions made during conduct of the study.

b. Interpret the results of sensitivity analysis
In a meta-analysis, sensitivity analysis tests if the results are sensitive to restrictions on the data included. Common examples are large trials only, higher quality trials only, and
more recent trials only. If results are consistent it provides stronger evidence of an effect and of generalizability.

9. Measurement
a. Understand the types of validity that relate to measurement
   - Face validity: superficial and subjective assessment of the extent to which a test appears to measure what it reports to measure
   - Construct validity: the extent to which a measure is affirmed by an external established indicator
   - Criterion validity: the extent to which a measure is related to an outcome (may be concurrent of predictive)
   - Predictive validity: the extent to which a score on a scale or test predicts scores on some criterion measure; useful for predicting performance or behavior in another situation
   - Content validity: the extent to which the measure reflects the dimensions of a particular problem

b. Distinguish validity from reliability
   - Validity refers to how well a test measures what it is purported to measure
   - Reliability is the degree to which an assessment tool produces stable and consistent results

c. Distinguish internal from external validity
   - Internal validity refers to the question of whether the findings are representative of the true association between exposure and outcome for the patients studied
   - External validity refers to the degree to which study findings can be generalized to other groups or populations

d. Distinguish accuracy from precision
   - Accuracy refers to the closeness of a measured value to a the true value
   - Precision refers to the closeness of two or more measurements to each other (reproducibility)

e. Understand and interpret measurements of interobserver reliability (eg, kappa)
   Kappa statistic: measure of the agreement between two observers who independently measure the same data. Ranges from -1.0 to +1.0.
   - kappa = 1.0: perfect agreement
   - kappa = 0: observed agreement would be expected by chance alone
   - kappa = -1.0: complete disagreement

f. Understand and interpret Cronbach's alpha
   Cronbach’s alpha is a measure used to assess the reliability, or internal consistency, of a set of scale or test items. The alpha coefficient ranges from 0 to 1. The higher the α coefficient, the more the items have shared covariance and probably measure the same underlying concept.