RESEARCH GUIDELINES

1. **Consider the research hypothesis:**
    a) Is there a clear statement of the research hypothesis?
    b) Does the study address a question that has clinical relevance?
2. **Consider the design of the study:**
    a) Is the study design appropriate for the hypothesis?
    b) Does the design represent an advance over previous approaches?
    c) Is the study design observational or experimental?
3. **Consider the outcome variable:**
    a) Is the outcome being studied relevant to clinical practice?
    b) What criteria are used to define the presence of disease?
    c) Is the determination of the presence or absence of disease accurate?
4. **Consider the predictor variables:**
    a) How many exposures or risk factors are being studied?
    b) How is the presence or absence of exposure determined?
    c) Is there an attempt to quantify the amount or duration of exposure?
    d) Are biological markers of exposure used in the study?
5. **Diagram the experimental methods**
6. **Consider the methods of analysis:**
    a) Are the statistical methods employed suitable for the type of variables (categorical vs continuous, normal vs nonparametric) in the study?
    b) Have the levels of type I and type II error been discussed appropriately?
    c) Is the sample size adequate the answer the research question?
    d) Have the assumptions underlying the statistical tests been met?
    e) Has chance been evaluated as a potential explanation of the results?
7. **Consider possible sources of bias (systemic error):**
    a) Is the method of subject selection likely to have biased the results (selection bias)?
    b) Is the measurement of either the exposure or the disease likely to be biased (information bias)?
    c) Have the investigators considered relevant confounders?
    d) In what direction would each potential bias influence the results?
8. **Consider the interpretation of the results:**
    a) How large is the observed effect?
    b) Is there evidence of a dose response relationship?
    c) Are the findings consistent with other known models?
    d) Are the effects biologically plausible?
    e) If the findings were negative, was there sufficient statistical power to detect an effect?
9. **Consider how the results of the study can be used in clinical practice:**
    a) Are the findings consistent with other studies of the same questions?
    b) Can the findings be generalized to other human populations or communities?
    c) Do the findings warrant a change in your clinical practice?

For more in-depth analysis, consider the McMaster University or the JAMA series.
The additional areas covered by the McMaster series include:

1. Approach to the article about harm
2. Approach to the article about a new treatment
3. Approach to the article about a new diagnosis
4. Approach to the article about prognosis
5. Approach to the article which provides an overview
6. Approach to the article about decision analysis
7. Approach to the article about quality of life
8. Approach to the article about cost effectiveness
9. Approach to the article about clinical practice guidelines
10. Approach to the article about screening
11. Approach to the article using surrogate end points
12. Approach to the article about prediction rules

These articles can be accessed at the Centres for Health Evidence website:
http://www.cche.net/userguides/main.asp

I also highly recommend the book, "Epidemiology in Medicine" by Charles Hennekens and Julie Buring (Little, Brown and Company Publishers)

Clinical studies reported in the literature may be classified as one of two types:

1. DESCRIPTIVE STUDIES

a) **Case reports:** A clinical description of a single patient
- used for hypothesis generation
-cannot demonstrate causality, poor generalizability

b) **Case series:** A clinical description of a number of patients with a disease
-used for illness characterization
-no control group; cannot determine which factors in the description are unique to the illness

c) **Cross-sectional surveys:** Survey of a sample of the population in which the status of individuals with respect to the presence or absence of exposure and/or disease is assessed at the same point in time
-used for hypothesis generation, can calculate prevalence, odds ratio
-cannot demonstrate timing of disease occurrence, or relative risk

2. ANALYTIC STUDIES

a) Observational studies:
1. Cohort studies (prospective or retrospective)
2. Case-control studies

b) Experimental studies:
1. Randomized controlled trial

Cohort Study

Definition: A study comparing patients with a risk factor/exposure to others without the risk factor/exposure for difference in outcome; can be retrospective, prospective, or ambidirectional

Use: The study of a number of outcomes from a single risk factor/exposure; useful when exposure of interest is rare or when proof of causality is needed but a RCT might not be feasible; allows direct calculation of relative risk

Outcomes measured: incidence, prevalence, relative risk, attributable risk, attributable proportion, number needed to treat

Relative risk- ratio of incidence in those exposed to a factor to the incidence in those not exposed

	Disease	No disease
Exposed	A	B
Unexposed	C	D

RR = $\frac{A/(A+B)}{C/(C+D)}$

A RR of 1 indicates that there is no association between exposure and disease; >1 increased risk among exposed; <1 decreased risk among exposed

Limitation: time consuming, costly, loss to follow-up; lg sample size needed for rare diseases

Questions to think about:

1. Is the cohort design appropriate for the question to be answered?
2. Is the sample size adequate?
3. Do the exposed and unexposed subjects come from different populations?
4. Are the exposed and unexposed subjects examined concurrently?
5. Has the exposure been well defined?
6. If trial enrolls patients over time has the technology or technique for assessing exposure changed?
7. Is the outcome of interest clearly defined? How is the presence of the outcome confirmed?
8. Is the methodology used for confirmation of the outcome standardized for all?
9. Were those who assessed disease status blind to exposure status?
10. Was the period of follow-up long enough to adequately assess development of disease?
11. Was loss to follow-up greater than 15% and what measures were taken to address?

SUMMARY STATISTICS USED FOR ANALYZING COHORT STUDIES

1. Incidence = $\frac{\text{number of new cases of a disease over a period of time}}{\text{number of people at risk of developing the disease during that time}}$
(also called cumulative incidence)
risk

2. Prevalence = $\frac{\text{number of existing cases of a disease at a specified point in time or period of time}}{\text{number of people in the total population at that specified time}}$
disease burden

3. Relative risk (RR) = $\frac{\text{incidence in the exposed group}}{\text{incidence in the unexposed group}}$
(also called rate ratio or incidence density ratio, when person-time is in the denominator)

4. Attributable risk (AR) = (incidence in the exposed group) – (incidence in unexposed group)
(also called risk difference and excess risk)

5. Attributable proportion

a) Attributable proportion (exposed) =

$$\frac{\text{(incidence of disease in exposed) – (incidence of disease in unexposed)}}{\text{incidence of disease in exposed}}$$

(proportion of disease in the exposed that is attributable to their exposure)

b) Population attributable risk proportion =

$$\frac{\text{(incidence of disease in population) – (incidence of disease in the unexposed)}}{\text{incidence of disease in the population}}$$

$$= \frac{P(RR-1)}{P(RR-1)+1} \times 100$$ (version easier for use in calculation)

Where P= proportion of the population with the exposure, and RR= relative risk

(proportion of disease in study population that is attributable to the exposure and thus could be eliminated if the exposure was eliminated)

6. Number needed to treat = $\frac{1}{|AR|}$

Case-Control Study

Definition: A study comparing diseased patients to non-diseased patients, looking for differences in risk factors

Use: The study of any number of risk factors or etiologies for a single disease, especially a relatively RARE disease. Also good for studying outcomes which have a long latency period after exposure of interest

Outcomes measured: Odds ratio- ratio of odds of exposure among cases to that among controls; RR can be estimated if disease is rare

	Exposed	Unexposed
Cases	A	B
Controls	C	D

OR = $\frac{a/b}{c/d}$ = AD/BC

Odds=Risk/(1-Risk)

Odds exposure given dz: $\frac{a/a+b}{1-(a/a+b)}$ **= A/B**

Odds of exposure given no dz: $\frac{c/c+d}{1-(c/c+d)}$ **= C/D**

Limitation: Certain specific biases must be avoided, e.g., historically obtained data must be complete and accurate

-recall bias
-selection bias
-interviewer bias
-confounding

Questions to think about:

1. What kind of population do the cases represent?
2. Are the cases a valid representation of the disease or outcome in question or a subset of the population for whom responses are not typical?
3. Do the cases truly reflect individuals with the outcome of interest or are they a mixture of potentially unrelated conditions?

4. Are the cases and controls drawn from similar populations, differing only in the absence of disease?
5. Has matching or other techniques been used to reduce confounding?
6. Have any of the 3 other biases been introduced by the way the study was conducted?
7. Was the sample size large enough to detect the difference of interest?

** Select cases and controls very carefully
****Be wary of matching-

- Consider a study of head and neck cancer and smoking
- You decide to match on ETOH use because it is elated to smoking and cancer
- Assume correlation between smoking and ETOH use is perfect
- What would OR be?

	Smokers	Nonsmokers
Cancer	A	B
No cancer	C	D

Does Coffee Cause Pancreatic Cancer?

How should we select cases?	Cancer Registry
	Hospitals
	GI Registries
How should we select controls?	Random selection from community
	Patients with nonpancreatic cancer
	Patients hospitalized for illness other than cancer
	Patients from the practices of GI specialists

How should we assess exposure?

1. **Macmahon et al: Coffee and cancer of the pancreas (NEJM 1981)**
   Cases: Patients discharged with cancer of the pancreas
   Controls: Hospitalized patients with cancer cared for by GI specialists, or hospitalized patients without cancer cared for by GI specialists
   Exposure: # cups per day prior to "getting ill"
   → EOR (≥ 3 cups/day) = 2.7

   Comments:
   -controls may not have been drawn from the true source population. Many pancreatic cancer pts are diagnosed by MDs who are not gastroenterologists
   -controls may have higher prevalence of GI disorders and may have reported lower coffee consumption biasing EOR up and away from 1
   -exposure assessment was imprecise

2. **Wynder et al: Epidemiology of coffee and pancreatic cancer (Cancer Research 1983)**
   Cases: Patients admitted with cancer of the pancreas
   Controls: Hospitalized patients with any diagnosis that was not "related" to the biliary tree
   Exposure: usual # cups/day
   →EOR (≥ 3 cups/day) =1.0

   Comments:
   -controls had broader range of disorders
   -control group does not represent true source population?

3. **Macmahon et al: Coffee and pancreatic cancer (NEJM 1986)**
   Cases: Patients discharged with cancer of the pancreas
   Controls: Hospitalized patients with cancer cared for by GI specialists
   Exposure: # cups per day 1, 10, and 20 years prior to getting ill
   →EOR (≥ 3 cups/day 10 years before dx) =1.3 (ns)

   Comments:
   -Inadequate exposure assessment can markedly influence the EOR

Randomized clinical trial

Definition: A study in which the risk factor/exposure of interest is controlled by the investigator; randomization is generally used

Use: Most convincing demonstration of causality

Limitation: logistic and ethical difficulties, costly; loss to follow-up may be a substantial problem

Causality criteria:

a) coherence with existing information; biologic plausibility?
b) time sequence; cause precede effect?
c) Specificity
d) Consistency
e) Strength- magnitude, dose-response

Questions to think about:

1. What was the outcome of interest?
2. What was thought to be a meaningful difference in outcome?
3. How was the study population for the trial selected?
    a. exclusion criteria
    b. random vs volunteer
4. What were the groups demographic and health characteristics
5. Was the sample size decided prior to the study?
6. Did the subjects know what intervention they received?
7. Did the investigators administer the intervention and if so were they aware of the outcome status of the patients?
8. Did the individuals who measured the outcome know the treatment status of the study subjects?
9. Were the treatment groups similar with regard to known prognostic factors?
10. Were side effects recorded and reported?
11. Who was included in the final analysis?
12. Who was lost to follow-up? Did the individuals lost to follow-up differ from those who completed the study?
13. Was an intention to treat analysis done?
14. Were known risk factors accounted for in the analysis?
15. If the results were negative was statistical power addressed?

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann Intern Med 2001;134:657-662.

Altman DG, Schulz KF, Moher D, et al. The Revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663-694.