Designing a Good Study

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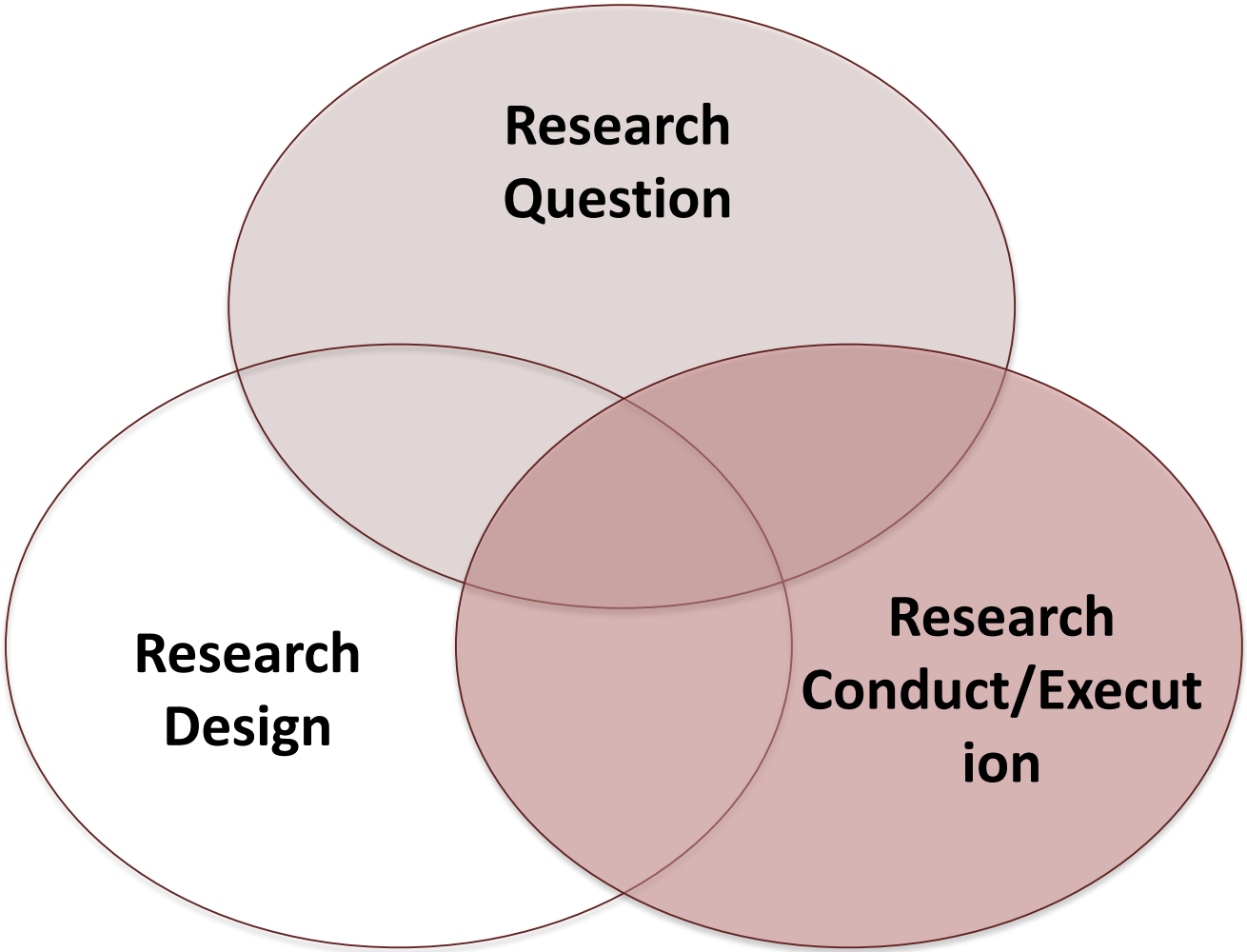
What makes a good study?



Research Question – Study Design

Non-Interventional (Observational) Study

•Frequency	How often does disease occur?
•Diagnosis	How accurate are diagnostic tests?
•Cause	What conditions lead to disease?
•Risk	What factors are associated with disease?
•Prognosis	What are the consequences of disease?

Interventional Study

•Treatment	How does treatment change the course?
•Prevention	Does an intervention prevent disease?
	Does early detection improve the course?

Fletcher et al. Clinical Epidemiology: The Essentials 1996

Developing a Research Question to a Research Project

- Start with a basic clinical question.

- Then, consider:
  - Is the question answerable?
  - Can internal validity be achieved?
    (Can the truth be obtained?)
  - To what extent is external validity (generalizability) achievable?
  - What will my circumstance permit?
  - What can I afford?
  - What is the best balance between “ideal” and “feasibility”?

Haynes et al. Clinical Epidemiology

Causality Criteria

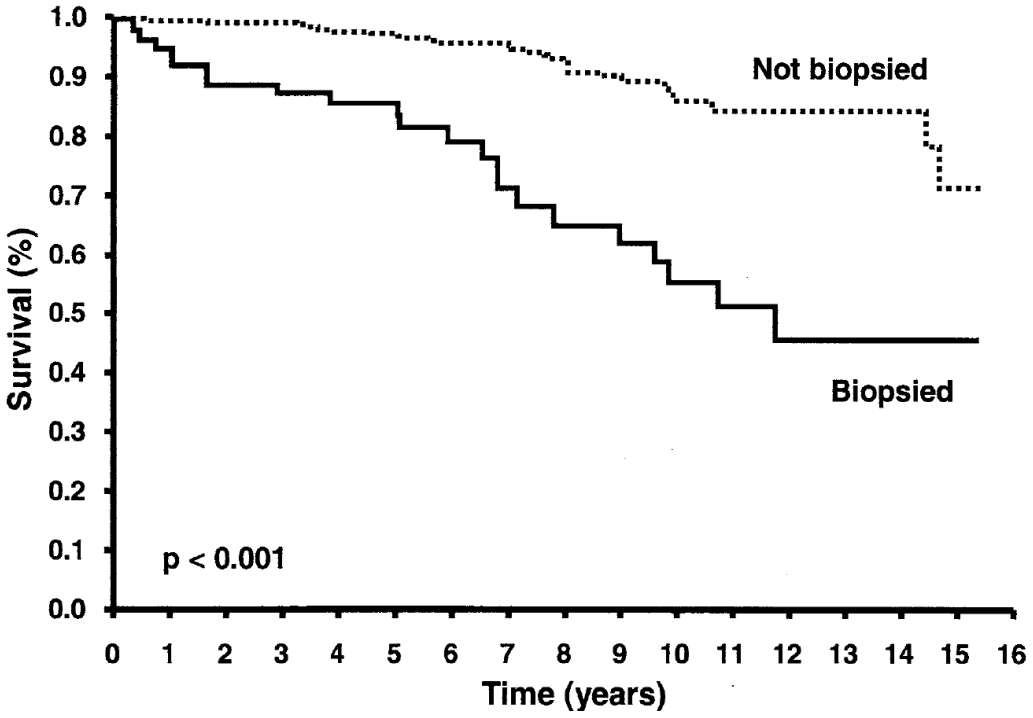
Criterion	Explanation
Temporality	Cause precedes effect
Strength	Large effect
Dose-response	Larger exposure associated with higher rate of disease
Reversibility	Reduction in exposure associated with lower rate of disease
Consistency	Repeated observation
Biologic plausibility	Makes sense based on available biological knowledge
Specificity	One cause leads to one effect
Analogy	Causality established for a similar exposure/disease

Epidemiology: Study of Causation

Design	Metric	Statistics
Observational Studies		
Cross-sectional	Difference in proportion	Chi-square
	Difference in distribution	t-test, ANOVA Wilcoxon, Kruskal-Willis
	Incidence/Prevalence	Poisson regression
Cohort	Time to event	Proportional hazards (Cox) regression
Case-control	Difference in proportion	Logistic regression
	Difference in distribution	Linear regression
Interventional Studies (Trials)		

(False) Association is everywhere…

- Liver biopsy and survival among community residents in Olmsted County with a diagnosis of NAFLD



	Bx	No Bx
Diabetes	42%	23%
Cirrhosis	9.2%	0.6%
Albumin <3.5g/dL	11%	3%

All p<0.05

Adams, Gastro 2005;113

Confounding

- A confounding variable correlates with both the predictor variable and the outcome variable
- Must be sought and eliminated using
  - Stratified analyses
  - Multivariable regression analysis
- Example (hypothetical):
  - Benefit of surgical resection for cholangiocarcinoma

	Alive	Dead	% Alive
Surgery	90	60	90/150 (60%) alive
No Surgery	60	90	60/150 (40%) alive

O.R. = 2.3 (Patients having surgery are 2.3 more likely to be alive)

Stratified Analysis

- It is likely that the analysis is confounded by disease stage.

	Alive	Dead	% Alive	OR
All Patients (n=300)				
Surgery	90	60	90/150 (60%) alive	2.3
No Surgery	60	90	60/150 (40%) alive	
Advanced stage (n=150)				
Surgery	10	20	10/30 (33%) alive	1.0
No Surgery	40	80	40/120 (33%) alive	
Early stage (n=150)				
Surgery	80	40	80/120 (67%) alive	1.0
No Surgery	20	10	20/30 (67%) alive	

Interaction (Effect Modification)

- Relationship between the predictor variable and outcome variable is modified by a third variable
- Important to identify
  - Stratified analysis
  - Multivariable analysis with interaction term
- Example (hypothetical):
  - Benefit of surgical resection for HCC

	Alive	Dead	% Alive
Surgery	90	40	90/130 (69%) alive
No Surgery	60	110	60/170 (35%) alive

O.R. = 4.1 (Patients having surgery are 4.1 more likely to be alive)

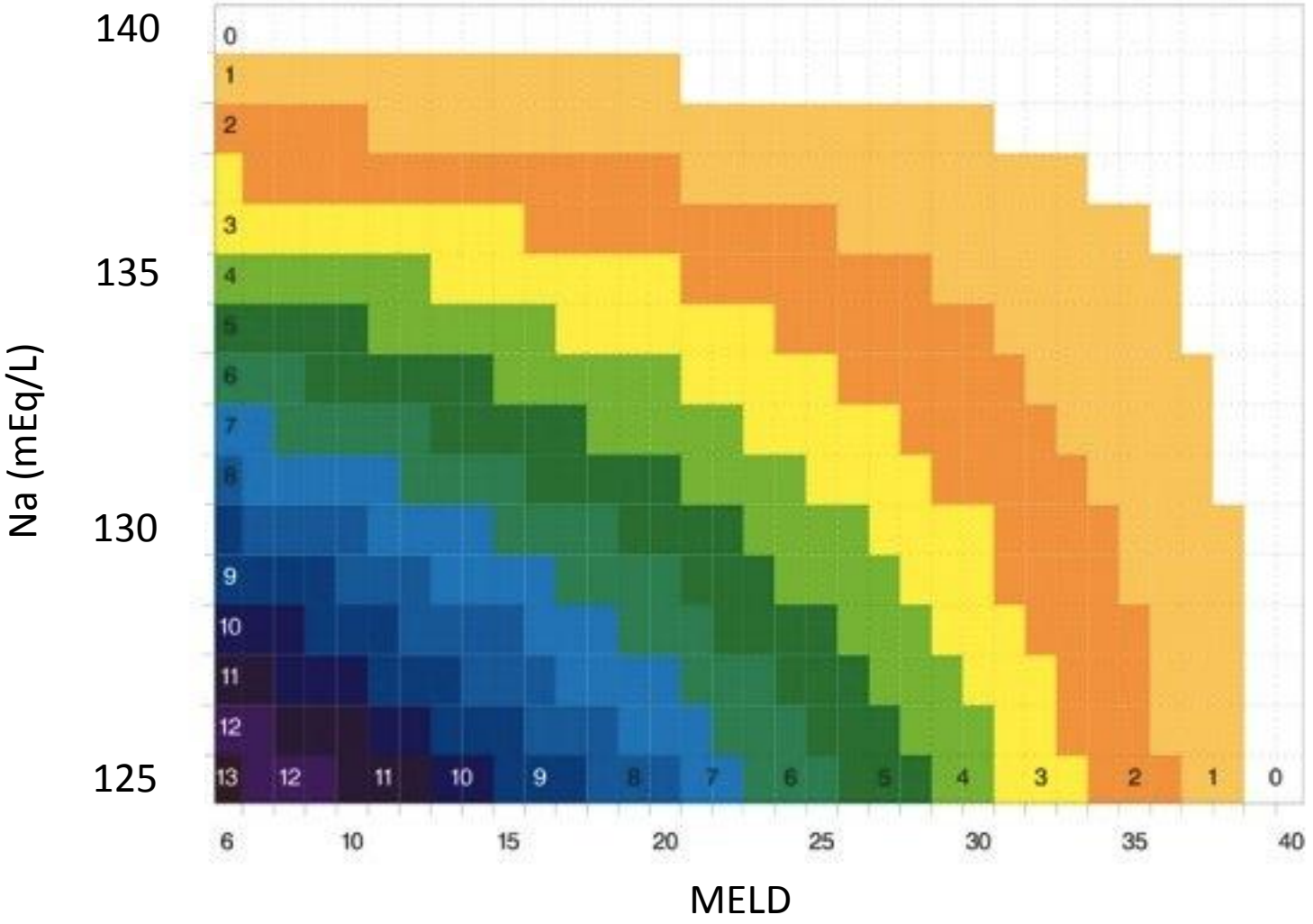
Stratified Analysis

- Is it possible that surgery is only effective in early stage HCC?

	Alive	Dead	% Alive	OR
All Patients (n=300)				
Surgery	90	40	90/150 (60%) alive	4.1
No Surgery	60	110	60/150 (40%) alive	
Advanced stage (n=150)				
Surgery	10	20	10/30 (33%) alive	1.0
No Surgery	40	80	40/120 (33%) alive	
Early stage (n=150)				
Surgery	80	20	80/100 (80%) alive	6.0
No Surgery	20	30	20/50 (40%) alive	

Real Life Example of Interaction

MELDNa = MELD - Na - 0.025*MELD*(140-Na) + 140



Kim NEJM 2008;1018

Feasibility

- Measurement issues
  - Accuracy
  - Precision
  - Generalizability
- Follow-up issues
  - Time
  - Money
  - Personnel
- Sample size
  - Needs to be addressed first not last
  - Work with a statistician
- $

Mentor

- Mentorship:
  - Necessary throughout academic career
  - Especially for junior scientists

- The ideal mentor
  1. Scientific competency
  2. Security
  3. Availability and willingness to mentor
  4. Willingness to listen
  5. Funding

- Look for a mentor outside your immediate area of clinical expertise

Collaborators

- Look for the same desirable qualities as mentors.

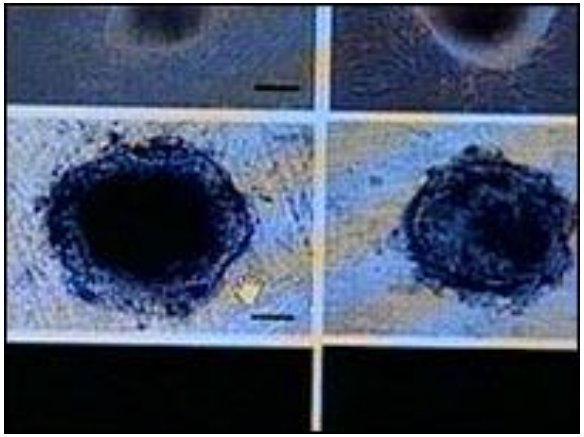
- Ask mentor identify appropriate collaborators.

- Effective collaboration
  - The right expertise
  - Mutual benefits
  - Trust and respect
  - Commitment
  - Chemistry

Integrity

- Ethical integrity:
  - First do no harm.
  - Be friends with IRB.
  - Pay attention to privacy issues

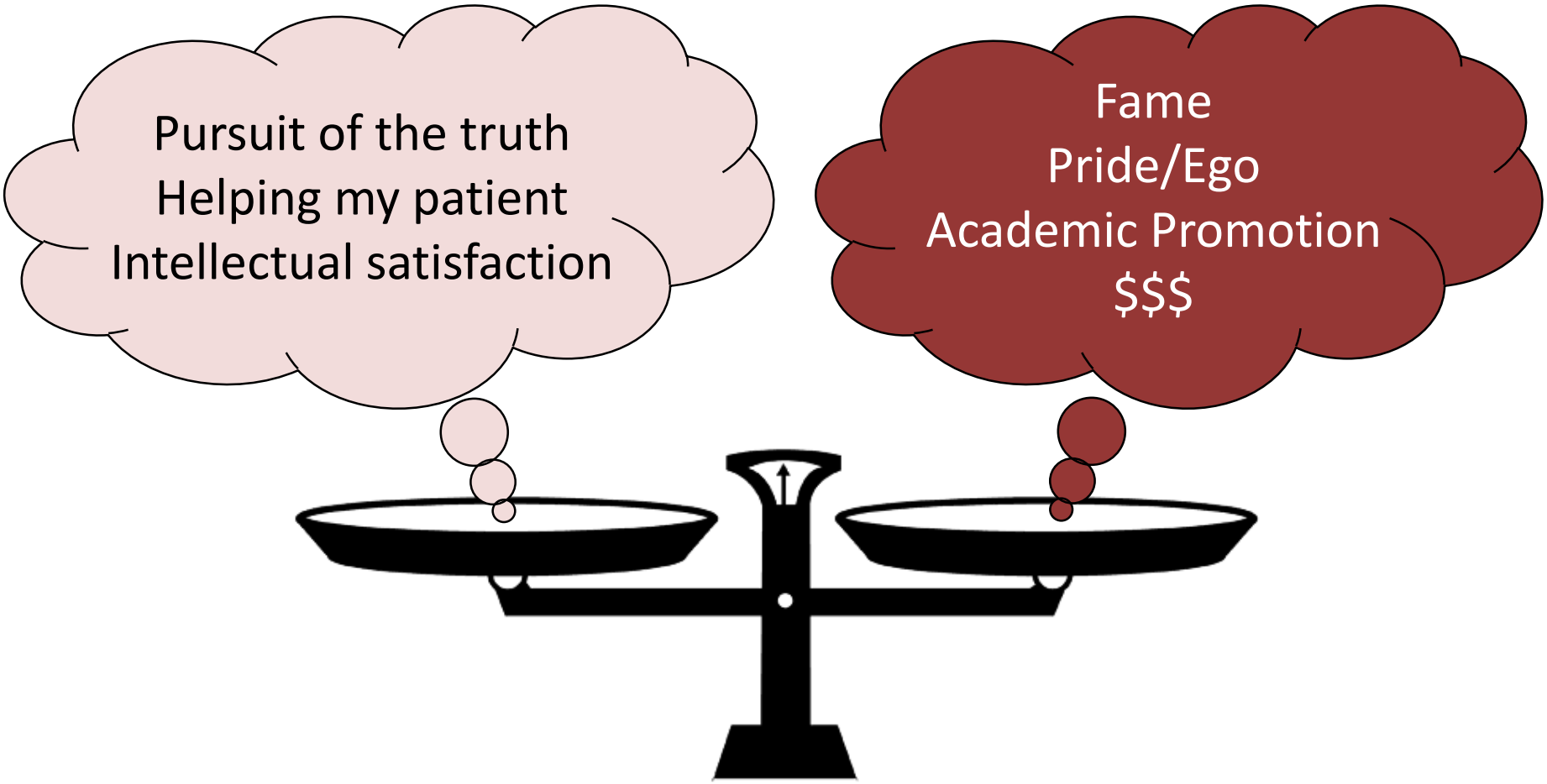
- Scientific integrity:
  - Impossible to regain once lost
  - Harm at many levels



Hwang science 2005;1777

Bottom Line

- Remember why you are doing this?



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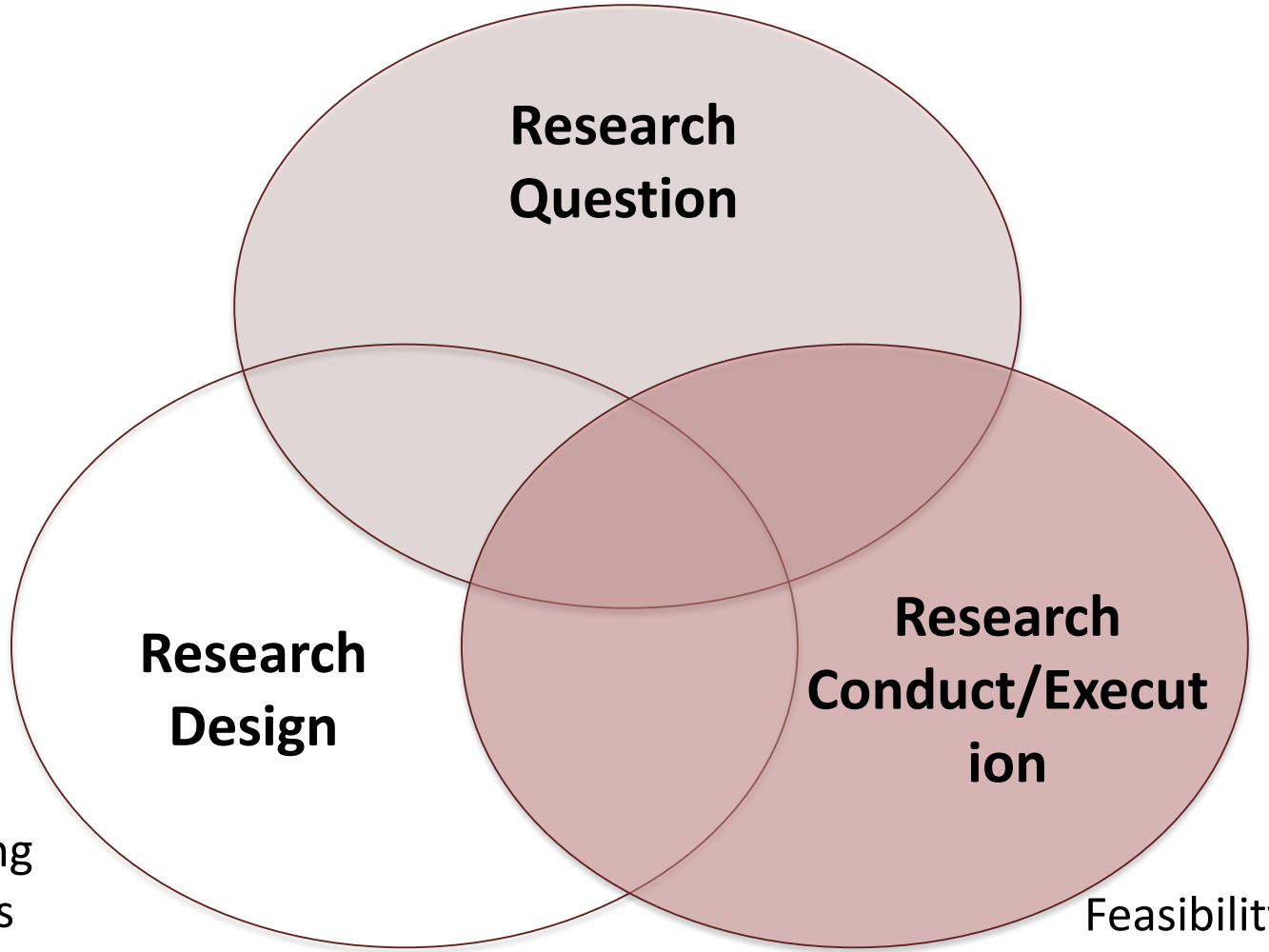

Confounding
Interactions
Biases

Feasibility
Mentor/Collaborator
Integrity