



Investigator-Driven Clinical Research

A McMaster Perspective

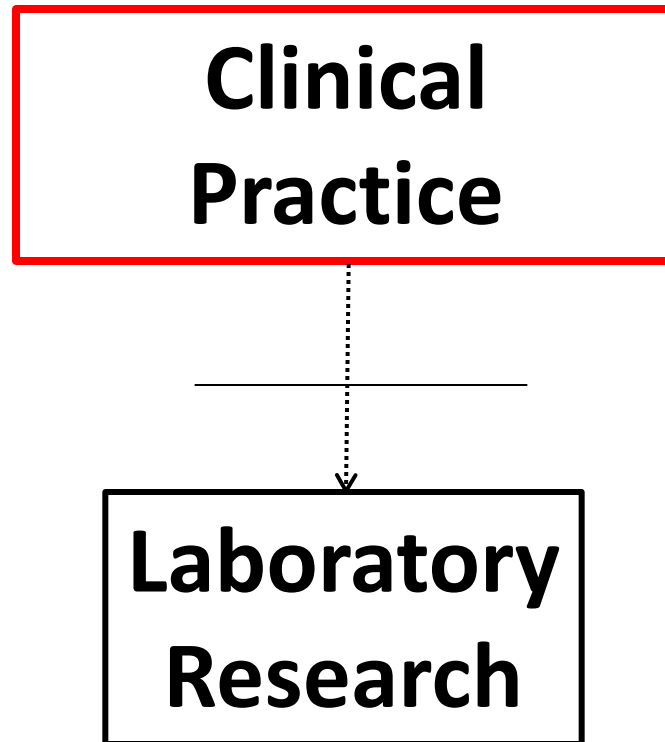
John Eikelboom
McMaster University

Key Questions

1. What does it take to be a clinical investigator?
2. Where do clinical research questions come from?
3. What else is required for successful investigator-driven clinical research?

**What does it take to be a
clinical investigator?**

Clinical Investigator in the 1960s



Spectrum of Research

1960s

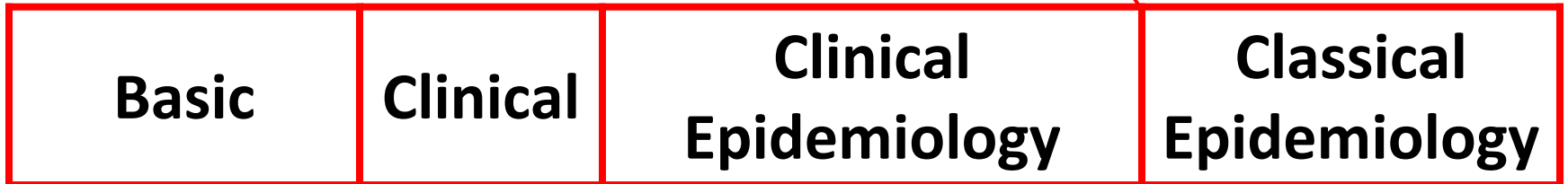


Spectrum of Research

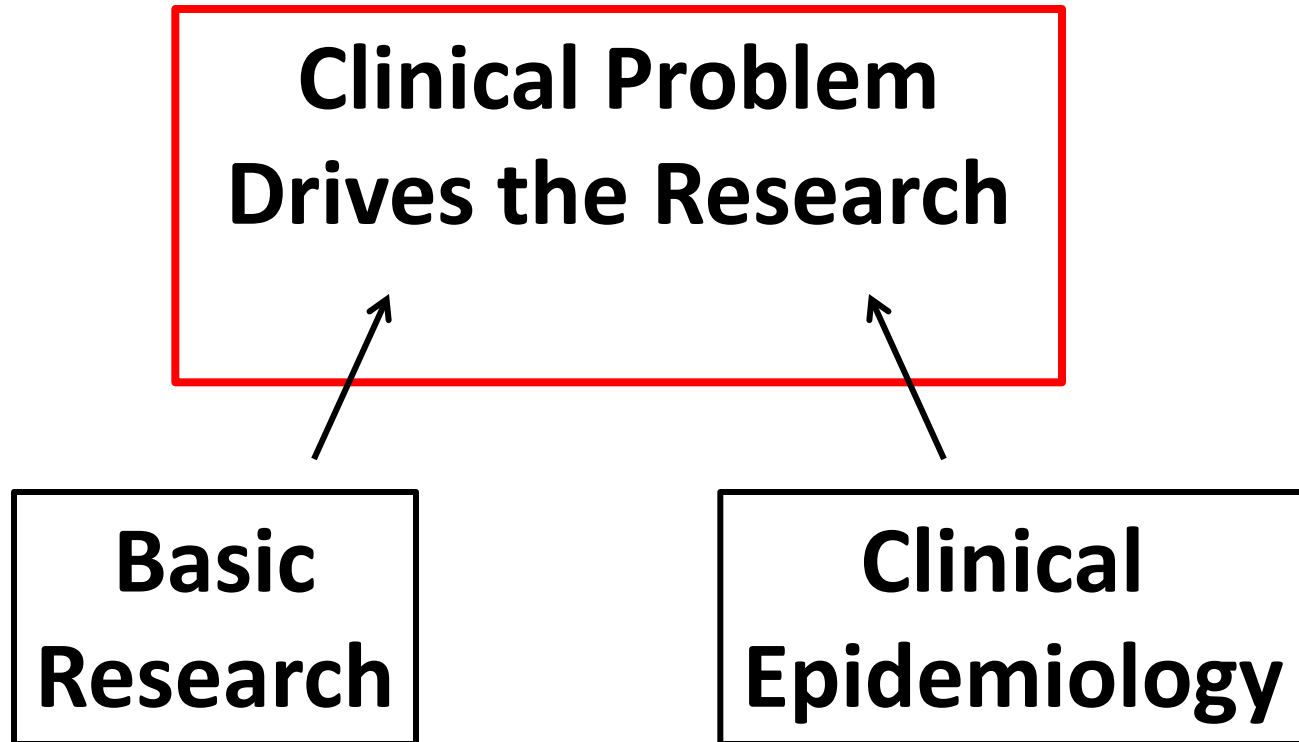
1960s



2010



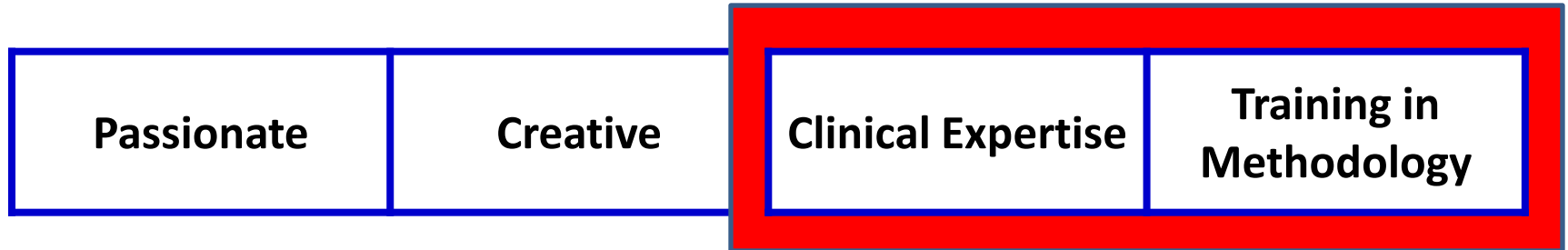
Clinical Investigator in Contemporary Times



The Clinical Investigator

Passionate	Creative	Clinical Expertise	Training in Methodology
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The Clinical Investigator



- Clinical expertise - patients are your laboratory
- Methodologic training – Clinical Epidemiology and Biostatistics Program

“Serve apprenticeship with an outstanding researcher and mentor”

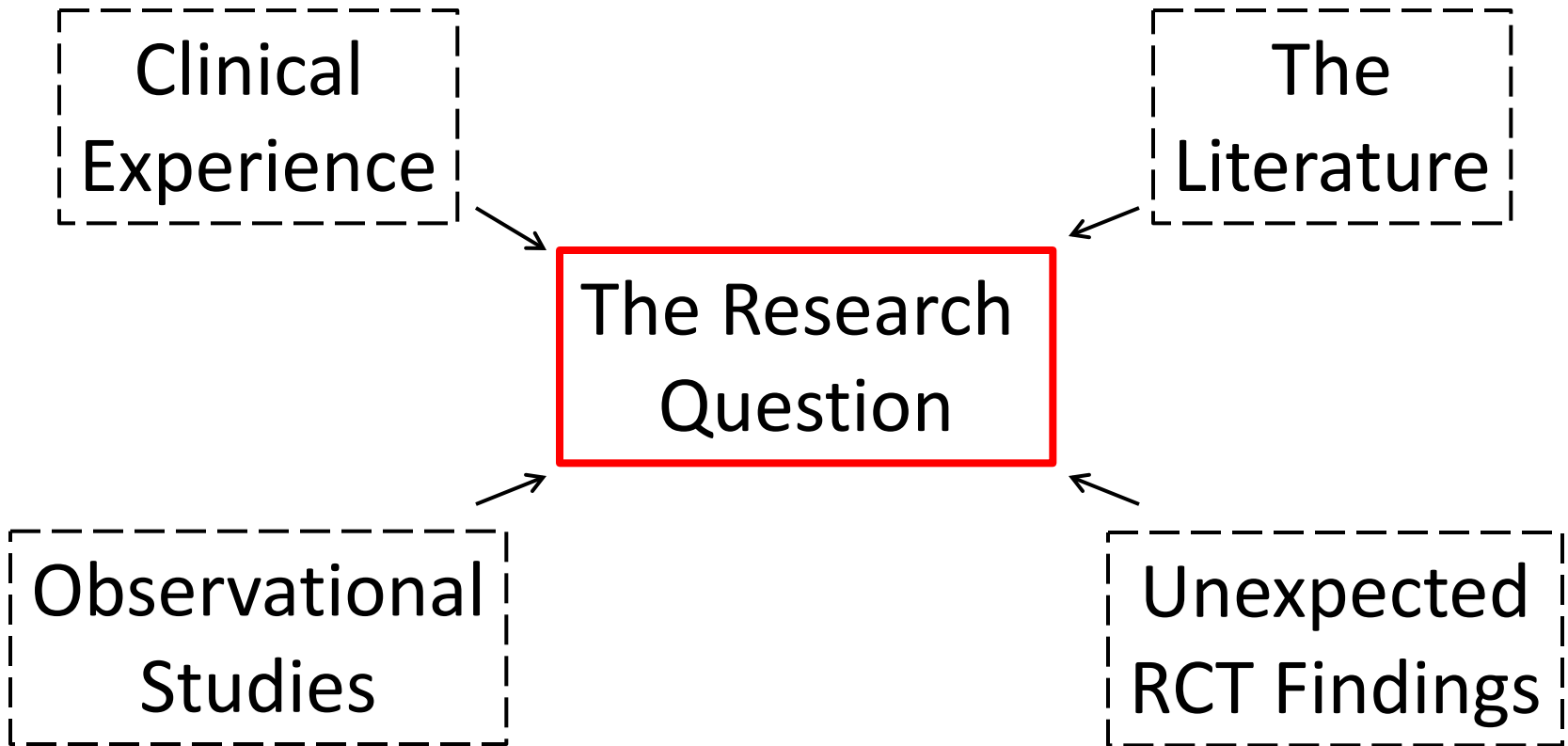
**Where do (good) clinical
research questions come from?**

The Question

If the question can be answered, will it provide:

- New information that will change practice?
- New information that will improve understanding of pathophysiology?
- Hypothesis-generating information that will form the basis of a more definitive study?
- Confirmatory information?
- Descriptive information?

Where do Clinical Research Questions Come From?



Question from Clinical Experience

- Aspirin is effective for prevention of cardiovascular events in ACS
- Some ACS patients receive low dose aspirin while others receive higher doses

Is 300-325 mg/d more effective than 100 mg/d for prevention of recurrent cardiovascular events in patients with ACS?

Question from Unexpected RCT findings

- More intensive antithrombotic therapy in patients with ACS reduces the risk cardiovascular events but at the cost of more bleeding
- In the OASIS-5 trial, fondaparinux compared with enoxaparin reduced the risk of recurrent vascular events and reduced bleeding.

Why did fondaparinux reduce bleeding?

Question from Observational Studies

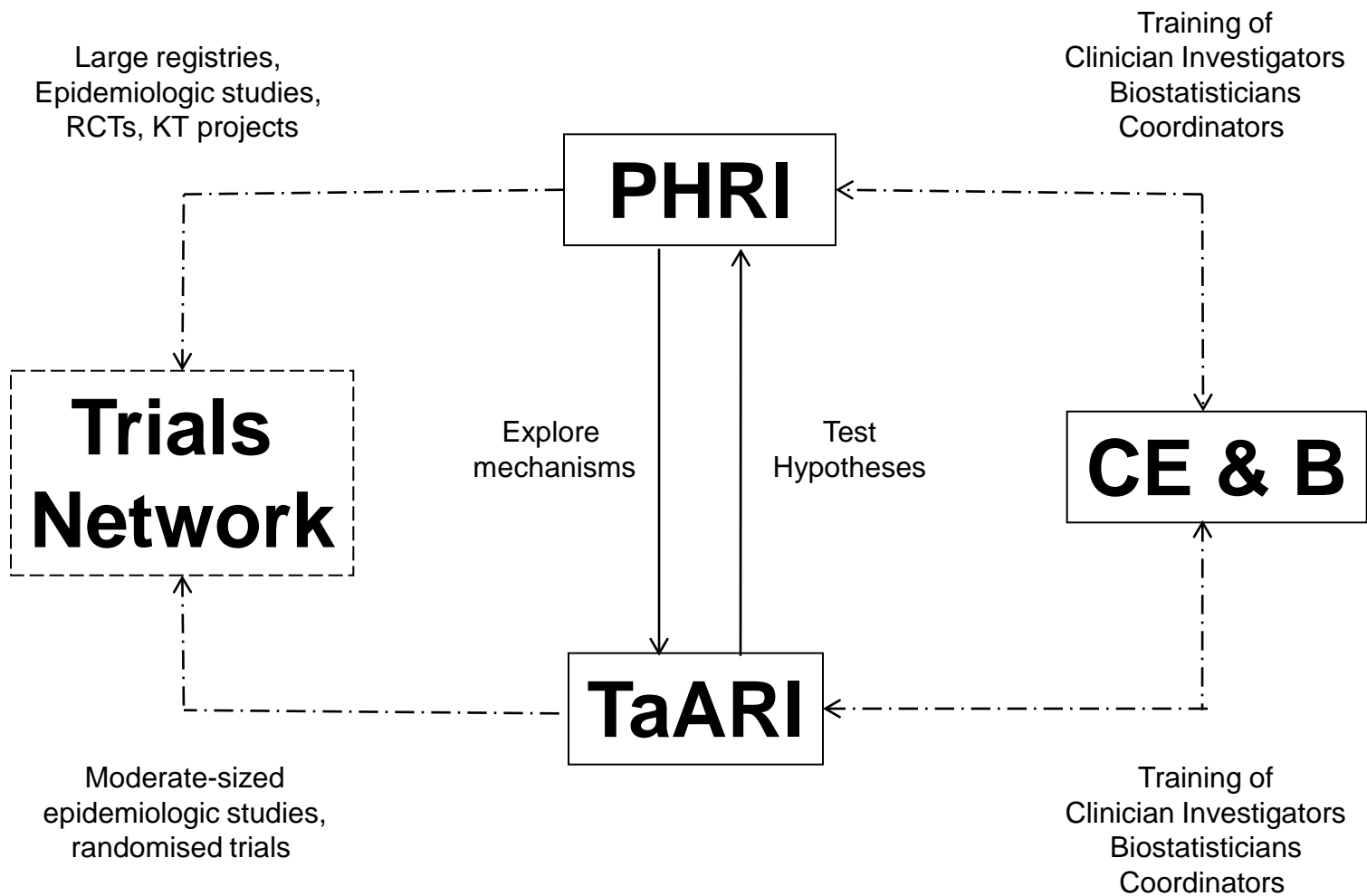
- Homocysteine levels in blood independently predict cardiovascular events
- Blood levels can be readily lowered with safe and inexpensive B-vitamin treatment

Does treatment with B-vitamins prevent cardiovascular events?

**What (else) is required to
reliably answer a good
clinical question?**

A Tale of Two Cities

Characteristic	Perth, Australia	Hamilton, Canada
Country Population	20 million	30 million
Regional Population	1.5 million	0.5 million
Medical Schools	1	1
<i>Researchers</i>	Few	Critical mass
<i>Training Capacity</i>	Limited	CEB program
<i>Expert Personnel</i>	Few	Extensive pool
<i>Infrastructure</i>	Limited	Well established
<i>Funding</i>	Challenging	Substantial



Challenges of Current Randomised Controlled Trials

- Restrictive regulatory requirements
- Complex trial design
- Limited expertise, infrastructure, training
- Lack of trial funding
 - randomized trials dominated by industry-sponsored studies
 - neglect of diseases, interventions, outcomes, populations, mechanisms

Synergies Between Industry and Investigator-initiated Research

- Factorial design
 - Address generic questions e.g., vitamin E in the HOPE trial, aspirin dose in the CURRENT trial
- Scientific substudies
 - Explore diagnostic, pathophysiologic or prognostic questions e.g., pharmacogenomics of warfarin therapy in the RE-LY trial

Synergies Between Industry and Investigator-initiated Research

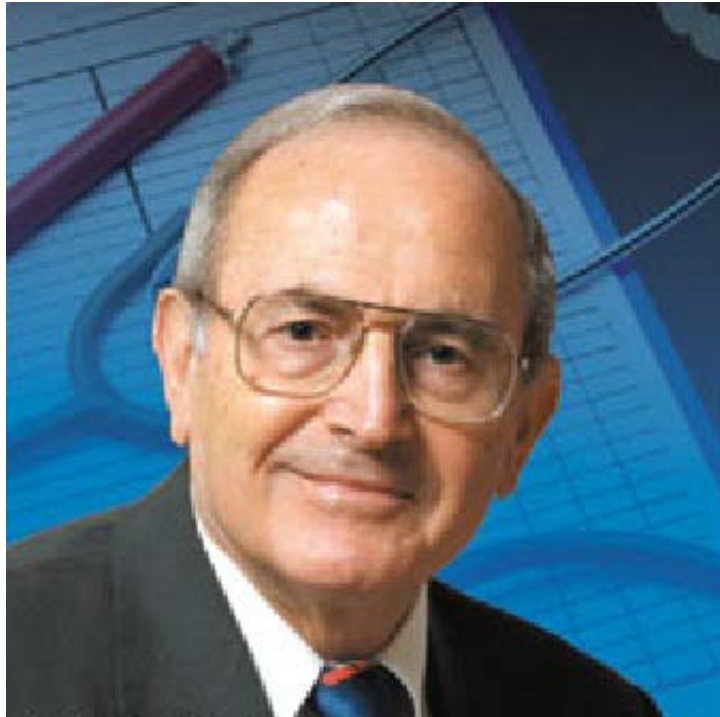
- Implement epidemiologic studies concurrently with RCTs
 - DREAM trial and EpiDREAM study
- RCTs inform the design of future studies
 - POISE-1 led to the VISION cohort study
 - RE-LY trial and RE-LY ABLE registry

Potential Solutions

- Simple trial design
- Streamline trial regulations
- Pragmatic monitoring
- Innovative trial design
- Long term investment in expertise, infrastructure and training
- Increased funding for investigator-initiated randomised controlled trials

Conclusion

- Trained clinical investigator
- A good question
- Expert personnel
- Research Infrastructure
- Funding



Jack Hirsh
Professor Emeritus
McMaster University

“...be passionate
about your
research, train with
the best in your
area of interest and
spend as long as it
takes....”