Investigator-Driven Clinical Research

A McMaster Perspective

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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

Clinical Practice

Laboratory Research
Spectrum of Research

1960s

Basic  Clinical  Epidemiology
Spectrum of Research

1960s

Basic  Clinical  Epidemiology

2010

Basic  Clinical  Clinical Epidemiology  Classical Epidemiology
Clinical Investigator in Contemporary Times

Clinical Problem Drives the Research

- Basic Research
- Clinical Epidemiology
The Clinical Investigator

- Passionate
- Creative
- Clinical Expertise
- Training in Methodology
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?

Clinical Experience

The Literature

Observational Studies

Unexpected RCT Findings
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?
More intensive antithrombotic therapy in patients with ACS reduces the risk of 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Perth, Australia</th>
<th>Hamilton, Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country Population</strong></td>
<td>20 million</td>
<td>30 million</td>
</tr>
<tr>
<td><strong>Regional Population</strong></td>
<td>1.5 million</td>
<td>0.5 million</td>
</tr>
<tr>
<td><strong>Medical Schools</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Researchers</strong></td>
<td>Few</td>
<td>Critical mass</td>
</tr>
<tr>
<td><strong>Training Capacity</strong></td>
<td>Limited</td>
<td>CEB program</td>
</tr>
<tr>
<td><strong>Expert Personnel</strong></td>
<td>Few</td>
<td>Extensive pool</td>
</tr>
<tr>
<td><strong>Infrastructure</strong></td>
<td>Limited</td>
<td>Well established</td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td>Challenging</td>
<td>Substantial</td>
</tr>
</tbody>
</table>
Large registries, Epidemiologic studies, RCTs, KT projects

PHRI

Explore mechanisms

Test Hypotheses

TaARI

Moderate-sized epidemiologic studies, randomised trials

Trials Network

Training of Clinician Investigators
Biostatisticians
Coordinators

Training of Clinician Investigators
Biostatisticians
Coordinators

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

Jack Hirsh
Professor Emeritus
McMaster University