The pathway from basic research to practices and policies

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The inability to overcome the death valleys is due to multiple factors, including the lack of methodological support.
The context of health research

- Development/evaluation of:
  - Drugs
  - Medical Devices
  - Diagnostics tests
  - Therapy protocols
  - Health Services Practices
  - Health status

- What is Clinical Research?
  - Study of drugs, devices, diagnostics and therapies in human subjects with the intent to discover potential beneficial effects and/or determine its safety and efficacy.

- Who does it involve?
  - Collaboration of many personnel with a variety of skills e.g.; medics, scientists, statisticians, nurses, data managers, pharmacists etc.
1 In 10,000 Succeed (to market/practice)

**Average Time:** 10-18 Years
**Average Cost:** €500 Million to €2 billion
(<20% of sales)

100,000 Examined by FDA and similar bodies
(Preclinical Evaluation)

100 Tested in Humans

10 Marketed Drugs

2 Drugs Return a Profit
Figure 1: The Drug Development Process

- **Molecule Discovery & Characterisation**: Period of discovery & learning about the molecule's chemistry.
  - Lab tests to understand if & how the molecule might work.
  - Tests in complex systems (animals) to understand if & how the molecule works in models, & potential dose.
  - Phase I - Is the molecule safe to be given to humans & at what dose? 20-100 people.
  - Phase II - Does the molecule work in humans? 100-500 people.
  - Phase III - Collecting more information on efficacy and safety of the molecule. 500-5000+ people.
  - Phase IV - More data collected on safety or 'real-use' of molecule. 100's - 1000's people.

- **Pre-Clinical**: Lab & Animal Tests
  - 2-5 years
  - 10 000 molecules

- **Clinical**: Human Tests
  - 5-8 years
  - 5 molecules

- **Review +/- Approval**: 1-2 per country

- Total **Number of Molecules**: 1
- Total **Number of Years**: 1-2
Diagnostics and Medical Devices Development

Basic Research → Prototype Discovery and design → Pre-clinical development → Phase I → Phase II → Phase III → FDA Approval and Launch

Clinical Development

Pre-Validation & Validation → Registration

Biomarkers Discovery

Diagnostic Development
A well thought out study should have the following methodological documents completed before recruitment/data collection starts:

- Study/Research Protocol
- Statistical Analysis Plan
- Data Management Plan
- Study Report Plan
In the HRB Application form...

- all stages of the study design - rationale for sampling strategy, justification of sample size and power calculation, full details on the design chosen to evaluate an intervention, methods of data collection, measures and techniques of analysis for quantitative and qualitative designs.
Table of Contents

- Study design
- Analysis Population Subsets
- Primary And Secondary Variables
  - i. Efficacy
  - ii. Safety
  - iii. Exploratory
- Demographic and General Characteristics
- Statistical Methodology
- Statistical Software
- Mock Tables and Listings
- Appendix
A great obstacle to a better health system (drugs, therapies, services etc.) is the difficulty in estimating the costs and benefits of any intervention.

A cost and benefit study start with a research question!

Fundamental conceptual assumptions:
- What do we include as costs and benefits?
- ‘How far’ do we measure the impact of an intervention? i.e. Direct and indirect benefits
- What methodology do we use to quantify them?
- Who should take the burden of such costs? The government, the industry or the patient?
Direct and Indirect Benefits and Costs

*Monetary value* of key parameters:

- Life
- Better quality of life and loss of life
- Prevention of late stage of disease vs the cost of implementing a new therapy
- Impact on families, children..
- Social costs

Methodologies are driven by policies and practices.

Many examples in the literature: Sir Nicholas Stern (UK) 2006, Orley Ashenfelter (Princeton) and Michael Greenstone (Chicago) 2002.
International Guidelines on Methodologies

- Minimum accepted standards to guarantee entry to next phase

- EMEA & ICH Guidelines:
  - ICH E9: Statistical Principles of Clinical Trials

- Bayesian Statistics for Medical Devices:

- FDA, Clin-Stat Guidance 1988

- See recommendations from HRB applications