

FUNDAMENTALS OF RESEARCH

Ask an important QUESTION

And

Answer it RELIABLY.

Why do We do Clinical Research? What are the Approaches?

WHY DO WE DO CLINICAL RESEARCH?

To answer important questions that can improve patient/people/population health

Important:

	<u>More</u>	<u>Less</u>
No. affected	Lots	Few
Type of outcome	Serious	Non-serious
Applicability	Broad	Narrow
Extrapolatability	Wide	Limited

A question is likely to be more important if it deals with a common condition, affects a clinically important (major) outcome, and the results are widely applicable, and there are general lessons for individuals not included in the study.

Where Do Questions Come From?

- Literature: Unanswered questions from previous studies
- Large disease burden which may be increasing, e.g. an epidemic
- Clinical experience: Bleeding in the CCU
Hi rates of post-op MI.
- A lack of agreement (uncertainty) re an issue
 - is the disease rate constant, going up, or down?
 - what causes it?
 - how can it be reduced/avoided?

“It is not the answer that enlightens,
but the question”

Eugene Ionesca

Good questions rarely are “light bulbs”, but more often
a results of “iterative” thinking

Good questions “grow”.

What are the Types of Questions?

1. How common is a disease/condition? (i.e. burden)
 - Prevalence (MI/Stroke/Cancer/Type of Cancer/BP/Smoking)
 - Incidence
2. Can I diagnose the condition with high certainty?
3. What are its outcomes? (prognosis/natural history)
 - Disease progression (surrogate)
 - Clinical progression
 - Major events (hospitalization, morbidity, deaths)
 - Disability/QOL
 - Economic impact
 - on the individual
 - on the health care system
 - on society

What are the Types of Questions?

4. What are the causes of the disease/condition?
5. Can we modify the causes and change the outcomes?
 - before the disease occurs
 - after the disease occurs
6. Is it “worth” implementing the intervention?
7. Can I apply it in practice and will I get similar results?

Registries

Hospital based

- specialized
- Non-specialized

Community-based

- MI
- Stroke
- Cancers

Follow patients prospectively for key outcomes

Useful step:

1. Documenting practice patterns
2. Event rates
3. Types of patients eligible for a specific trial

Interventions and Their Evaluation

Clinical Outcomes:

-Effect size to be detected needs to be several times the size of the errors of the methods used for evaluation

Interventions and Their Evaluation

Errors: Systematic:

- Failure to randomize
 - biases in allocation of the therapies
 - biases in other treatments
 - biases in follow-up approach
- Failure to blind
 - biases in outcome evaluation (PROBE vs Open vs Blinded design)
- In RCTs, failure to conduct an intention to treat analysis
- Emphasizing subgroup analyses, especially data-derived subgroups (of patients or outcomes, e.g. ART)
- Failure to consider ALL the trials (all the evidence)

WHY RANDOMIZE?

- Randomization tends to equalize both measured and unmeasured (including unknown) risk factors.
- Randomization tends to cushion the effects of “noises” and “non-systematic errors” and even sloppiness as they are likely to occur to a similar extent across the two groups.
- Randomization provides the basis for statistical comparisons as any differences are real or due to chance(which is quantified by the “p- value”).

Errors

Random errors: “Noise”
Inadequate nos of events
Play of chance

If effect sizes are VERY large, or if outcomes are invariable, no need for RCTs :

- e.g. - Defibrillation for VF vs ICD to prevent SCD
- TB meningitis vs pulmonary TB
- early days of penicillin
- oral rehydration therapy

If effects are MODERATE or MODEST (but still humanly worthwhile), then:

- Avoid all systematic errors
- Minimize random errors:
 - Large number of events
 - lots of patients
 - High, rather than low risk
 - Long, rather than short follow-up

Theoretical Example of a Trial Post-MI of a Treatment that Reduces Mortality Risk by 20%

	Active 1000	Control 1000	RRR	
Trial A	80 (8%)	100 (10%)	20%	NS
Trial B	70 (7%)	110 (11%)	35%	0.001
Trial C	90 (9%)	90 (9%)	0%	-
Total (3000 v 3000)	240 (8%)	300 (10%)	20%	0.01

Given that Most Treatments in Chronic Diseases Reduce Major Events by Only 15% to 20%, We Need Trials of:

>600 events	to detect a	20% RRR reliably
>1000 events	to detect a	15% RRR reliably
>2000 events	to detect a	10% RRR reliably

How can Such Large Trials be Achieved with 1000 to 2000 events at an Affordable Cost?

1. Very large trials at modest effort per subject:

-simplify enrollment -wide eligibility

-simple data collection

-simplify follow-up -few if any special tests

-clear major outcomes - easy/unbiased evaluation

ENSURE INTEGRITY OF RANDOMIZATION,

ENSURE ADHERENCE AND UNBIASED EVENT

ASCERTAINMENT

How can Such Large Trials be Achieved with 1000 to 2000 events at an Affordable Cost?

2. Meta-analysis:

-Bring key data together from ALL relevant trials

Useful – meta-analyses of small trials → develop large trials

MA of Moderate sized trials → overall clear effect

Individual Large trials → overall clear effect

MA of Large trials → overall clear effect

+

reliable subgroup effects

Internal Validity v External Validity

THREE KEY PRINCIPLES:

1. In the absence of clear indications/contraindications
 - quantitative interactions are common, whether detected or not
 - unanticipated qualitative interactions are generally spurious, so do not believe it, even if you observe it! (e.g. PRAISE)

Internal Validity v External Validity

THREE KEY PRINCIPLES:

2. Never do a trial/study in which internal validity cannot be assured.
3. External validity (generalizability) depends on:
 - a) how narrow or broad the population included in the trial is
 - b) How internally consistent the results are
 - c) Epidemiology
 - d) Separately apply efficacy and safety to other populations (using ?decision analyses)

Answering Important Questions in a Stepwise Fashion

ISIS-1: BB in AMI

1. Develop measures of infarct size in humans and validate it (n=60)
2. Pharmacokinetics of oral vs IV β -blockers (n=50)
3. Pilot study of 477 patients
4. ISIS-1: 16,000 study with mortality as the outcome
Steps 1 to 4 took 11 years
5. Do BB work in a broader and higher risk population?(COMMIT).....another 5 yrs..!

Lesson: Breakdown a Question Into Answerable Steps and Tackle Them Systematically

What you can do at a specific time depends upon:

- State of previous knowledge
- Resources: People, network, infrastructure
- Funds
- Your experience, training and reputation
- Your own motivation and passion
- Your ability to focus and to prioritize

Answering important generic or orphan questions with few resources

- Factorial designs(one question that is “fundable” and a generic interesting question: HOPE and vit E, CREATE and GIK, ASA dose in ACS)
- Substudies (eg partial factorial designs: TIMACS, RIVAL)
- Obtain blood or urine (or cog measures) for future analysis to learn more about the disease and its predictors(ASA resistance, clopidogrel polymorphisms,etc).

How each of us can contribute to research and generating knowledge ?

- By doing what we can in our own settings, with limited resources...(water supply project in Mallur).
- By collaborating with others with like minded ideas.
- By being good organizers (locally, nationally and internationally).
- By sharing ideas, resources and enthusiasm (INTERHEART was conducted on a shoe string budget that was “stretched” across the world due to common goals to answer an important question, friendship and genuine collaboration).
- By leading/participating in the development, conduct, reporting and dissemination and application of results.

Training to be a good researcher.

- Needs more years than to become a good clinician.
- Work with generous people and successful teams.
- Open to ideas (insight and intuition), yet being focussed....need tremendous initiative...nothing comes/is given to you..!
- Need time to think....!
- Persistence, passion and commitment..
- Learning from unexpected results and understanding mistakes and bounce back from failures.
- Ability to write well and persuasively (protocols , publications, etc)...practice, practice, practice..!

Why do research?

- You must be mad, a sadomasochist, little to do, or a failed clinician.
- You are passionate about reliably answering an important question.
- You want to continue to satisfy your curiosity.
- You want to make a lasting difference.
- You want to be a child forever, never grow up, and forever to be an adventurer and explorer...think of a lifetime of being Sherlock Holmes or Indiana Jones!

Wrong reasons to do research

- You have failed at everything else.
- Making lots of money (individuals, corporations, CROs).
- You want to be famous.

Why do WE primarily do research?

- To solve important questions, and make a LASTING difference.
- To have fun through intellectual stimulation, by discovering, by being able to “go where no man has gone before”(Star Trek), “to dream the impossible dream” (Don Quixote).
- To work with interesting and passionate people.
- To pass on our knowledge, experiences...deep satisfaction through sharing...” Knowledge is one of the few things that you can share without it being diminished”
- GREAT ACHIEVEMENTS ARE ALWAYS TEAM EFFORTS