The characteristics of your trial participants are important – and in ways that you may not even know about.

Research Participant Selection

How do you decide which participants to study?

You often – but not always - have an interest in a particular disorder or population to begin with. This is where you START (not end).

How do you decide how generalizable the participant sample should be?

How do you ensure that you’re studying who you want to study?

It's all in the details…
General Outline

- Why do you need to think about participant selection factors?
- What factors are important to consider?
- An example – the ENRICHD Trial
- General conclusions

Why do you need to think about participant selection?

- It can clarify your question
- It can help clarify study design
- It will determine your ability to generalize
- It will impact feasibility
- It will impact your outcomes
- The specific decisions you make regarding who you study will markedly influence the causal inferences you can make

The Research Continuum of a Clinical Trial (#1)

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Efficacy</td>
<td>Effectiveness</td>
<td>Post-marketing</td>
</tr>
<tr>
<td>Dose-ranging</td>
<td>Highly controlled</td>
<td>Less control</td>
<td>Real-life</td>
</tr>
<tr>
<td>Healthy people</td>
<td>Selected Patients</td>
<td>All patients</td>
<td>Community</td>
</tr>
<tr>
<td>Very Small</td>
<td>Small</td>
<td>Big</td>
<td>on-going</td>
</tr>
</tbody>
</table>
The Research Continuum of a Clinical Trial (#2): Translational Perspective

Are specific genetic signatures associated with risk of atherosclerosis?

What is the predictive value in individuals at risk?

Does testing reduce incidence or improve outcomes of atherosclerosis?

T0 Identify problems
Basic research

T1 Foundational research

T2 Observational Phase I

T3 Observational Phase II

T4 Dissemination & Implementation

Practice to population

Is there an association between these specific alleles and atherosclerosis?

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Internal vs external validity – a delicate balance
The Balance Between Internal and External Validity

<table>
<thead>
<tr>
<th>Risk of Type I Error</th>
<th>Risk of Type II Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>External Validity</td>
<td>Internal Validity</td>
</tr>
<tr>
<td>Maximize Generalizability</td>
<td>Maximize Control</td>
</tr>
<tr>
<td>Across participants</td>
<td>History effects</td>
</tr>
<tr>
<td>Across situations</td>
<td>Bias of all sorts</td>
</tr>
<tr>
<td>Across time and place</td>
<td>Experimenter effects</td>
</tr>
<tr>
<td></td>
<td>Measurement effects</td>
</tr>
</tbody>
</table>

Internal and external validity – which is more important?

The balance you strike between internal and external validity in designing your study (ie, who your participants are) depends on what you worry about the most.

And what you worry about the most depends in large measure on where your question lies on the research continuum.

Why do you need to think about participant selection?

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Feasibility

- Access to research participants with the desired demographic and clinical characteristics
- Likelihood of adherence
- Ethical questions – randomization to placebo, adverse event rates, participant burden, vulnerable participants. Consider for all arms
- Timing of intervention (acute post-event, pre-event, etc.)

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Selection of Outcomes

- “Hard” outcomes
  - Morbidity
  - Mortality
- “Medium” outcomes
  - Resvascularization (e.g., CABG, PTCA)
  - Hospitalizations
- “Soft” outcomes
  - Pain/symptoms
  - Quality of Life/PROs
- Intermediate (biomarkers/surrogate measures)
- Combined outcomes
How does selection of participants influence outcomes?

- Are the targeted outcomes feasible to measure, given participant characteristics (e.g., stage of disease)?
- Can they change within the parameters of the trial, given participant characteristics?

Example: Measuring "hard" CV endpoints in 50-year-old healthy women with moderate BP elevation would not be feasible.
Planning to measure change in carotid artery IMT over the course of a 6 month trial would not show differences over time.

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Factors to consider in participant characteristics

- Entry Criteria
  - Inclusionary
  - Exclusionary
  - Target of the intervention (e.g., individual, dyad, caregiver, health care delivery system, etc).
- Context
- Access
- Recruitment & retention
- Adherence

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Factors to consider- Entry Criteria

Inclusionary Criteria – main purpose is:
- for targeting participants likely to be relevant to your outcomes
- for reporting/CONSORT
- for balancing between-participant variance

Ex: In a study of a new treatment for migraine, inclusionary criteria might include the type, duration, & frequency of migraine attacks, and would stipulate the specific classes of other medications that may be used.
Factors to consider - Entry Criteria

- Exclusionary Criteria – main purpose is:
  - safety
  - control/confounding
  - feasibility

  *Ex: In a study of a new medication for the treatment of hypertension, it may be reasonable to exclude those with advanced heart failure (safety), those with diabetes (confounding), and those who are bed-ridden (feasibility)*

When should entry criteria be determined?

EARLY! Before the first participant is recruited, before the IRB approves (sees) your protocol, before the NIH sees and funds your study.

Stipulating entry criteria is a key place for unintentional bias to emerge. Determining these factors well before recruitment minimizes this bias.

Factors to consider in participant characteristics

- Entry Criteria
  - Target of the intervention (e.g., individual, dyad, caregiver, health care delivery system, etc).
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“To different degrees, all causal relationships are context dependent, so the generalization of experimental effects is always at issue”

Shadish et al., 2002
The MAPEC Study (Ambulatory BP monitoring for prediction of CV events)

Factors to consider in participant characteristics

- Entry Criteria
  - Target of the intervention (e.g., individual, dyad, caregiver, health care delivery system, etc).
  - Inclusionary
  - Exclusionary
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- Recruitment & retention
- Adherence

Patient selection – Access

- Access to participants should be considered early in the planning phases
- Often requires building an interdisciplinary team
- May require multiple sites
- Generally should not include your own patients or practice
Factors to consider in participant characteristics

- Entry Criteria
  - Target of the intervention (e.g., individual, dyad, caregiver, health care delivery system, etc).
  - Inclusionary
  - Exclusionary
- Context
- Access
- Recruitment & retention
- Adherence

Recruitment and Retention

- Critical for success of a trial
- Respondent burden
  - Assessments
  - Intensity, duration and complexity of treatment
- Health of participant
- Logistics – transportation, etc.
- Intention to treat
Patient Selection - Adherence

Measure it.
Enhance it.
Optimize it.

Consider selecting participants based on some run-in data to determine potential adherence.

*Ex: In a trial of CPAP for OSA, a sham CPAP run-in would provide estimates of adherence to real CPAP.*

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Example: ENRICHED

Enhancing Recovery in Coronary Heart Disease Patients
Depression Following Myocardial Infarction: Impact on 6-Month Survival (N = 222)

6-Month HR associated with major depression = 5.7 (95% CI, 4.6 – 6.9)

Frasure-Smith, et al, JAMA 1993

Objective - ENRICHD

To test the hypothesis that treatment of depression and low social support early after an acute myocardial infarction will reduce death and nonfatal recurrent infarctions

Study Design - ENRICHD

- 2,481 post-MI patients with depression or low social support
- Randomized, parallel-group clinical trial to compare the efficacy of a psychosocial intervention vs. usual care on cardiovascular endpoints
- Average 3.4 years of follow-up
- Blinded ascertainment of primary endpoint
- Intent to Treat analysis
Inclusion Criteria

Recruited within 28 days after AMI
- Enzyme increases 2 x ULN (except for CKMB), and either:
  - Symptoms compatible with acute MI, or
  - Characteristic evolution electrocardiographic ST-T changes or new Q waves
Identification of
- major or minor depression, and/or
- low social support

ENRICHD Participant Selection

33,780 screened
- 1534 did not meet MI criteria
32,246 met MI criteria
- 22,967 medically ineligible
  - 6698 did not meet criteria for depression or low social support
2481 randomized
- 1243 usual care
- 1238 psychosocial intervention

Patient Enrollment - ENRICHD

- For every 100 participants screened, only 7 patients were actually enrolled
- To enroll 1 participant, more than 14 participants had to be screened
- Not all sites were able to adequately enroll participants
Recruitment & Retention - ENRICHD

- Access—(MD, PhD, etc)
- Competition—competing trials/supply-demand
- Lack of true medical support/collaboration
- Respondent burden
  - Assessments
  - Treatment
  - Duration of study
- Restrictive eligibility criteria
- Logistical issues

CONCLUSIONS - 1

- Know the literature and the history
- Really know these things well – not only what was found, but what was done, to whom, where, how, etc.
- Your job in understanding this literature is to evaluate not only data but also the appropriateness of the study design for the question and outcomes examined.

CONCLUSIONS - 2

- Know your question
- Have a good understanding of the participant characteristics you are targeting
- Match your participants to your outcomes
- Think about where your question fits on the research continuum
- Is this the right time for this question and these participants?
CONCLUSIONS - 3

- Think about, in the context of all the relevant literature, what is **most** important – controlling external or internal validity?
- In other words, for your question, with what is known today, what is most damaging – missing an effect that is there (Type II error) or finding an effect that isn't there (Type I error)?

Questions?