Research Participant Selection

• How do you decide which participants to study?

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

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

- **Phase 1**
  - Safety
  - Dose-ranging
  - Healthy
  - Very Small

- **Phase 2**
  - Efficacy
  - Highly controlled
  - Selected
  - Small

- **Phase 3**
  - Effectiveness
  - Less control
  - Less selected
  - Big

- **Phase 4**
  - Post-marketing
  - Real-life
  - Community
  - on-going
Reasons 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
Internal vs external validity – a delicate balance
The Balance Between Internal and External Validity

Risk of Type I Error (false positive - $\alpha$)

External Validity
Maximize Generalizability
Across participants
Across situations
Across time and place

Risk of Type II Error (false negative - $\beta$)

Internal Validity
Maximize Control
History effects
Bias of all sorts
Experimenter effects
Measurement effects
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 what your question is and where it lies on the research continuum.
### The Research Continuum of a Clinical Trial

<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</td>
<td>Less control</td>
<td>Real-life</td>
</tr>
<tr>
<td>Healthy</td>
<td>Selected</td>
<td>Less selected</td>
<td>Community</td>
</tr>
<tr>
<td>Very Small</td>
<td>Small</td>
<td>Big</td>
<td>on-going</td>
</tr>
</tbody>
</table>
Reasons 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
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.)
Reasons 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 could impact your outcomes
- The specific decisions you make regarding who you study will markedly influence the causal inferences you can make
Selection of Outcomes

- Event outcomes
  - Morbidity
  - Mortality
- Surrogate/biomarker outcomes
  - Resvascularization (e.g., CABG, PTCA)
- Patient-specific outcomes
  - Pain/symptoms
  - Quality of Life/PROs
- Composite 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?

  - Ex: Measuring CV events 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.
Reasons 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
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
  - Response bias, patient expectations
  - Therapeutic allegiance
- Access
- Recruitment & retention
- Adherence
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
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).
  - Inclusionary
  - Exclusionary

- Context
  - Response bias, patient expectations
  - Therapeutic allegiance

- Access
- Recruitment & retention
- Adherence
“To different degrees, all causal relationships are context dependent, so the generalization of experimental effects is always at issue”

Shadish et al., 2002
Context is important

Personal Experiences

Social Environment

Culture
Women with History of Childhood Physical Abuse are at Risk for Incident Metabolic Syndrome

- No Physical Abuse
- Yes Physical Abuse

Percent of women with incident metabolic syndrome:
- 10% for No Physical Abuse
- 40% for Yes Physical Abuse

NIH National Heart, Lung, and Blood Institute
The MAPEC Study (Ambulatory BP monitoring for prediction of CV events)

Hermida et al., 2010
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
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 – and most challenging part of many RCTs
- Respondent burden
  - Assessments
  - Intensity, duration and complexity of treatment
- Health of participant
- Logistics – transportation, etc.
- Intention to treat
Improving Recruitment Using a Layered Approach

- Use community-based and social marketing strategies
- Targeted distribution of mailings
- Presentations at health fairs and community settings
- Referrals
- Set goals that are manageable at both ends of the study and monitor carefully
- Run-in period for acceptability
Improving Retention

- Manage (minimize) participant burden
- Employ shortest possible time period and least complex study requirements
- Optimize visits – convenient hours, efficient, culturally competent staff, provide attention,
- Reduce barriers (parking, child care, gas costs)
- Incentives
- Appointment reminders
- Schedule at BEGINNING of follow-up window
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
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*
80 chronic pain patients were studied for 21 days, recording pain levels.

A microchip was imbedded into paper diaries that detected when the diary was opened.

Patients reported 89% adherence with entering pain data within the 30 min window.

Actual adherence (based on the microchip data) was 11%.

Diary was not opened on 32% of days, but patients reported an average of 90% adherence on those days.
Optimizing Adherence

• Motivational Interviewing – to decrease ambivalence, increase retention

• Orientation session – provide information, outline expectations, answer questions, develop partnership, transparency

• Maintain contact back-ups

• Maintain contact with phone calls, birthday cards, newsletters, retention events
Example: ENRICH:D

- 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 - ENRICHHD

- 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 - ENRICHDD

- 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
ENRICH-D 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 - ENRICHED

- 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
• 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.
• 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)?