Considerations in the Selection of Research Participants
Research Participant Selection – Basic Questions

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?

How do you appropriately match participant characteristics to the outcomes of interest?
Reasons to think about participant selection

It can clarify your question
It can help clarify study design
Characteristics of your study participants 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

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Internal vs external validity – a delicate balance

The Balance Between Internal and External Validity

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

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Feasibility
Access to research participants with the desired demographic and clinical characteristics
Likelihood of participation and, once participating, adherence to protocol and tx
Ethical questions – randomization to placebo, adverse event rates, participant burden, vulnerable participants,
representativeness. Consider for all arms
Timing of intervention (acute post-event, pre-event, etc.)
Reasons to think about participant selection

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It could impact your outcomes
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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 (eg, stage of disease)? *A study measuring hard CV events (eg, myocardial infarction) in 50-year-old healthy women with moderate BP elevation could not be powered adequately.*
Can outcomes change within the parameters of the trial, given participant characteristics?

Planning to measure change in carotid artery IMT over the course of a 6-month trial would not show differences over time.
Are participants able to provide PROs? Asking 2 year-old children to report pain symptoms may yield unreliable data
Reasons to think about participant selection

- It can clarify your question
- It can help clarify study design
- Characteristics of your study participants 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

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  Inclusionary
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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

Example: 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

Example: In a study of a new medication for the treatment of hypertension, it may be reasonable to exclude those with advance 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 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. Be specific!

Should entry criteria ever be changed?
Factors to consider in participant characteristics

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

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  • Response bias, patient expectations
  • Therapeutic allegiance

Access
  Recruitment & retention
  Adherence

Context is important

“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
The MAPEC Study (Ambulatory BP monitoring for prediction of CV events)
Factors to consider in participant characteristics

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Target of the intervention (e.g., individual, dyad, caregiver, health care delivery system, etc).
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Context
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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

Inclusionary and representative
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
Employ strategies for ensuring participants are representative

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 (except in some types of studies).

Consider selecting participants based on some run-in data to determine potential adherence
Example: In a trial of CPAP for OSA, a sham CPAP run-in would provide estimates of adherence to real CPAP

Measuring Adherence
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: ENRICHD

Enhancing Recovery in Coronary Heart Disease Patients

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
ENRICHED Participant Selection
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
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?