Research
Patient/Participant Selection
Introduction to the Principles & Practice of Clinical Research
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The characteristics of your trial participants are important – and in ways that you may not even know about.
Research Participant/Patient Selection

How do you decide which participants/patients to study? You usually already have an interest in a particular disorder or population to begin with – this is where you START (not end)

How do you make sure 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 ENRICH-D 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)

Phase 1
Safety  Dose-ranging Healthy people Very Small

Phase 2
Efficacy Highly controlled Patients Small

Phase 3
Effectiveness Less control Patients Big

Phase 4
Post-marketing Real-life Patients on-going
The Research Continuum of a Clinical Trial (#2): Translational Perspective

Are specific genetic signatures associated with risk of atherosclerosis?

**T0**
Identify problems
Develop approaches
Basic research
(Are specific genetic signatures associated with risk of atherosclerosis)

**T1**
Foundational research
Observational
Phase I & II
(Is there an association between these specific alleles and atherosclerosis?)

**T2**
Phase III
Observational guideline development
(What is the predictive value in individuals at risk?)

**T3**
Dissemination & Implementation
(What is an effective implementation strategy to increase testing of at-risk individuals?)

**T4**
Practice to population
(Does testing reduce incidence or improve outcomes of atherosclerosis?)
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Internal vs external validity – a delicate balance

Photo: skateboarder doing a trick on the skateboard on the edge of a beam
The Balance Between Internal and External Validity

Risk of Type I Error
External Validity
Maximize Gernalizability

Across participants
Across situations
Across time and place

Risk of Type II Error

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 where your question lies on the research continuum.
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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. 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?

Ex: 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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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
Access
Recruitment & retention
Adherence
Factors to consider in participant characteristics

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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 advance heart failure (safety) and those with diabetes (confounding)
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.
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Context
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

Graph that shows how personal experiences, social environment and culture are all part of a person’s make-up.
Women with History of Childhood Physical Abuse are at Risk for Incident Metabolic Syndrome

Graph showing Percent of women with incident metabolic syndrome (10% - 40%).

No physical abuse – 18%

Yes physical abuse – 35%
The MAPEC Study (Ambulatory BP monitoring for prediction of CV events)
Graph showing Duration of follow up & Probability of event free survival
Hermida et al., 2010
Factors to consider in participant characteristics

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  - 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
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
Intention to treat
Respondent burden
  Assessments
  Intensity, duration and complexity of treatment
Logistics – transportation, etc.
Health of participant
Patient Selection - Adherence
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
Example: ENRICHED

Enhancing Recovery in Coronary Heart Disease Patients
Objective
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.
Depression Following Myocardial Infarction: Impact on 6-month Survival (N=222) Graph from Frasure-Smith, et al, JAMA 1993
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
ENRICHHD Participant Selection
Flow chart
Patient Enrollment - ENRICHHD
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 - ENRICHED
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 Regarding Participant Selection - 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 Regarding Participant Selection - 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?
Conclusions Regarding Participant Selection - 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)?