Considerations in the Selection of Research Participants

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Introduction to the Principles & Practice

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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?

Participant Selection: Outline

Reasons to consider participant selection

Translational continuum of clinical trials

Internal vs external validity

Factors to consider

ENRICHD: An example

Conclusions

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

Phase 1	Phase 2	Phase 3	Phase 4
Safety	Efficacy	Effectiveness	Post-marketing
Dose-ranging	Highly controlled	Less control	Real-life
Healthy	Selected	Less selected	Community
Very Small	Small	Big	on-going

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Internal vs external validity – a delicate balance

The Balance Between Internal and External Validity

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.

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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 treatment

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.)

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Selection of Outcomes

Event outcomes

- Morbidity
- Mortality

Surrogate/biomarker outcomes*

- Revascularization (e.g., coronary bypass)
- cholesterol (reduction)
- cognitive scores

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

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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

Response bias, patient expectations

Therapeutic allegiance

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

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?

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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)

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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

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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

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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

Masked ascertainment of primary endpoint (death or non-fatal recurrance)

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

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

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, Con't.

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, Con't.

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?