



Considerations in the Selection of Research Participants


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Introduction to the Principles & Practice of Clinical Research
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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
- ENRICH: 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

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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
<i>Very Small</i>	<i>Small</i>	<i>Big</i>	<i>on-going</i>


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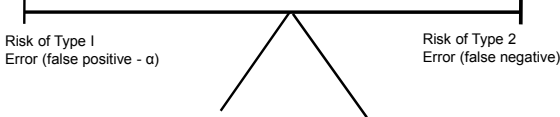
Internal vs external validity – a delicate balance



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The Balance Between Internal and External Validity

External Validity <u>Maximize Generalizability</u>	Internal Validity <u>Maximize Control</u>
Across participants Across situations Across time and place	History effects Bias of all sorts Experimenter effects Measurement effects




Risk of Type I Error (false positive - α)

Risk of Type 2 Error (false negative)

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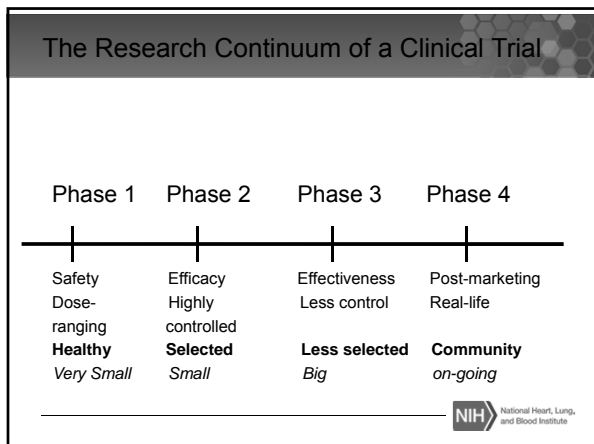
Internal and external validity – which is more important?

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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Reasons to think about participant selection


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- Characteristics of your study participants will determine your ability to generalize
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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

*a biomarker intended to substitute for a clinical endpoint




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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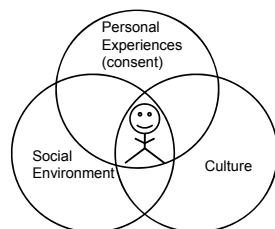
Context is important

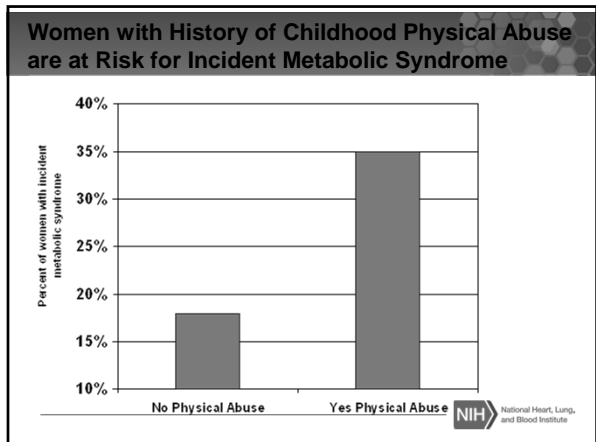
“To different degrees, **all causal relationships are context dependent**, so the generalization of experimental effects is always at issue”

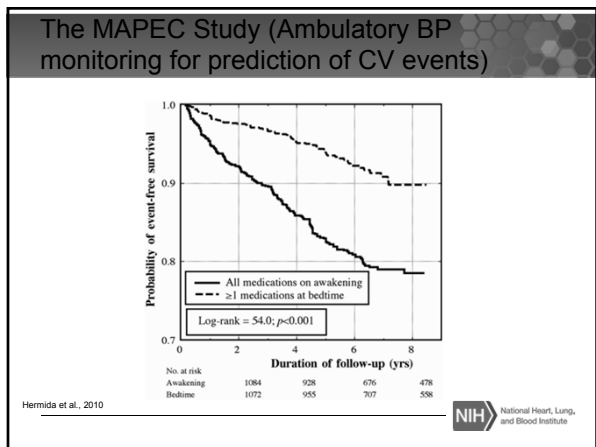
Shadish et al., 2002



Context is important








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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




Factors to consider in participant characteristics

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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

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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

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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

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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.

BMJ, 2002

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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

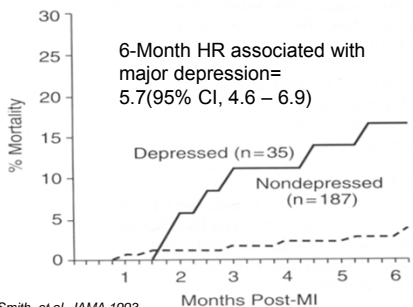
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Example: ENRICHD

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)


Months Post-MI	Depressed (n=35) % Mortality	Nondepressed (n=187) % Mortality
1	0	0
2	6	1
3	11	2
4	14	3
5	16	3
6	17	4

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
- Masked ascertainment of primary endpoint (death or non-fatal recurrence)
- Intent to Treat analysis

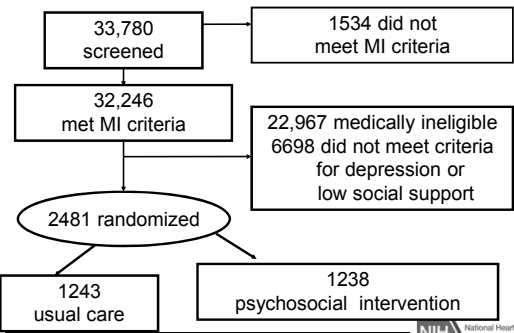


Inclusion Criteria

- 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



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graph TD
    A[33,780 screened] --> B[32,246 met MI criteria]
    A --> C[1534 did not meet MI criteria]
    B --> D[2481 randomized]
    B --> E[22,967 medically ineligible  
6698 did not meet criteria for depression or low social support]
    D --> F[1243 usual care]
    D --> G[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

- 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?

