Generalizability and Temporality in Assessing Impact

National Academies of Sciences, Engineering, and Medicine

Accelerating the Use of Findings from Patient-Centered Outcomes Research in Clinical Practice to Improve Health and Health Care

Session #3

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Outline

- **Generalizability**
  - External validity: extent to which study findings apply to target populations
  - Minimizing discrepancies between study samples and target populations
    - Randomized Evaluation of Trial Acceptance by Incentive (RETAIN)
    - Behavioral Economics to Transform Trial Enrollment Representativeness (BETTER)

- **Temporality**
  - Mediation and sequential impact
    - Being Responsible for Ourselves (BRO)

External Validity in Clinical Trials

- In ***whom*** are we measuring impact?
  - Trial samples vs. target populations

- Challenges to external validity in clinical trials
  - Non-representative trial samples
  - Interest in impact in different target population

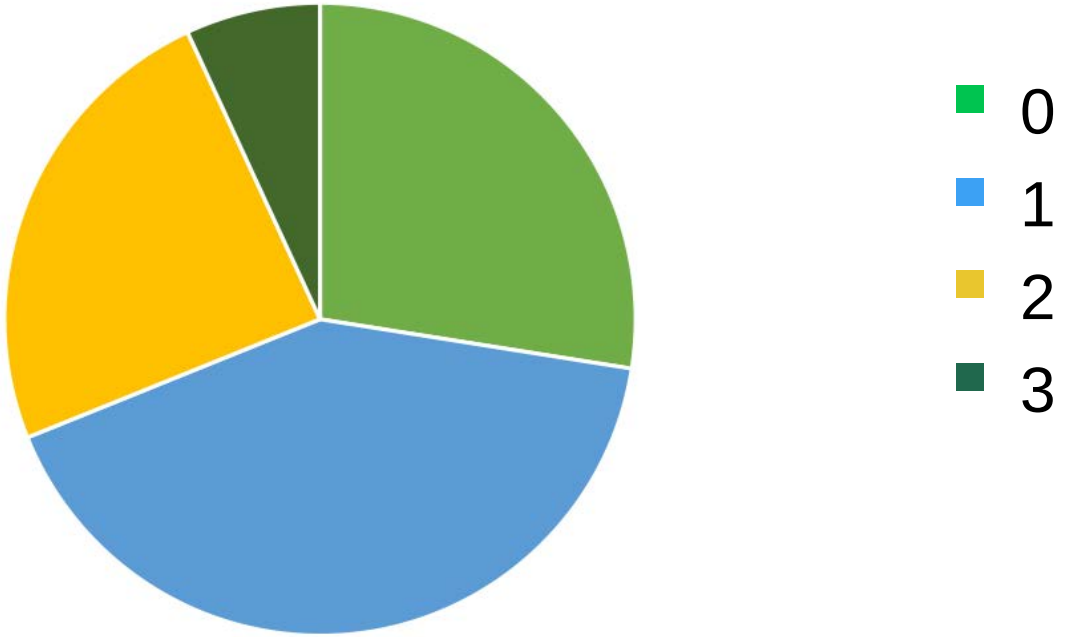
⇒ Over- or under-estimation of intervention effect in target population

⇒ Limited data to assess treatment effect heterogeneity

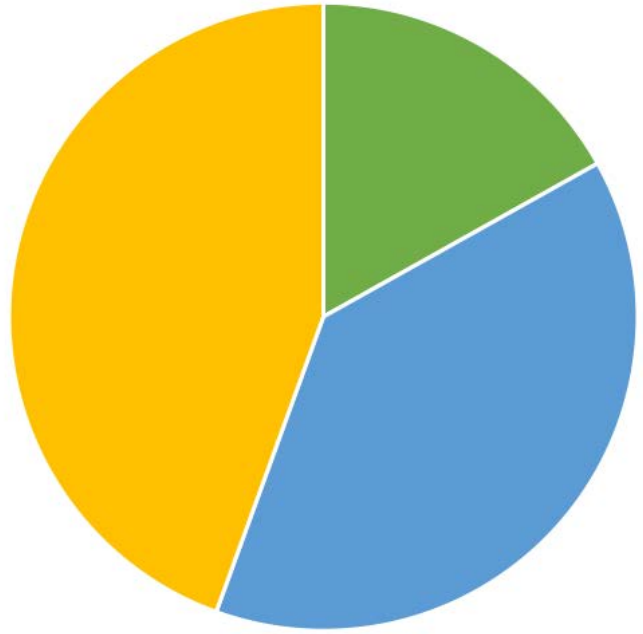
Real World and Trial Cohorts in the Study of Urothelial Carcinoma

- Performance status in EHR and clinical trial cohorts were used to examine the impact of a novel cancer therapy (Getz, 2022)

Electronic Health Record Cohort



Clinical Trial Cohort



Randomized Evaluation of Trial Acceptance by Incentive (RETAIN) (Halpern, 2022)

Motivating challenges in conducting RCTs:

1. Failure to recruit sufficient participants
2. Lack of generalizability of trial samples

Potential implications of incentives

- (+) Increased enrollment and representativeness
- (-) Unethical consequences

Objectives

1. Evaluate the effectiveness of financial incentives
2. Evaluate the ethics of financial incentives
   - Undue inducement: blunting of perceived risk
   - Unjust inducement: disproportionately increasing enrollment among disadvantaged populations

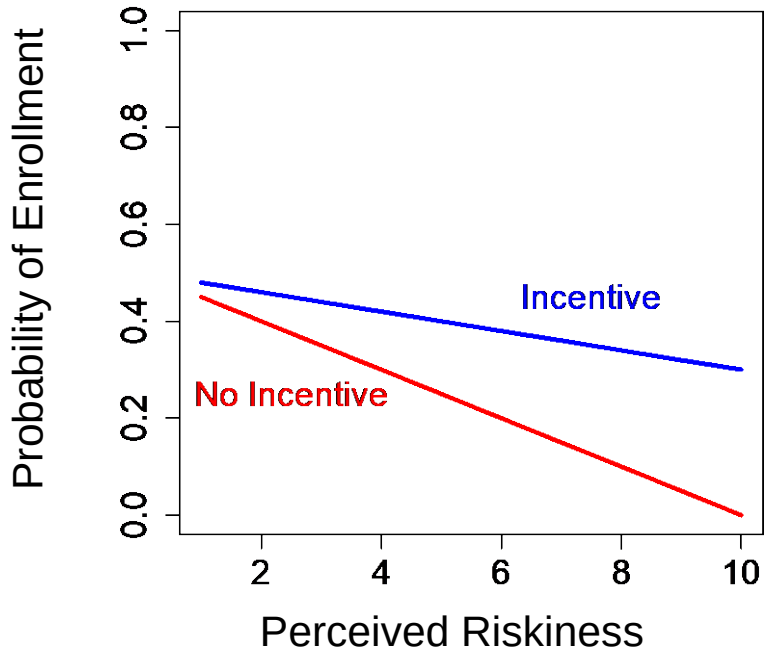
RETAIN Design

- **Two embedded, single-blinded 3-arm randomized trials**
  - Parent RCT 1: 4-arm trial of smoking cessation interventions among outpatients with depression
  - Parent RCT 2: gamification intervention vs. usual care to promote ambulation among inpatients
- **Primary outcome (both trials):** signed consent to participate in parent trial
- **Incentive (Intervention) Arms:**

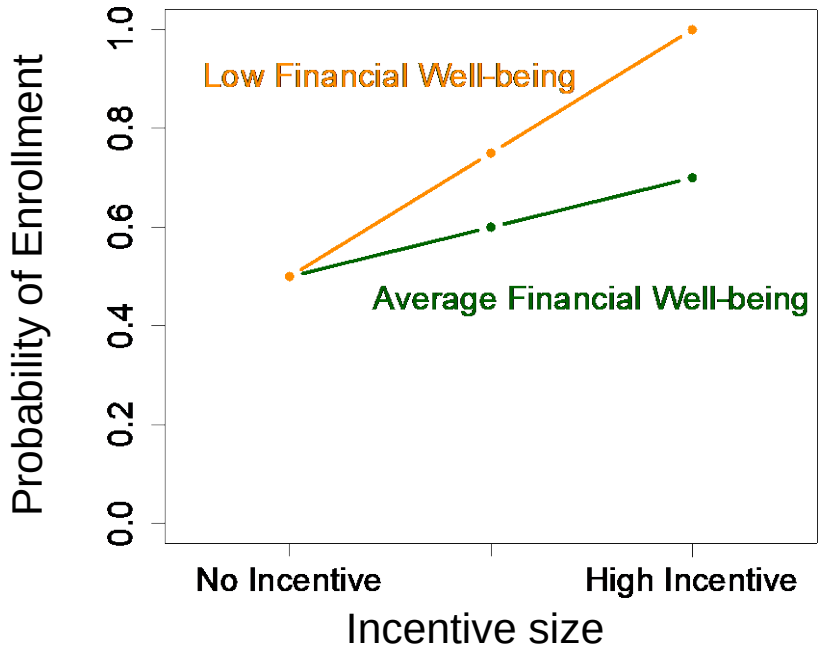
Smoking Cessation Trial	Ambulation Trial
$0	$0
$200	$100
$500	$300

Characterization of Undue and Unjust Inducement

Undue inducement: Large difference in slope of risk and enrollment according to incentive size



Unjust inducement: Large difference in slope of enrollment and incentive size according to economic status



Question: *Can we rule out large (> γ) differences in slopes?*

Statistical Issues

- **Selection of margin**
  - What is tolerable change in slopes?
  - Selected interaction odds ratio of $\gamma = 2.0$ as margin

- **Scale dependence of margin and effect modifiers as interactions**
  - 'Meaningful' magnitude of difference in slope varies by predictor type (eg. Continuous or binary)
  - Raises question as to selected margin

Effect of Incentives on Enrollment

Financial incentives increased the proportion enrolled in Smoking Cessation Trial but not Ambulation Trial

		$0	$200	$500	p
Smoking Cessation Trial	No.	216	217	221	
	Proportion Consented	47/216 21.8%	78/217 35.9%	104/221 47.1%	<0.001

		$0	$100	$500	p
Ambulation Trial	No.	216	212	214	
	Proportion Consented	98/216 45.4 %	102/212 48.1%	92/214 43.0%	.62

Effect of Incentives on Representativeness

- Financial Incentives equalized enrollment between Black and White participants in Smoking Cessation Trial

Incentive	Black patients	White patients
$0	17%	30%
$200	36%	36%
$500	46%	49%

Evaluation of Unjust and Undue Inducement

Data provide evidence against presence of undue and unjust inducement

		Upper 95% Confidence Limit*	p
Unjust Inducement	Financial Well-being	1.17	0.003
	Income	1.21	0.01
Undue Inducement	Perceived Riskiness	1.15	< 0.001

*Compared to margin of 2.0

Sensitivity Analyses for Size of Margin

- Lack of undue inducement would be concluded for margin as low as 1.6

	Risk Interaction p-value	
Odds Ratio Margin	Smoking Trial	Ambulation Trial
1.1	0.71	0.69
1.2	0.48	0.53
1.3	0.28	0.39
1.4	0.14	0.26
1.5	0.06	0.17
1.6	0.02	0.11
1.7	0.01	0.06
1.8	0.02	0.04
1.9	0.008	0.02
2.0	0.003	0.01

RETAIN Conclusions and Limitations

RETAIN concluded that financial incentives

- increased enrollment in 1 of 2 trials
- did not produce undue or unjust inducements
- **resulted in a more representative trial sample**

Limitations

- Smoking and Ambulation trials were low risk; need evaluation of incentives in higher risk trials
- Uncertainty regarding tolerable margin for ‘unjust’ or ‘undue’ inducement

RETAIN provides evidence to challenge existing notions for trial participation compensation.

Behavioral Economics to Transform Trial Enrollment Representativeness

- American Heart Association-funded initiative to and test **behavioral economic interventions** that surmount the barriers to RCT participation faced by disenfranchised racial and ethnic groups, women, persons of low socioeconomic status (SES), and others with or at risk for cardiovascular disease

BETTER CENTER

Project 1	Identification of barriers and facilitators of RCT enrollment diversity via systematic review, secondary data analysis of prior RCTs, and prospective exploratory analysis
Project 2	Evaluation of promising behavioral economics recruitment interventions combined with outreach strategies in cohort studies
Project 3	Embedded RCT of optimal recruitment strategies

Key Outcomes in BETTER

- **Enrollment Fraction (*EF*)**

$$EF = \frac{\#\ enrolled}{\#\ contacted}$$

  - Primary Outcome: Black and Hispanic Participants
  - Secondary Outcome: Overall, stratified by socioeconomic status

- **Population to Prevalence Ratio**
  - Enrollment fraction of specific subgroups divided by overall enrollment fraction

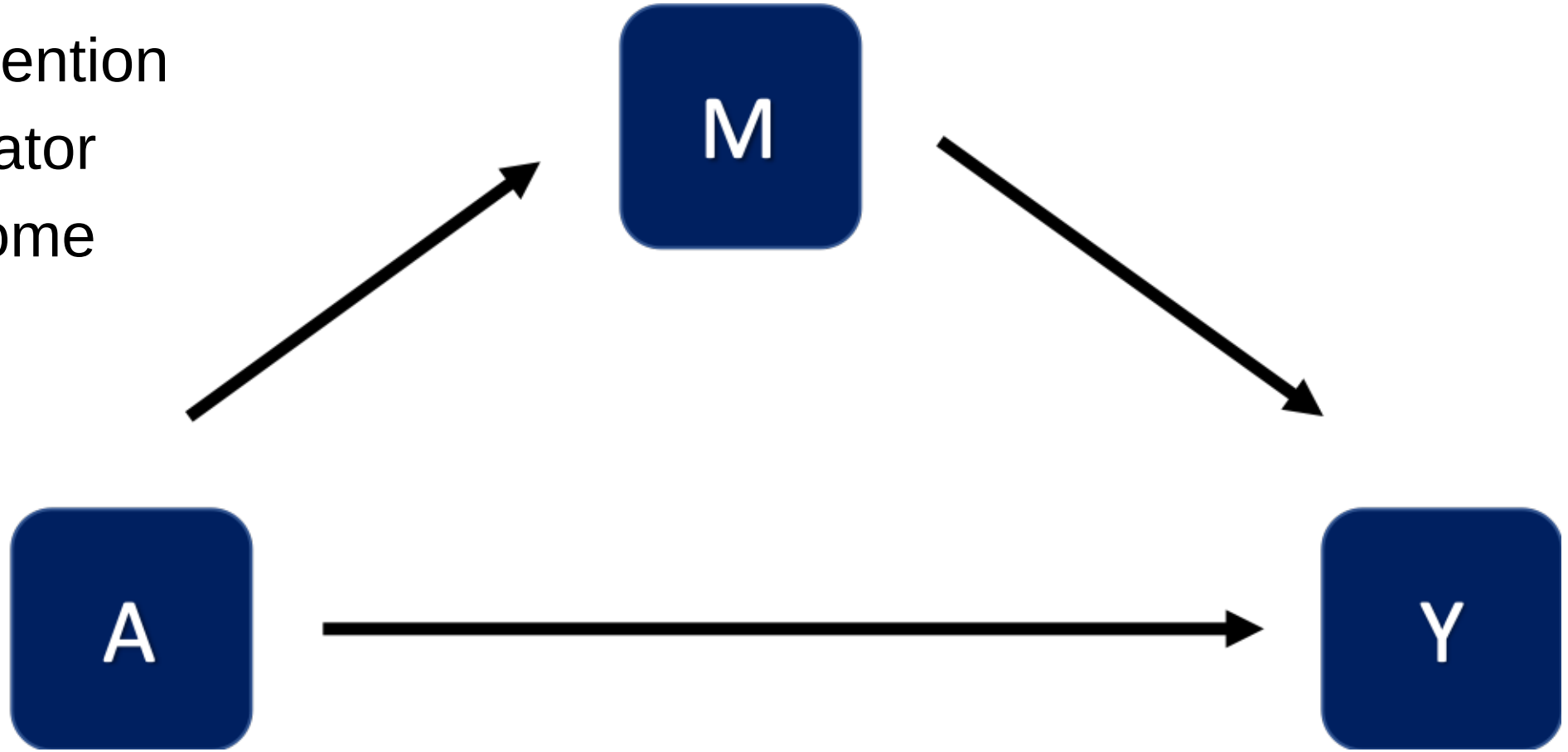
Temporality: Assessing Sequential Impact by Mediation

Baron and Kenny (1986)

A: Intervention

M: Mediator

Y: Outcome



Being Responsible for Ourselves (BRO) (Jemmott, 2014)

- **BRO:** Longitudinal, randomized trial of behavioral intervention to reduce risky sexual behavior in African-American MSM

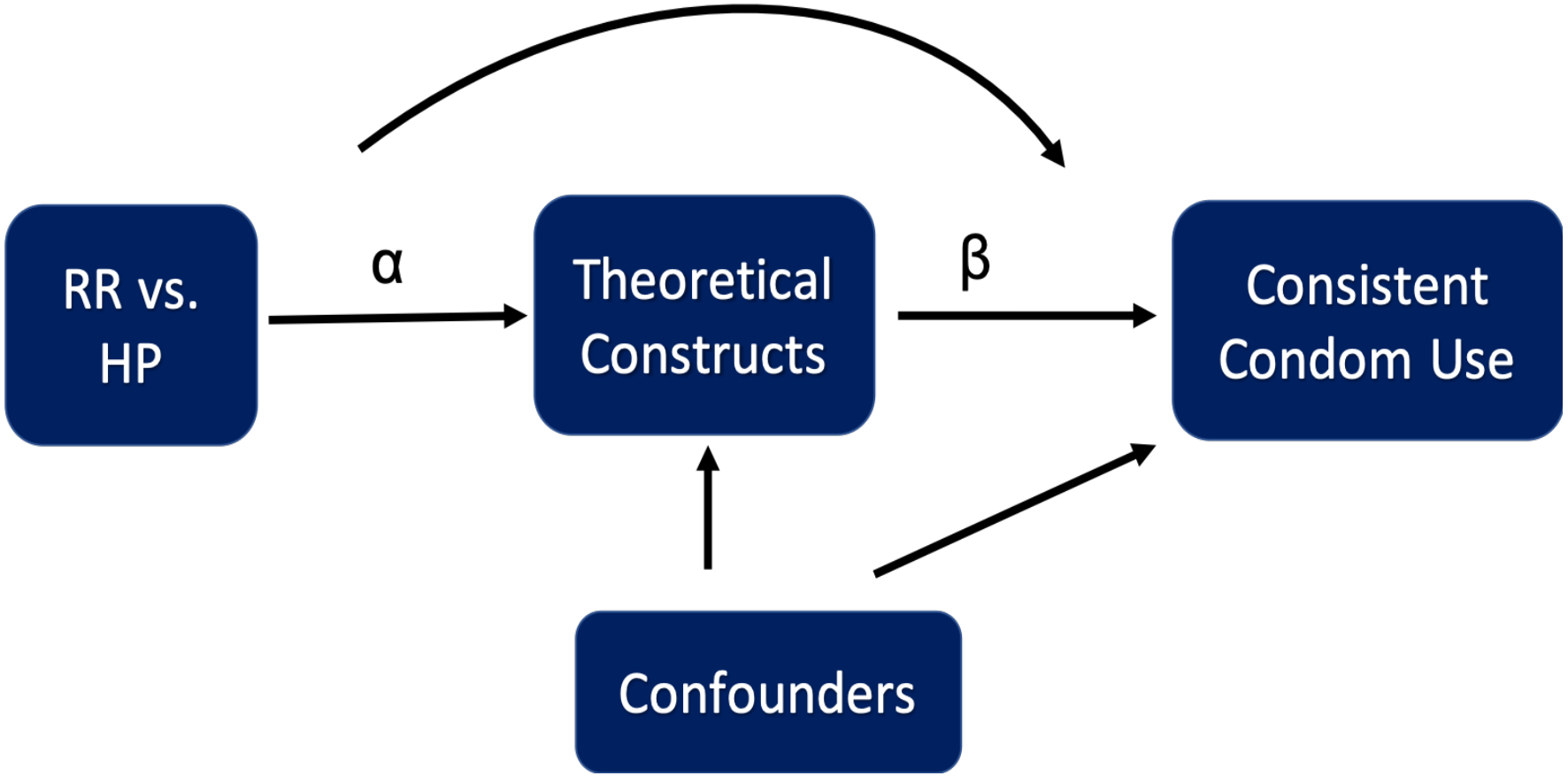
- **Arms:**
  - Risk Reduction (RR), intervention
  - Health Promotion (HP), attention control

Design characteristics

- n = 595 participants
- Primary outcome: consistent condom use

Potential Mediating Theoretical Constructs in BRO

- Outcome expectancies
  1. Hedonistic
  2. Prevention
  3. Self-evaluative
- Self-efficacy
  4. Availability
  5. Negotiation
  6. Technical Skill
  7. Impulse Control
- Knowledge
  8. HIV/STI Risk
  9. Condom use
- Peer norms
  10. Subjective
  11. Descriptive



BRO Results

- **Risk Reduction intervention effect**

  Odds Ratio (95% CI): 1.03 (0.73, 1.45), p=0.87

- **Theoretical constructs associated with condom usage but NOT impacted by intervention**
  - Negotiation skill
  - Peer descriptive norms

Considerations for Assessing Impact

1. How well do the data used to evaluate impact reflect the population in which we want to apply conclusions?
   - How can we minimize relevant gaps?

2. Are thresholds and benchmarks used in evaluating impact meaningful?

3. Have we generated sufficient longitudinal data to assess sequences of effect and provide insight into mechanisms of impact or lack thereof?