If you're a person with a disability or using assistive technology and are having difficulty accessing any of the content in this file, please contact Marie Rienzo at marie.rienzo@nih.gov.

Methods: Mind the Gap Webinar Series

Causal Inference With Instrumental Variables

Presented by

Stuart G. Baker, Sc.D.

What you will learn

- How to analyze randomized trials with all-or-none compliance
- How to implement and analyze the paired availability design for historical controls
- Emphasis
  - Simple formulas
  - Concepts, assumptions, and interpretation

Terminology

- **Causal inference**
  - Potential outcomes viewpoint

    Neyman (1923, thesis) and Rubin (1974)
  - What is the outcome if you went back in time and received a different treatment?
- **Instrumental variable Z**
  - Affects outcome **Y** only through treatment received T

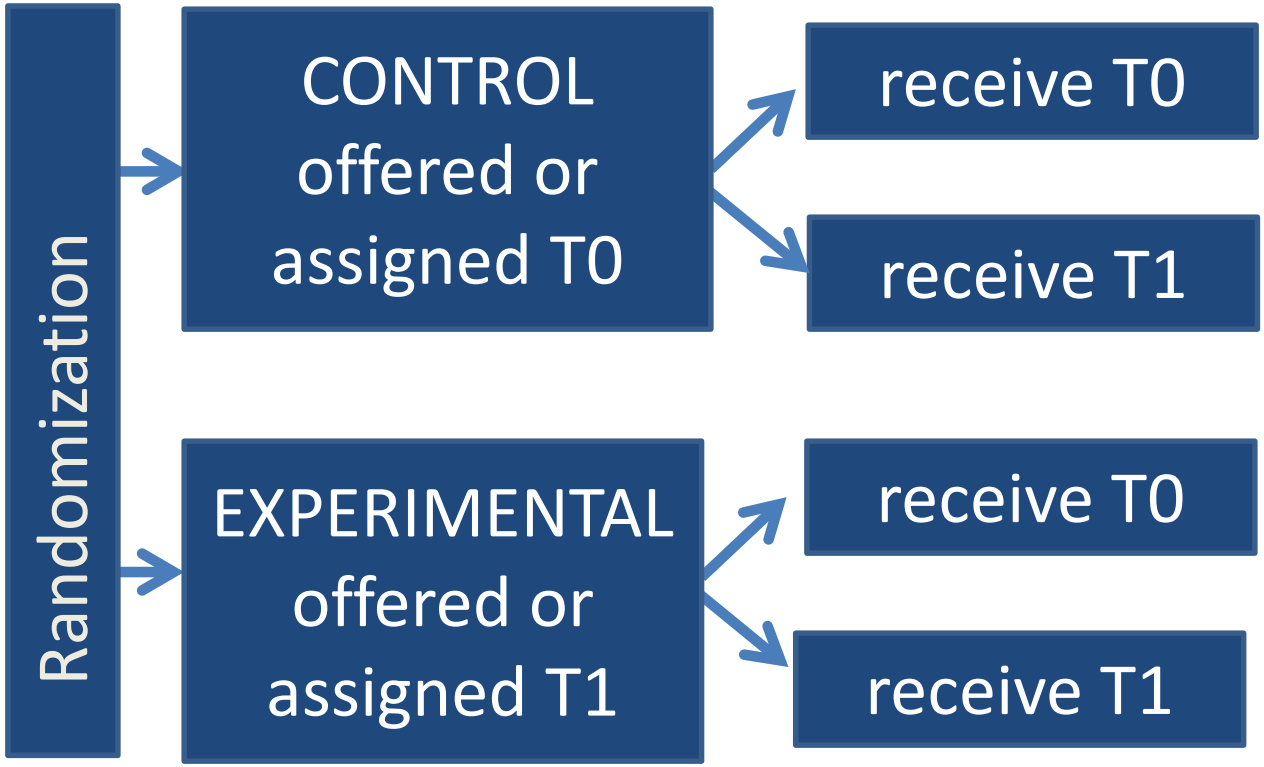
    Z → T → **Y**
  - Example: Z = randomization group

    Z= time period (if assumptions hold)

Outline

- Randomized trial with all-or-none compliance
- The paired availability design

A randomized trial with all-or-none compliance: Treatments T0 and T1



Goal:

Estimate effect of receipt of treatment T1 versus T0

Why estimate the effect of treatment received instead of the effect of treatment assigned?

Patient decision making	Patients what to know the effect of treatment received
Cost-effectiveness	Compare cost of treatment received with the benefit of treatment received
Non- Inferiority study	Tolerance is based on the effect of treatment received
Meta-analysis	Contribution from each trial is the effect of treatment received

To estimate the effect of treatment received
with all-or-none compliance:

Latent class instrumental variables

this terminology from Baker, Kramer, Lindeman (2016) *Stat Med*

All-or-none compliance	**Key papers (multiple independent developments)**
One-sided	Baker (1983, *technical report, Harvard Biostatistics*) Bloom (1984) *Evaluation Review* Sommer and Zeger (1991) *Stat Med* Connor, Prorok, Weed (1991) *J Clin Epidemiol*
Two-sided	Imbens and Angrist (1994) *Econometrica* Baker and Lindeman (1994) *Stat Med* Angrist, Imbens, Rubin (1996) *JASA* *These 3 papers were called seminal by Swanson et al (2018) JASA*

Latent class instrumental variables

Latent classes based on treatment received if randomized to each group

	Treatment received if randomized to	
Latent class	**Group assigned T0**	**Group assigned T1**
Always-taker	**T1**	**T1**
Never-taker	**T0**	**T0**
Complier	**T0**	**T1**
Defier	**T1**	**T0**

Monotonicity	Assume no **Defier**
Exclusion restriction (instrumental variable)	Assume randomization group does not effect outcome for **Always-takers** and **Never-takers**
Estimated **causal effect** in **Compliers** LATE (local average treatment effect) CACE (complier average causal effect)	Estimated difference in potential outcomes (outcome if receive T1 instead of T0) in **Compliers** Difference in outcomes between groups Difference in fraction receiving T1 between groups

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	80	**Never-taker**		
				Complier		
	T1	20000	60	**Always taker**		
				Defier		
Assigned T1	T0	10000	50	**Never-taker**		
				Defier		
	T1	30000	120	**Complier**		
				Always taker		

	Treatment received if randomized to	
Latent class	**Group assigned T0**	**Group assigned T1**
Always-taker	**T1**	**T1**
Never-taker	**T0**	**T0**
Complier	**T0**	**T1**
Defier	**T1**	**T0**

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**		
				Complier		
	T1	20000	80	**Always taker**		
				Defier		
Assigned T1	T0	10000	50	**Never-taker**		
				Defier		
	T1	30000	120	**Complier**		
				Always taker		

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**		
				Complier		
	T1	20000	80	**Always taker**	**20000**	**80**
				Defier		
Assigned T1	T0	10000	50	**Never-taker**	**10000**	**50**
				Defier		
	T1	30000	120	**Complier**		
				Always taker		

Monotonicity	**No Defiers**

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**		
				Complier		
	T1	20000	80	**Always taker**	**20000**	**80**
Assigned T1	T0	10000	50	**Never-taker**	**10000**	**50**
	T1	30000	120	**Complier**		
				Always taker		

Monotonicity	**No Defiers**

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**		
				Complier		
	T1	20000	80	**Always taker**	**20000**	**80**
Assigned T1	T0	10000	50	**Never-taker**	**10000**	**50**
	T1	30000	120	**Complier**		
				Always taker	**20000**	**80**

Monotonicity	**No Defiers**
Exclusion restriction	Treatment effect not depend on group: **Always-takers**

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**		
				Complier		
	T1	20000	80	**Always taker**	**20000**	**80**
Assigned T1	T0	10000	50	**Never-taker**	**10000**	**50**
	T1	30000	120	**Complier**	**10000**	**40**
				Always taker	**20000**	**80**

Monotonicity	**No Defiers**
Exclusion restriction	Treatment effect not depend on group: **Always-takers**

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**	**10000**	**50**
				Complier		
	T1	20000	80	**Always taker**	**20000**	**80**
Assigned T1	T0	10000	50	**Never-taker**	**10000**	**50**
	T1	30000	120	**Complier**	**10000**	**40**
				Always taker	**20000**	**80**

Monotonicity	**No Defiers**
Exclusion restriction	Treatment effect not depend on group: **Always-takers** Treatment effect not depend on group: **Never-takers**

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**	**10000**	**50**
				Complier	**10000**	**10**
	T1	20000	80	**Always taker**	**20000**	**80**
Assigned T1	T0	10000	50	**Never-taker**	**10000**	**50**
	T1	30000	120	**Complier**	**10000**	**40**
				Always taker	**20000**	**80**

Monotonicity	**No Defiers**
Exclusion restriction	Treatment effect not depend on group: **Always-takers** Treatment effect not depend on group: **Never-takers**

		Observed			Estimated	
Group	Receive	Number	deaths	Latent class	Number	deaths
Assigned T0	T0	20000	60	**Never-taker**	**10000**	**50**
				Complier	**10000**	**10**
	T1	20000	80	**Always taker**	**20000**	**80**
Assigned T1	T0	10000	50	**Never-taker**	**10000**	**50**
	T1	30000	120	**Complier**	**10000**	**40**
				Always taker	**20000**	**80**

Monotonicity	**No Defiers**
Exclusion restriction	Treatment effect not depend on group: **Always-takers** Treatment effect not depend on group: **Never-takers**
Estimated causal effect in **Compliers**	**Difference in outcomes between groups** / **Difference in fraction receiving T1 between groups** $= \frac{(40 - 10)/40000}{(30000 - 20000)/40000} = 0.003$

Latent class instrumental variables: Summary

Four latent classes	Always-taker, Never-taker, Complier, Defier
Monotonicity	No Defiers
Exclusion restriction	Same treatment effect per group for Never-takers and Always-takers

Estimated causal effect in compliers

$$\frac{\text{Difference in outcomes between groups}}{\text{Difference in fraction receiving T1 between groups}}$$

Other names for this estimate:

Estimated effect of receipt of treatment Baker, Lindeman(1994)
Local Average Treatment Effect (LATE) Imbens, Angrist (1994)
Complier Average Causal Effect (CACE) Imbens, Rubin (1997)

Example 1: Effect of breast cancer screening on breast cancer mortality

Group	Treatment	Number	Breast cancer mortality rate at 5 year follow-up
Control	No screen	31000	0.0020
Screening invitation	No screen	31000	0.0013
	Screen (65%)		

Method	Estimate
Intent-to-treat	0.0013 – 0.0020 = – 0.0007
Causal effect in compliers	– 0.0007 /0.65 = – 0.0011

Data from Freedman et al, 2004

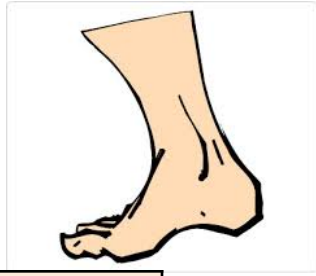
Example 2. Effect of Vitamin A supplement on mortality in pre-school children

Group	Treatment	Number	Mortality rate
Control	No vitamin A	11588	0.0064
Assigned Vitamin A	No vitamin A	12094	0.0036
	Vitamin A (80%)		

Method	Estimate
Intent-to-treat	0.0036 – 0.0064 = – 0.0028
Causal effect in compliers	– 0.0028 /0.80 = – 0.0035

Data from Sommer and Zeger, 1991

Example 3. Effect of ankle rehabilitation exercises on re-injury



Group	Treatment	Number	Fraction with ankle re-injury
No rehab	No exercise	269	0.33
Rehab invitation	No exercise	259	0.22
	Exercise (61%)		

Method	Estimate
Intent-to-treat	0.22 – 0.33 = – 0.11
Causal effect in compliers	– 0.11/ 0.61 = – 0.18

Data from Shrier et al., 2014

Example 4. Effect of job training seminar in unemployed persons on subsequent depression

Group	Treatment	Mean depression score
Control	No seminar	0.057
Seminar invitation	No seminar	0.016
	Seminar (56%)	

Method	Estimate
Intent-to-treat	0.016 – 0.57 = – 0.41
Causal effect in compliers	– 0.41 / 0.56 = – 0.73

Data from Little and Yau, 1998

Example 5. Effect of stopping maternal smoking on birth weight

Group	Treatment	Number	Fraction with low birth weight
Control	Continue	438	0.089
	Stop (20%)		
Encourage stop smoking	Continue	429	0.068
	Stop (43%)		

Method	Estimate
Intent-to-treat	0.068 – 0.089 = – 0.021
Causal effect in compliers	– 0.021 /(0.43 – 0.20) = – 0.091

Data from Sexton and Hebel, 1984; Permutt and Hebel, 1989

Example 6. Effect of flu vaccine on hospitalization

Group	Treatment	Number	Fraction hospitalized
Control	No vaccine	1236	0.090
	Vaccine (26%)		
Vaccine reminders to physicians	No vaccine	1236	0.062
	Vaccine (43%)		

Method	Estimate
Intent-to-treat	0.062 – 0.090 = – 0.028
Causal effect in compliers	– 0.028 /(0.43 – 0.26) = –0.165

Data from McDonald et al., 1980-81 for Fall vaccines

Risk difference confidence intervals

	Intent-to-treat (ITT)	Causal effect in compliers
estimate	$D_{ITT} = p_1 - p_0$	$D_{complier} = D_{ITT} / (f_1 - f_0)$
std. err	$SE_{ITT} = \{p_1(1-p_1)/n_1 + p_0(1-p_0)/n_0\}^{1/2}$	$SE_{complier} \approx SE_{ITT} / (f_1 - f_0)$
95% CI	$D_{ITT} \pm 1.96\ SE_{ITT}$	$D_{complier} \pm 1.96\ SE_{complier}$

p_g = fraction with outcome 1 in randomization group g

f_g = fraction receiving treatment T1 in randomization group g

n_g = number in randomization group g

Statistical significance approximately the same for ITT and casual effect in compliers

$$D_{ITT} / SE_{ITT} \approx D_{complier} / SE_{complier}$$

Subtle point 1. Treatment definition

- **Commonly occurring scenario**
  - T0 is standard treatment and T1 is new treatment
  - Exclusion restriction requires T0 and T1 start at randomization
  - What if some persons receiving T1 do not fully comply?
- **Need to re-interpret**
  - T1 is starting new treatment
  - Estimate the causal effect of starting the new treatment
  - Still more informative than intent-to-treat, which estimates the effect of assignment to the new treatment

Subtle point 2. If extra data are available, check assumptions for risk difference

Group	Treatment Received	Minimal data for risk difference		Extra data
		Number	Number outcome=1	Number outcome=1
Assigned T0	T0	N_{00}	D_0	D_{00}
	T1	N_{01}		D_{01}
Assigned T1	T0	N_{10}	D_1	D_{10}
	T1	N_{11}		D_{11}

Quantity	Estimate	Needs
Pr(outcome=1| complier, group 0)	$Q_0 = (D_{00}/N_0 - D_{10}/N_1)/F$	$Q_0 \geq 0$
Pr(outcome=1| complier, group 1)	$Q_1 = (D_{11}/N_1 - D_{01}/N_0)/F$	$Q_1 \geq 0$
Difference in fraction who are compliers	$F = N_{11}/N_1 - N_{01}/N_0$	

Aside: $RR = Q_1/Q_0$ (Baker, 1997, Baker and Kramer, 2004)

Relative risk needs more data than risk difference

Subtle point 3. Generalizability of estimated causal effects in compliers

Complier generalizability

Compliers ➔ All randomized trial participants

(Causal generalizability plot)

Randomized trial generalizability

All randomized trial participants ➔ Population

Meta-analysis with latent class instrumental variables

$D_{complier(i)}$ = estimated causal effect in compliers in trial i

$V_{complier(i)}$ = variance of estimated causal effect in compliers in trial I

Fixed effects meta-analysis

Estimate	$D_{meta} = \sum D_{complier(i)} w_i$
Standard error	$SE_{meta} = \{\sum V_{complier(i)} w_i^2\}^{1/2}$
95% confidence interval	$D_{meta} + 1.96\ SE_{meta}$

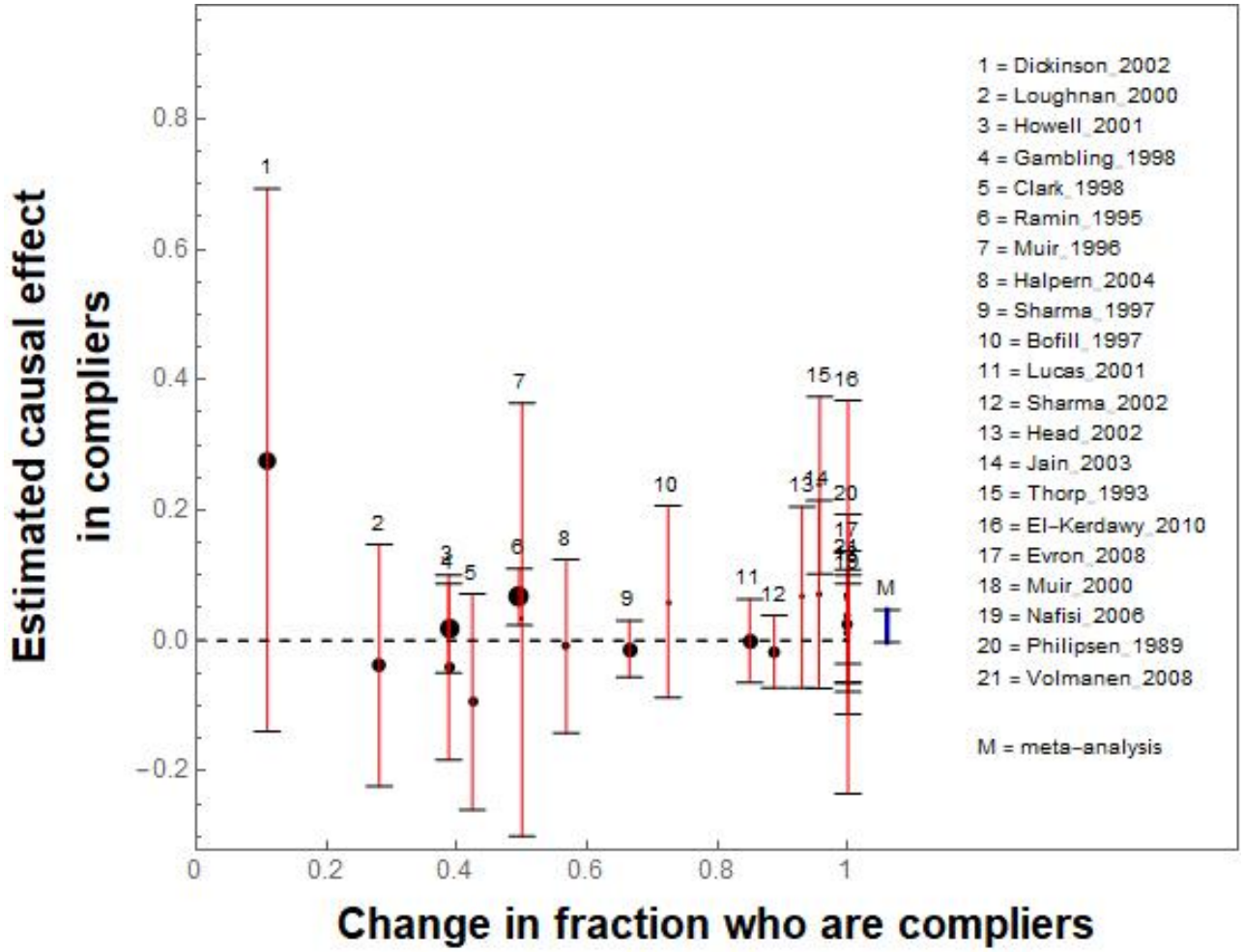
$w_i = (1/V_{complier(i)}) \sum (1/V_{complier(i)})$

Example 7. Meta-analysis of randomized trials: Effect of labor epidural analgesia on the probability of C-section

- Caveat
  - Not all-or-none compliance
  - Some cross-overs occurred after randomization
- Exclusion restriction approximately holds
  - Timing of epidural analgesia does not effect probability of C-section (Chestnut et al, 1994)

Causal generalizability plot

Effect of epidural analgesia on the probability of C-section



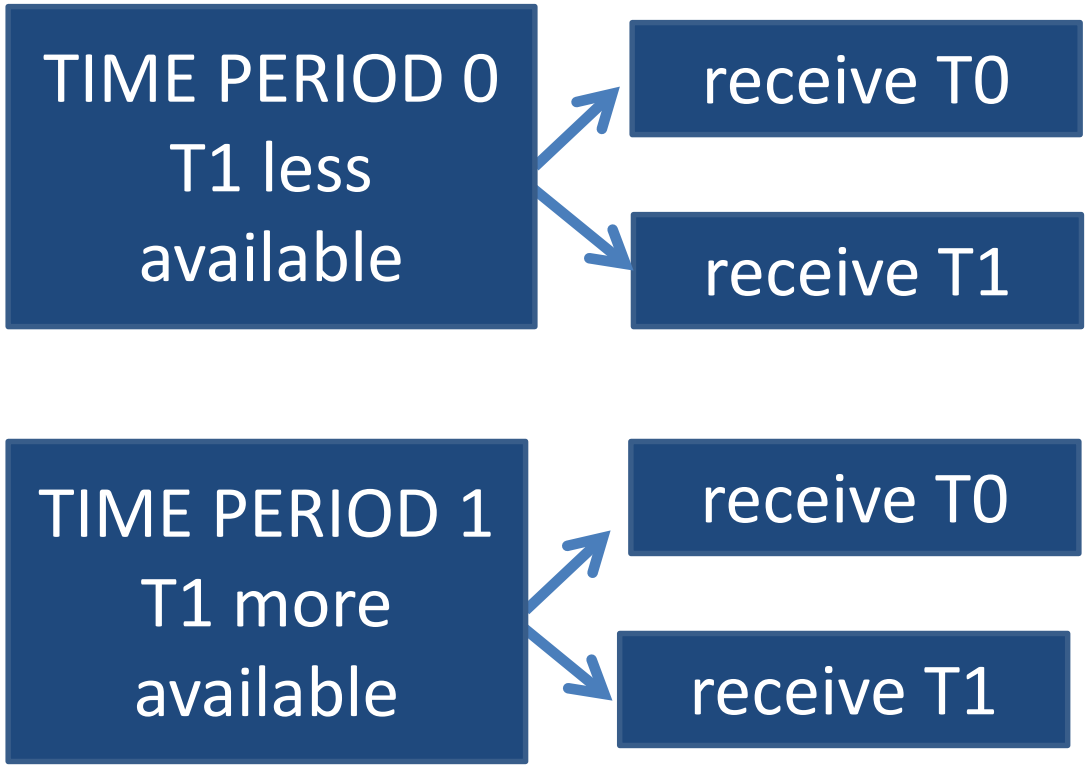
No trend

Meta-analysis: Small effect with borderline statistical significance

Outline

- Randomized trials with all-or-none compliance
- The paired availability design

Paired Availability Design



Baker and Lindeman, 1994

<u>Goal:</u> Estimate effect of receipt of T1 versus T0

"paired"	because pairs of time periods in multiple medical centers
"availability"	because availability changes over time
"design"	because investigators can choose medical centers where they will increase T1 availability

When to use the paired availability design

- **Randomized trial not feasible**
  - Blinding not possible
- **Multivariate adjustment is problematic**
  - Bias from unmeasured confounder
  - Missing data on covariates
- **Paired availability design is feasible**
  - Short-term endpoint
  - Multiple medical centers

Latent class instrumental variables with the paired availability design

	Treatment received if the person were to arrive (all else the same) in	
Latent class	Time period 0 when T1 is less available	Time period 1 when T1 is more available
Always-receiver	T1	T1
Never-receiver	T0	T0
Consistent-receiver	T0	T1
Inconsistent-receiver	T1	T0

Example: T0 = no epidural analgesia
T1= epidural analgesia

Assumptions so time period is like randomization group (an instrumental variable)

Assumption	Unchanged over time	Example of violation	Strengthen design
Stable population	Composition of population related to outcome	Seek out new treatment	-Geographic isolation -Army medical center
Stable ancillary care	Management of patient unrelated to treatment	New staff	-Same staff, -Strict protocol -Short-term study
Stable disease	Natural history of disease	New strain of virus	
Stable evaluation	Method to evaluate outcome	Test to stage cancer	

To estimate the effect of treatment received
with all-or-none compliance:

Latent class instrumental variables

this terminology from Baker, Kramer, Lindeman (2016) *Stat Med*

All-or-none compliance	**Key papers (multiple independent developments)**
One-sided	Baker (1983, *technical report, Harvard Biostatistics*) Bloom (1984) *Evaluation Review* Sommer and Zeger (1991) *Stat Med* Connor, Prorok, Weed (1991) *J Clin Epidemiol*
Two-sided	Imbens and Angrist (1994) *Econometrica* Baker and Lindeman (1994) *Stat Med* Angrist, Imbens, Rubin (1996) *JASA* *These 3 papers were called seminal by Swanson et al (2018) JASA*

Stable Preference Assumption

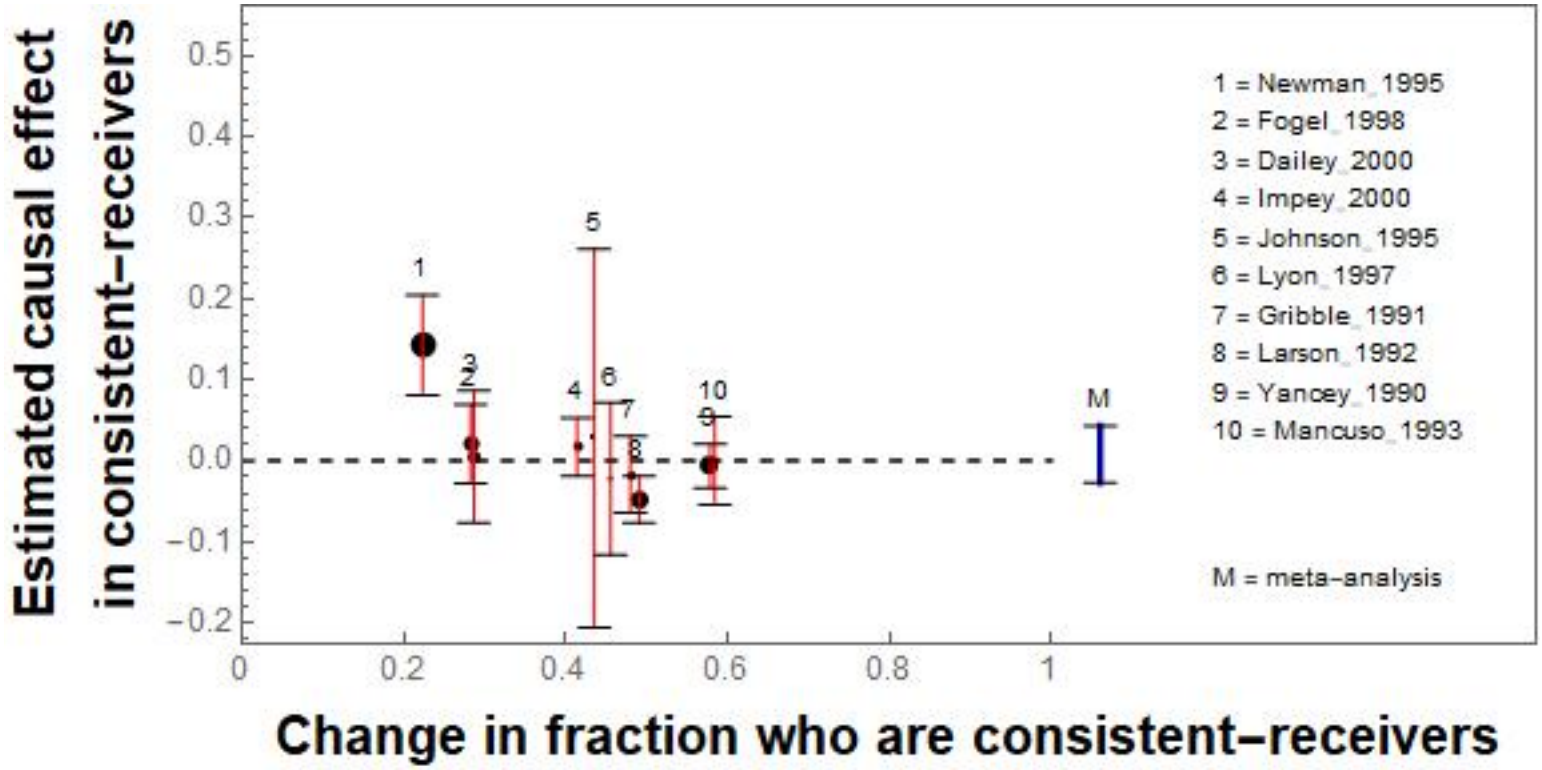
Availability of T1 (epidural)		Assumption	
Fixed	9 to 11 AM epidural service	No Inconsistent-receivers	Monotonicity
Random	Varying schedule of anesthesiologist	Same treatment effect for Consistent-receiver and inconsistent-receiver	Randomicity

Estimated causal effect in consistent-receivers = $\frac{\text{Difference in outcomes between time periods}}{\text{Difference in fraction receiving T1 between time periods}}$

Latent class	Time period 0	Time period 1
	T1 less available	T1 more available
Always-receiver	T1	T1
Never-receiver	T0	T0
Consistent-receiver	T0	T1
Inconsistent-receiver	T1	T0

Causal generalizability plot

Effect of epidural analgesia on the probability of C-section



No trend

Meta-analysis: no statistical significance; narrow confidence interval

Effect of epidural analgesia on the probability of C-section

(1) Meta-analysis of randomized trials with adjustment for cross-overs

Risk difference = 0.022 with 95% CI (-0.002, 0.047)

(2) Multivariate analyses of concurrent observational data

	Covariates	RR (95%CI)
Lieberman et al (1996)	Age, race, insurance, pre-pregnant weight, height ,birth weight, ….	3.7 (2.4, 5.3)
Bannister-Tyrrell et al (2014)	Age, born in Australia, married, parity, smoking, induction, gestational age,….	2.5 (2.5, 2.6)

Major concern: unmeasured confounder of pain in labor

(3) Paired availability design

Risk difference = 0.008 with 95% CI (-0.027, 0.043)

Conclusion

Randomized trials with all-or-none compliance

Estimated causal effect in compliers = Difference in outcomes between groups / Difference in fraction receiving T1 between groups

Based on reasonable assumptions with latent class instrumental variables

Paired availability design

Estimated causal effect in consistent-receivers = Difference in outcomes between time periods / Difference in fraction receiving T1 between time periods

Based on reasonable assumptions with latent class instrumental variables

Key design considerations: Multiple medical centers

Short-term endpoint

Staff and protocol same over time

Supplementary slides to answer possible questions

Partial compliance is not identifiable with 2 groups

T0= placebo; T1 = new pills then stop; T2 = new pills continuously

Latent class	Treatment received if randomized to		Assumption
	Group assigned T0	Group assigned T2	
Always-taker	T2	T2	Exclusion restriction
Always-taker	T1	T1	Exclusion restriction
Never-taker	T0	T0	Exclusion restriction
Complier	T0	T1	
Complier	T0	T2	
Complier	T1	T2	
Defier	T1	T0	None
Defier	T2	T0	None
Defier	T2	T1	None

14 parameters: = 5 independent latent class probabilities (dropping defiers) +
9 outcome probabilities (2 always-takers + 1 never-taker + 6 compliers)

10 independent counts: = {3 treatments x 2 binary outcomes – 1} × 2 groups

Partial compliance in three randomization groups

For women in labor, effect of walking on rate of C-section;

Baker, Frangakis, Lindeman (2007)

Group	Treatment assigned	
0	T0	No walking
1	T1	Walk 1 to 2 hours
2	T2	Walk at least 2 hours

Monotonicity extension

only T0 in group 0 (empirical support)

T1 in group 2 → T1 in group 1 (consistent preferences)

T2 in group 2 → T1 in group 1 (by design)

Randomized trials with all-or-none compliances: Extension: missing or censored outcomes

Assumption	Description
Latent ignorability	Missing or censoring depends on group and latent class but not outcome
Compound exclusion restriction	Applies to missing-data or censoring mechanisms

Treatments	All-or-none compliance	Outcome	Missing	Reference
-No screen -Screen	Refused screen	Breast cancer death	Censored data	Baker (1998)
-Mailing, -Mailing + course	Not take course	Breast self exam skill on questionnaire	Missing question-naire	Mealli et al (2004)
-Placebo -Finasteride	Not take treatment	Prostate cancer on biopsy	Missing biopsy	Baker (2000)

Paired availability design: proposed application

	Epidural analgesia on rate of C-section	**Proposed application to cancer screening**
New treatment	Epidural analgesia	New screening modality
Locations of studies	Medical centers	Geographic regions
Outcome	C-section rate in time period	Interval cancer rate in year following time period