Statistical Challenges in the Design of a Pragmatic Trial of Primary Care-based Treatment for Opioid Use Disorders

The PROUD Trial

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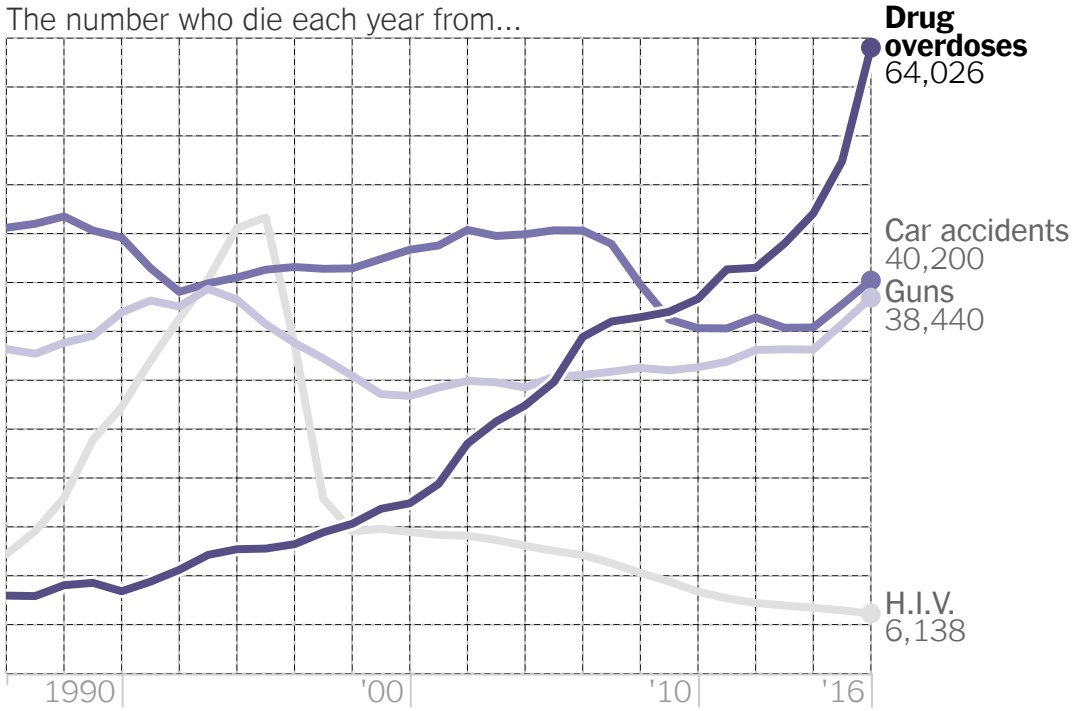
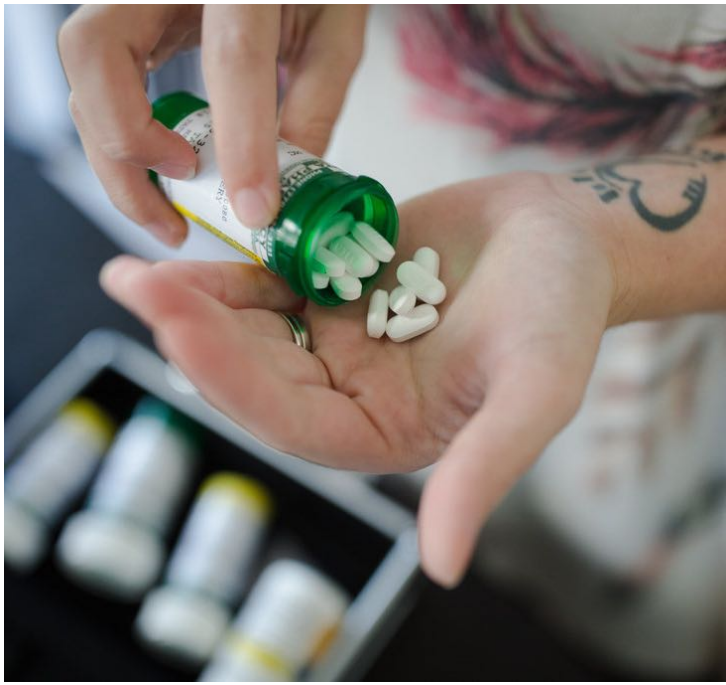
Outline

- Motivation for the PROUD trial
- Overview of PROUD trial design
- Background on pragmatic clinical trials
- Challenges of the PROUD trial
- Addressing potential for “identification bias” in design and analysis
- Discussion

The New York Times

The Opioid Epidemic: A Crisis Years in the Making





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Gap in opioid use disorder (OUD) treatment

- Medication treatment for OUD
  - Buprenorphine
  - Injectable naltrexone
  - Methadone

  } Can be prescribed in primary care (PC)
- Most people with OUD not receiving treatment
- Need new approaches to ensure access to and retention in evidence-based treatment, especially in PC

Massachusetts (MA) Model

- Collaborative care management for OUDs
- Nurse care manager partners with PC team
- Found to be successful: persistent treatment
- Persistent treatment: associated with increased survival and lower health care utilization
- Predominantly in publicly financed community clinics
- Evidence based on case series design

Evidence gap

- Effectiveness of MA Model over usual PC has not been tested in a randomized controlled trial
- Lack of evidence in diverse health systems, heterogeneous populations

The PRimary care Opioid Use Disorders Treatment (PROUD) Trial

Pragmatic, cluster-randomized implementation trial

PROUD intervention:

- Money to hire nurse care manager for the MA Model
- Technical assistance
- Require 3 prescribers to be waivered for buprenorphine

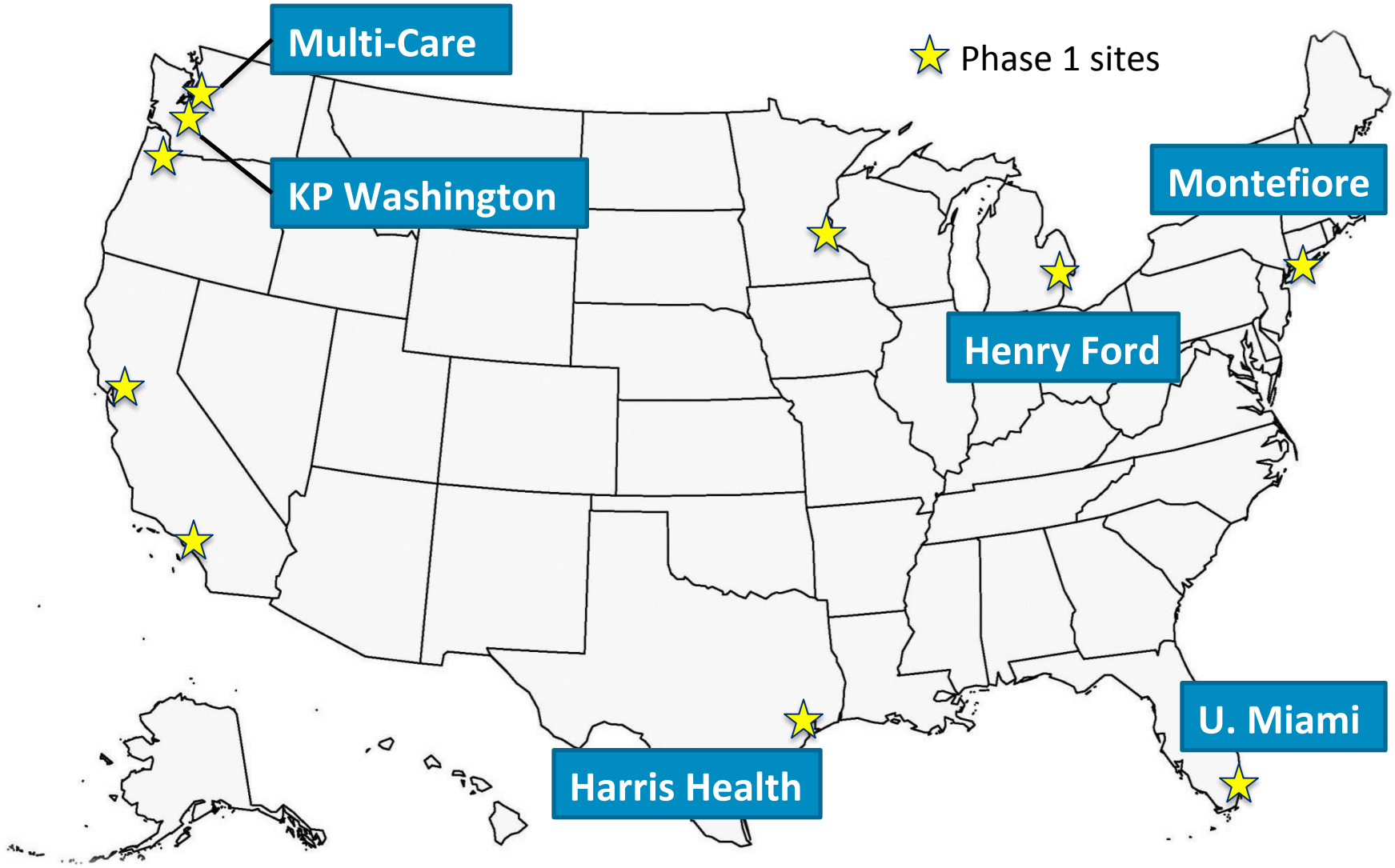
Sample: 12 PC clinics within 6 health care systems (HCS)

- 295,000 PC patients (2014-2016)
- 1,428 active OUD diagnosis

Randomization: stratified on the HCS (1 PROUD, 1 usual PC clinic)

PROUD Phase 1: preliminary studies

PROUD sites: 6 diverse health systems



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PROUD Trial objectives

Evaluate the effectiveness of the PROUD intervention in 6 diverse health care systems:

1. Does MA Model increase access to and retention in evidence-based treatment?
2. Does MA Model reduce acute care utilization (emergency department and hospital care) among patients with OUD?

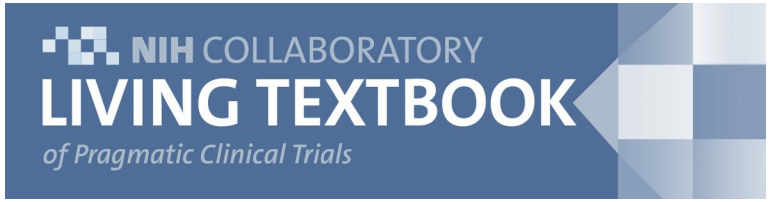
Outcomes assessed using electronic health record (EHR) data

Aim 1:
Number of patient-days of OUD treatment (clinic-level), scaled (divided) by number of patients seen in the clinic

Aim 2:
Number of days of acute care utilization (patient-level)

Pragmatic clinical trials (PCTs)

"Pragmatic clinical trials are performed in real-world clinical settings with highly generalizable populations to generate actionable clinical evidence at a fraction of the typical cost and time needed to conduct a traditional clinical trial."



Advantages of PCTs

- Large sample sizes
- Opportunity to study a diverse population including subgroups (e.g., youth, pregnant women) that are often excluded from explanatory trials
- Generalizability

Challenges of PCTs

- Rely on big, often messy clinical and claims data not collected for research purposes
- Often randomized at a cluster level
- May have a small number of clusters; correlation of participants from same cluster

Challenges of the PROUD study

Challenge of PCTs: clinical and claims data not collected for research purposes

In PROUD: 2 sites are integrated health systems; 4 are not

- Clinic population not well characterized: visit-based sample
- Reliance on medication orders data (rather than dispensings)
- Potential for incomplete ascertainment of outcomes

Approach:

- Stratified randomization
- Sensitivity analyses among 2 integrated systems

Challenges of the PROUD study

Challenge of PCTs: may have a small number of clusters

In PROUD: only 12 clinics (6 per arm)

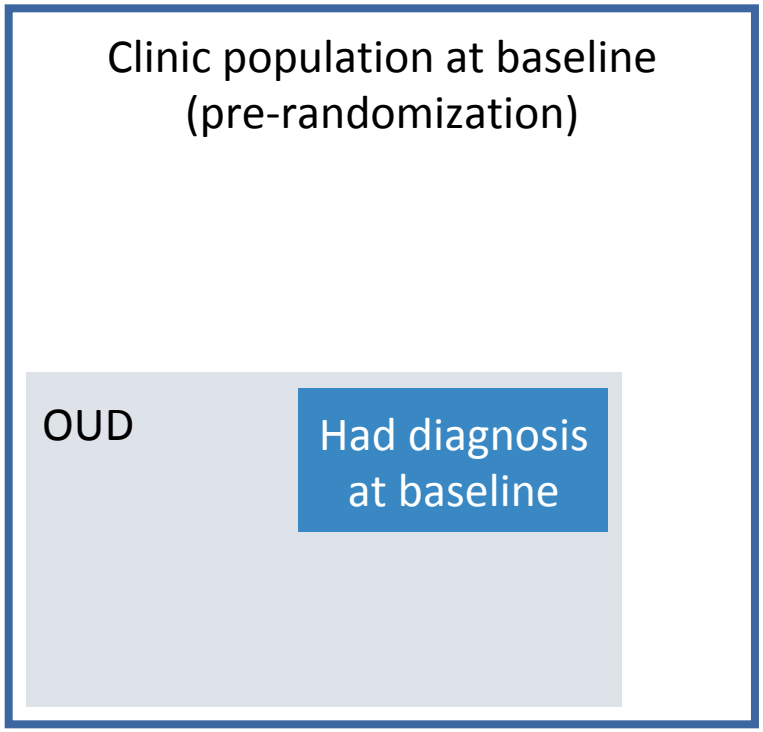
- Concerned about potential for chance imbalance in clinic size, other covariates

Approach:

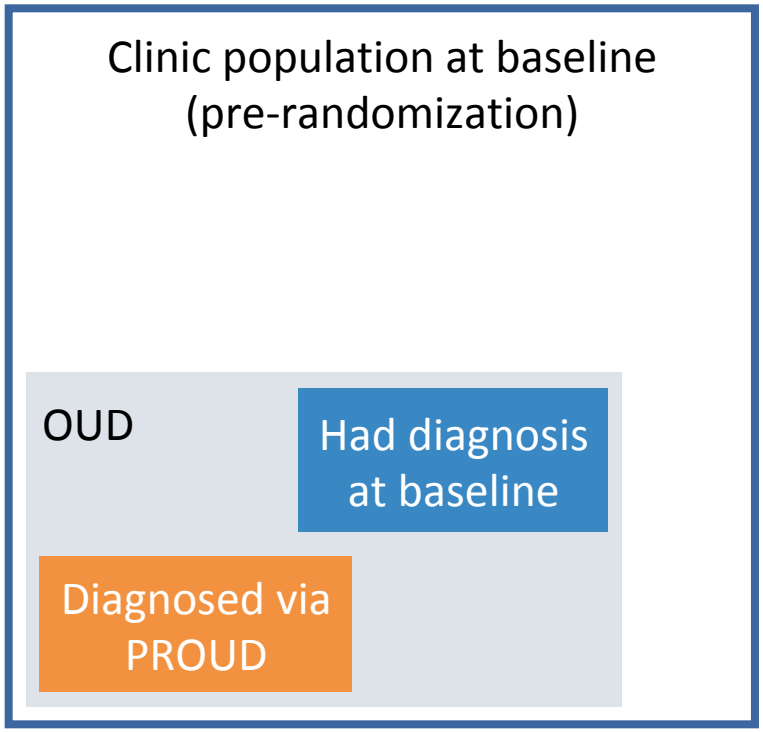
- Primary outcome is scaled measure (divided by number of patients seen)
- Considered using constrained randomization
- Secondary analyses adjusting for covariates

Challenges of the PROUD study

1. Latent population of individuals with OUD
   - OUD is under-diagnosed (Phase 1 prevalence: 0.50%)



Challenges of the PROUD study



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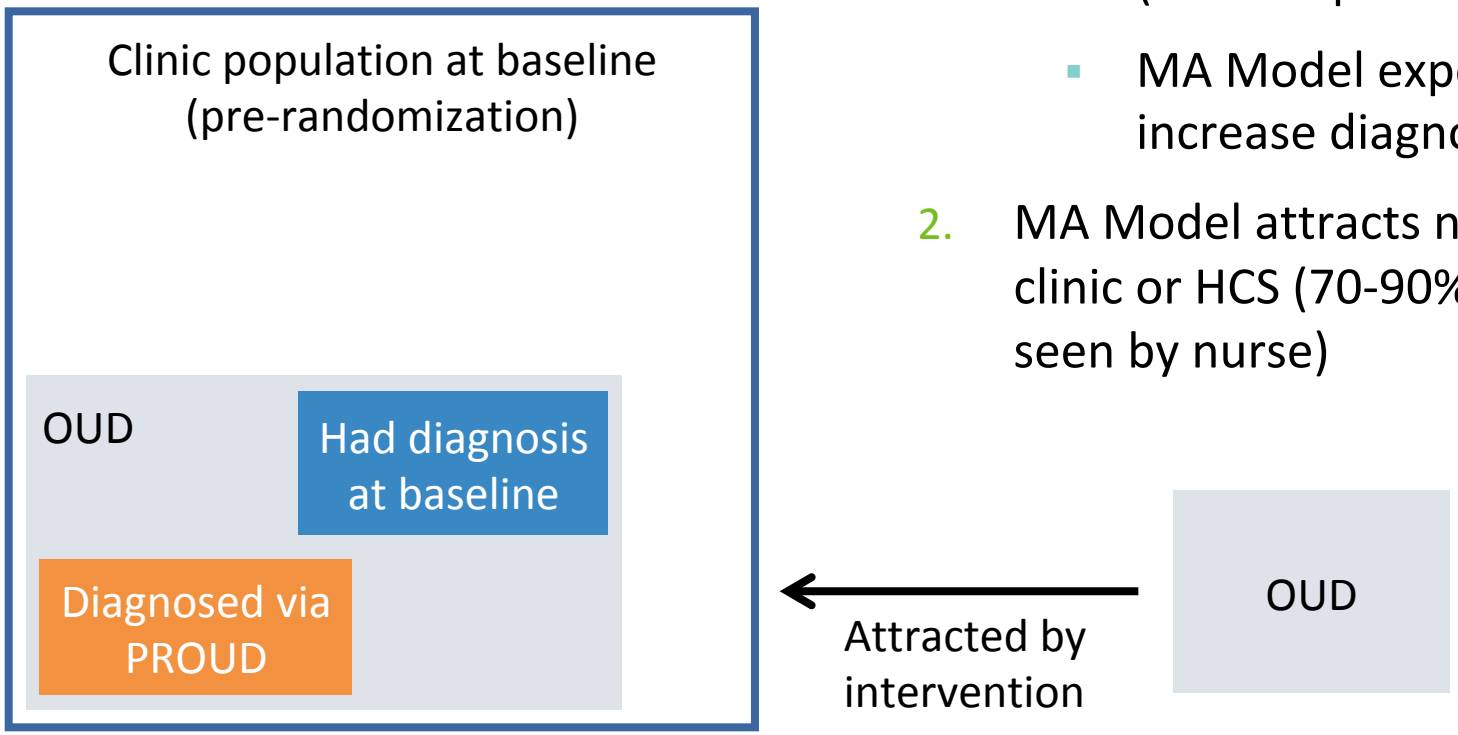
   - MA Model expected to increase diagnosis

Challenges of the PROUD study

1. Latent population of individuals with OUD
   - OUD is under-diagnosed (Phase 1 prevalence: 0.50%)
   - MA Model expected to increase diagnosis
2. MA Model attracts new people to clinic or HCS (70-90% of patients seen by nurse)



Potential for identification bias

Identification bias: form of selection bias that can occur when the intervention affects who is identified as being eligible

Aim 2 effectiveness outcome (number of days of acute care utilization):

- Example analytic study population: patients with an OUD diagnosis
- Intervention affects who is diagnosed with OUD
- Patients diagnosed in the intervention arm are likely to be different (either sicker or healthier) than patients diagnosed in the control arm.
- Bias can be in either direction

Addressing identification bias

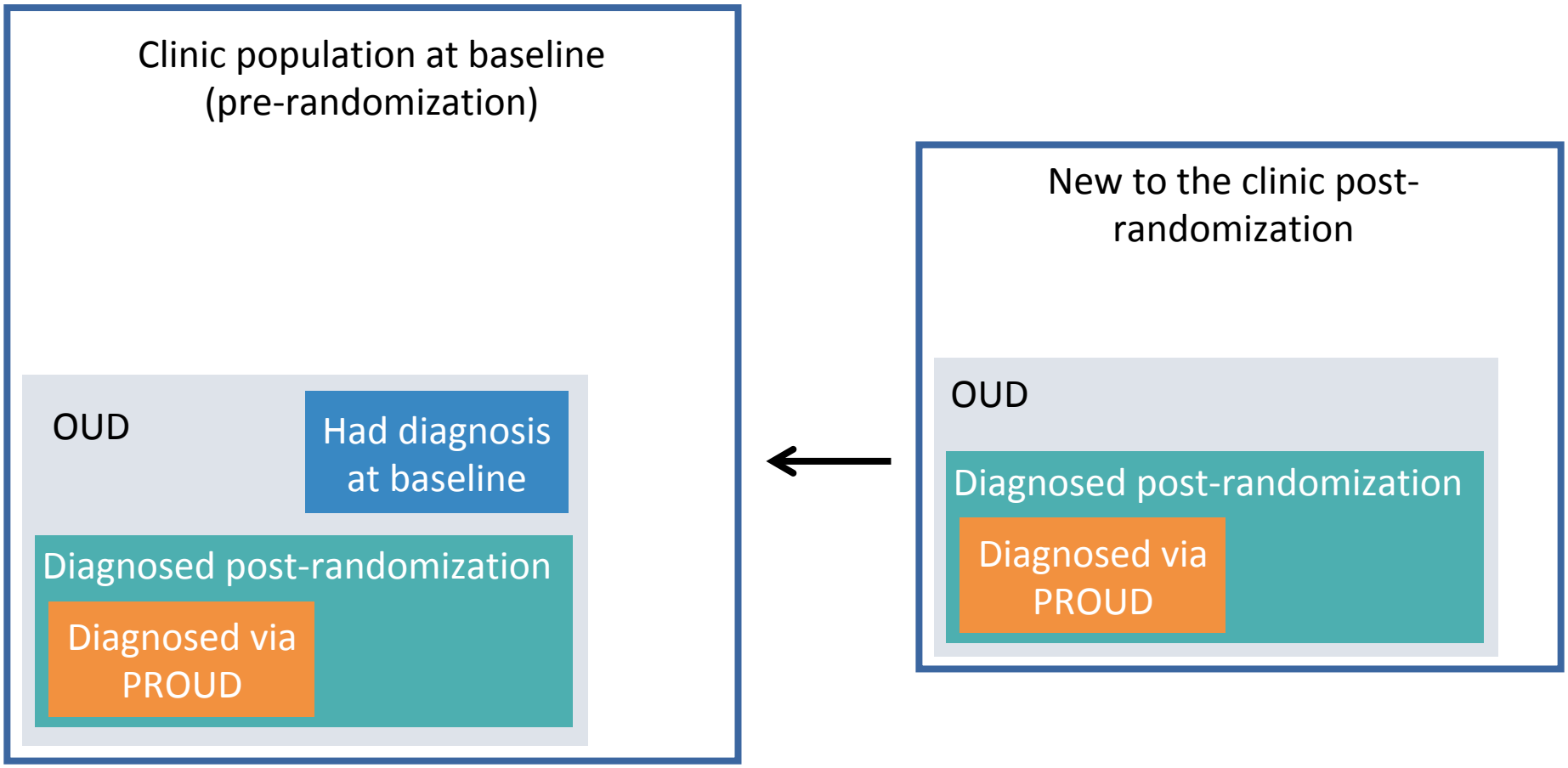
Design solution: only include individuals identified pre-randomization

- Randomization ensures comparability across intervention groups
- Aim 2 example: patients with an OUD diagnosis pre-randomization

Limitations:

- Misses a large number of patients potentially affected
- Patients identified pre-randomization may not reflect broader population with OUD

Potential for identification bias



Considerations in addressing identification bias

Competing goals:

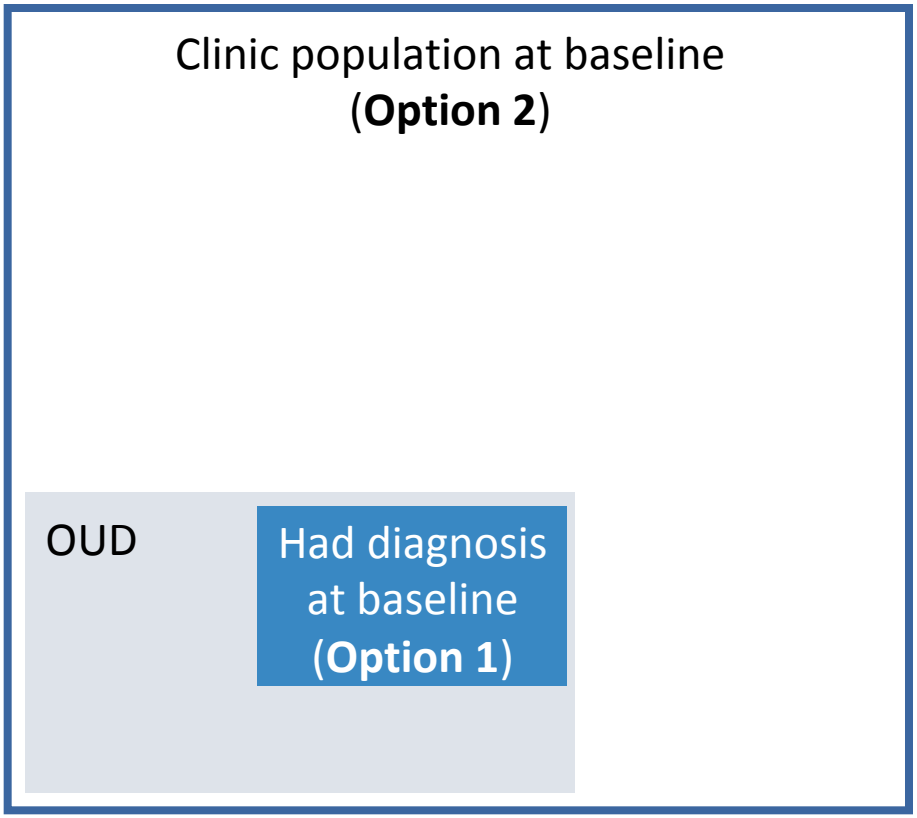
- Avoiding potential for identification bias
- Capture full effect of intervention

Approach for Aim 2 effectiveness outcome (number of days of acute care utilization):

- Primary: analytic study population identified pre-randomization
- Secondary: include individuals diagnosed post-randomization

Acute care utilization (Aim 2) primary analysis

Options for defining the analytic study population based on pre-randomization data



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Acute care utilization (Aim 2) primary analysis

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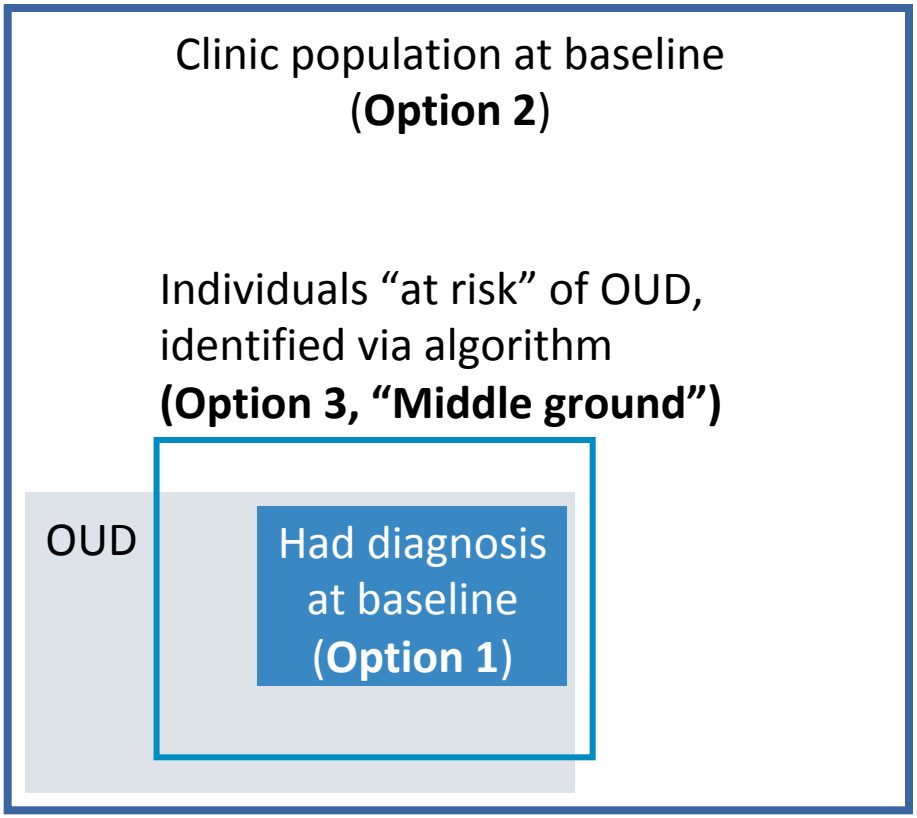

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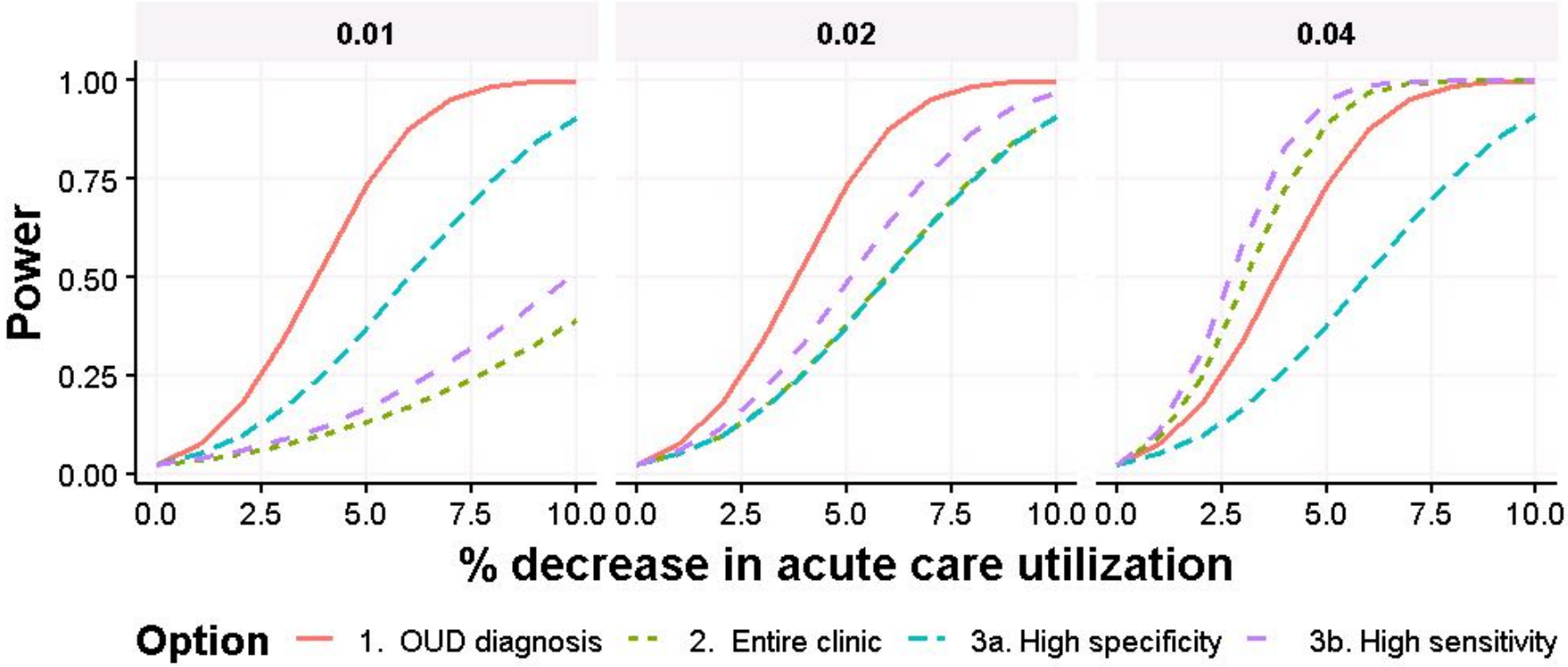
Power evaluation guiding choice of study population

Considered different scenarios that varied

- prevalence of OUD: 1%, 2%, 4%
- (sensitivity, specificity) corresponding to each option for the analytic study population:

Option	
1	OUD diagnosis
2	Entire clinic
3a	High specificity
3b	High sensitivity

Power evaluation guiding choice of study population



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Acute care utilization (Aim 2) secondary analysis

Limitations of primary analysis:

- Does not capture full effect of PROUD intervention
- Misses patients without prior OUD diagnosis, or who are new to the clinic or HCS

Secondary analyses:

- Consider individuals diagnosed post-randomization
- Adjust for **measured factors** that differ across patients identified post-randomization in the intervention vs. control clinics
- Investigate the potential for **unmeasured factors** to cause bias

Acute care utilization (Aim 2) secondary analysis

Clinic-specific random intercept

$$log\ E(y_{ijk}) = \alpha_0 + \alpha_1 \text{period}_{ijk} + (\beta_0 + \beta_1 \text{period}_{ijk}) trt_{ij} + \gamma z_{ijk} + \theta_{ij}$$

Number of days of acute care utilization for person *k* in clinic *j* of HCS *i*

Acute care utilization (Aim 2) secondary analysis

Clinic-specific random intercept

$$log\ E(y_{ijk}) = \alpha_0 + \alpha_1 \text{period}_{ijk} + (\beta_0 + \beta_1 \text{period}_{ijk}) trt_{ij} + \gamma z_{ijk} + \theta_{ij}$$

Number of days of acute care utilization for person *k* in clinic *j* of HCS *i*

Covariates that could explain differences between individuals newly diagnosed (post-randomization) with OUDs in the PROUD intervention clinics as compared to UPC clinics

Acute care utilization (Aim 2) secondary analysis

Indicator for the period when the patient had their first documented OUD (post- vs. pre-randomization)

Clinic-specific random intercept

$$log\ E(y_{ijk}) = \alpha_0 + \alpha_1 \text{period}_{ijk} + (\beta_0 + \beta_1 \text{period}_{ijk}) trt_{ij} + \gamma z_{ijk} + \theta_{ij}$$

Number of days of acute care utilization for person *k* in clinic *j* of HCS *i*

Covariates that could explain differences between individuals newly diagnosed (post-randomization) with OUDs in the PROUD intervention clinics as compared to UPC clinics

Summary

- Identification bias is an important issue to consider when designing PCTs in settings where the intervention may affect identification of the study population of interest
- Potential for bias is heightened in settings of underdiagnosed conditions such as OUD, and where the intervention increases diagnosis relative to usual care
- Tradeoff between minimizing potential for identification bias and capturing the full effect of the intervention
- PROUD trial has power to estimate intervention effects on acute care utilization among individuals with an OUD diagnosis pre-randomization, but this would miss full impact of the intervention (including 70-90% of patients new to clinic)

Summary

- Identification bias may be addressed in both the design and analysis stage
  - **Design:** it can be avoided by specifying the analytic study population based on pre-randomization data
  - **Analysis:** methods can be applied to adjust for this source of bias, and sensitivity analysis may be conducted
- A guidance document on this issue is currently being developed for the NIH Collaboratory

Acknowledgments

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Co-investigators
Data and analytics team

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Definition of “increased risk” of OUD

Includes individuals with any OUD diagnosis at baseline or anyone with:

- Chronic opioid therapy (outside of end of life, palliative care, or active cancer treatment) and
- At least one of the following risk factors: high morphine equivalent dose, alcohol or other substance use disorders, mental health disorders, concurrent sedative use, or pain in 2 or more body regions (e.g., headache and back pain).

Details on power evaluation scenarios

1	OUD diagnosis	• Assumes all individuals with an active OUD diagnosis do in fact have OUD (specificity = 1) • Sensitivity selected to be consistent with the observed proportion of patients with an active OUD diagnosis in Phase 1 data (0.43%) and the specific choice of the prevalence of OUD (π)
2	Entire clinic	By definition, sensitivity = 1 and specificity = 0
3a	High specificity	Selected to have slightly higher sensitivity than scenario 1 (1.2 times the value), at the cost of slightly reduced specificity
3b	High sensitivity	• Sensitivity was selected based on a previously developed algorithm to identify individuals with opioid abuse and addition, among patients on long-term opioid therapy • We considered a lower specificity (0.5 versus 0.64) given that our initial sample is the entire clinic population, not restricted to long-term opioid users
3c	Equal sens./spec.	Selected to have lower sensitivity and higher specificity than option 3b