Does starting buprenorphine prevent suicidal behavior:

What trial should we emulate?

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Supported by NIMH Cooperative Agreement U19 MH121738
No other relevant financial interests or conflicts to disclose

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Motivation: Intertwining crises of OUD and self-harm or suicide

- Overlap of Opioid Use Disorder (OUD) and mood/anxiety disorders
- OUD (and other SUD) associated with increased risk for self-harm
- Fuzzy boundary between self-harm and accidental overdose

What we knew (or believed) when we started

- Buprenorphine increases abstinence / reduces relapse into OUD
  - Randomized efficacy trials, compared to placebo
- Buprenorphine reduces risk of opioid poisoning or overdose
  - Observational studies, compared to time off treatment
- Acute administration of buprenorphine reduces suicidal ideation
  - Pre-clinical studies, compared to placebo

Study Question

Among people with diagnosed OUD does starting (vs. not starting) buprenorphine reduce risk of a self-harm event over the next 90 days?

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Design (specified in advance)

- Observational study with target trial emulation:
  - Consider visits where buprenorphine could have been started
  - Compare outcomes after visits where buprenorphine was/was not started
  - Includes all eligible visits per person
- Setting: Henry Ford, KP Northern California, KP Southern California, KP Washington
- Eligible outpatient visits:
  - Age >=13
  - Visit diagnosis of OUD (including in remission)
  - Enrolled in health system at time of visit
  - No current/recent medication treatment for OUD (buprenorphine, methadone, naltrexone)
  - Eligible visit types vary across health systems
    - KPWA – Primary care
    - KPNC – SUD Specialty care
    - Henry Ford & KPSC – Either
- Outcomes
  - Primary: Any self-harm diagnosis in next 90 days (could include opioid poisoning)
  - Secondary:
    - Any opioid poisoning diagnosis (self-harm, accidental, undetermined intent)
    - Any injury or poisoning diagnosis

Design (informed by data)

- Definition of buprenorphine start:
  - Dispensings cluster 0 to 3 days after eligible visit with few >7 day (and those usually have intervening visit)
  - Decision: Define start as dispensing within 7 days of eligible visit
- Definition of buprenorphine interruption
  - Initial dispensings all for 7 days, often shifting to 14 days and sometimes to 28 days (within first 90 days)
  - Decision: Interruption if gap > 7 days AND > 125% of days supply
- Primary analytic strategy
  - Starting buprenorphine varied considerably across health systems, NOT strongly related to usual risk factors for self-harm, decreased markedly with long duration (time or visits) of OUD diagnosis
  - Decision: Match each visit with buprenorphine start to 2 or 3 visits without start, matching on site and # days with OUD Dx in prior 3 mos, Adjust for site, # OUD days, and suicide risk prediction score

Self-harm risk prediction score

- Developed and validated in these and 3 other health systems
- 94 predictors extracted from health records
- AUC=0.86 for prediction of self-harm event in 90 days following a mental health visit

Eligible visit sample

183,809 visits

- 15,508 (8.4%) followed by buprenorphine start within 7 days
  - Generally similar to other cohorts of outpatients with OUD diagnoses
- 2260 (1.2%) followed by self-harm event within 90 days
  - Modestly higher than mental health specialty outpatient samples

	All Eligible Visits	Visits Followed by Buprenorphine Start	All Visits Not Followed by Buprenorphine Start	Matched Visits Not Followed by Buprenorphine Start
Total	183809	15508	168301	36649
Sex				
Female	71502 (39%)	5376 (35%)	66126 (39%)	14497 (40%)
Male	112307 (61%)	10132 (65%)	102175 (61%)	22152 (60%)
Age at visit				
13-17	1083 (1%)	35 (0%)	1048 (1%)	349 (1%)
18-29	66384 (36%)	7357 (47%)	59027 (35%)	12339 (34%)
30-44	50937 (28%)	4212 (27%)	46725 (28%)	9855 (27%)
45-64	55419 (30%)	3434 (22%)	51985 (31%)	11589 (32%)
65+	9986 (5%)	470 (3%)	9516 (6%)	2517 (7%)
Race				
Asian	5412 (3%)	445 (3%)	4967 (3%)	1085 (3%)
Black	10690 (6%)	869 (6%)	9821 (6%)	2189 (6%)
Hawaiian/Pacific Islander	1102 (1%)	124 (1%)	978 (1%)	211 (1%)
Native American / Alaskan Native	2220 (1%)	178 (1%)	2042 (1%)	412 (1%)
Multiple	224 (0%)	35 (0%)	189 (0%)	55 (0%)
Other	299 (0%)	21 (0%)	278 (0%)	76 (0%)
Unknown	15408 (8%)	1404 (9%)	14004 (8%)	3296 (9%)
White	148454 (81%)	12432 (80%)	136022 (81%)	29325 (80%)
Hispanic Ethnicity				
Non-Hispanic	73654 (40%)	5323 (34%)	68331 (41%)	13475 (37%)
Unknown	73587 (40%)	6909 (45%)	66678 (40%)	15718 (43%)
Hispanic	36568 (20%)	3276 (21%)	33292 (20%)	7456 (20%)

	All Eligible Visits	Visits Followed by Buprenorphine Start	All Visits Not Followed by Buprenorphine Start	Matched Visits Not Followed by Buprenorphine Start
Total	183809	15508	168301	36649
# OUD Dx in past 24 mos				
0 days	35064 (19%)	4530 (29%)	30534 (18%)	11421 (31%)
1 day	23373 (13%)	3848 (25%)	19525 (12%)	8736 (24%)
2 days	16890 (9%)	2333 (15%)	14557 (9%)	6106 (17%)
3-4 days	24024 (13%)	2319 (15%)	21705 (13%)	4971 (14%)
5-10 days	71502 (39%)	71502 (39%)	71502 (39%)	71502 (39%)
11-30 days	42179 (23%)	531 (3%)	41648 (25%)	1571 (4%)
31-92 days	4377 (2%)	25 (0%)	4352 (3%)	72 (0%)
Diagnoses in Prior Year				
Depressive Disorder	87061 (47%)	6455 (42%)	80606 (48%)	16638 (45%)
Anxiety Disorder	96749 (53%)	7363 (47%)	89386 (53%)	18359 (50%)
Bipolar Disorder	16215 (9%)	1068 (7%)	15147 (9%)	3210 (9%)
Alcohol Use Disorder	54042 (29%)	3247 (21%)	50795 (30%)	9595 (26%)
Non-Opioid SUD	103814 (56%)	8630 (56%)	95184 (57%)	17993 (49%)
Pain Condition	107728 (59%)	8550 (55%)	99178 (59%)	22557 (62%)
Service Use in Prior Year				
Inpatient with MH Dx	47621 (26%)	2895 (19%)	44726 (27%)	8220 (22%)
ED Visit with MH Dx	11338 (6%)	772 (5%)	10566 (6%)	2600 (7%)
Inpatient with MH Dx	53899 (29%)	4590 (30%)	49309 (29%)	10636 (29%)
ED Visit with MH Dx	30839 (17%)	2428 (16%)	28411 (17%)	6280 (17%)
Prior Self-Harm Events				
Last 3 months	4666 (3%)	311 (2%)	4355 (3%)	875 (2%)
Last 12 months	4659 (3%)	296 (2%)	4363 (3%)	837 (2%)
Last 60 months	8476 (5%)	690 (4%)	7786 (5%)	1650 (5%)
Never	166008 (90%)	14211 (92%)	151797 (90%)	33287 (91%)

	Visits Followed by Buprenorphine Start – NO Self-Harm w/in 90 d	Visits Followed by Buprenorphine Start – YES Self-Harm w/in 90 d	Matched Visits Not Followed by Buprenorphine Start – NO Self-Harm w/in 90 d	Matched Visits Not Followed by Buprenorphine Start – YES Self-Harm w/in 90 d
Diagnoses in Prior Year				
Depressive Disorder	6330 (41%)	125 (63%)	16303 (45%)	335 (70%)
Anxiety Disorder	7251 (47%)	112 (57%)	18006 (50%)	353 (73%)
Bipolar Disorder	1036 (7%)	32 (16%)	3095 (9%)	115 (24%)
Alcohol Use Disorder	3182 (21%)	65 (33%)	9360 (26%)	235 (49%)
Non-Opioid SUD	8477 (55%)	153 (78%)	17610 (49%)	383 (79%)
Pain Condition	8433 (55%)	117 (59%)	22231 (61%)	326 (68%)
Service Use in Prior Year				
Inpatient with MH Dx	2836 (19%)	59 (30%)	7962 (22%)	258 (54%)
ED Visit with MH Dx	752 (5%)	20 (10%)	2503 (7%)	97 (20%)
Inpatient with MH Dx	4484 (29%)	106 (54%)	10335 (29%)	301 (62%)
ED Visit with MH Dx	2364 (15%)	64 (32%)	6084 (17%)	196 (41%)
Prior Self-Harm Events				
Last 3 months	290 (2%)	21 (11%)	801 (2%)	74 (15%)
Last 12 months	278 (2%)	18 (9%)	791 (2%)	46 (10%)
Last 60 months	670 (4%)	20 (10%)	1608 (4%)	42 (9%)
Never	14073 (92%)	138 (70%)	32967 (91%)	320 (66%)

Buprenorphine dispensed after index visit

Buprenorphine days supply dispensed over 90 days	
Visits Followed by Buprenorphine Start	Matched Visits Not Followed by Buprenorphine Start
44.3 (32.1)	1.1 (7.6)

Days to first interruption of buprenorphine (among starters)				
Min	25th %ile	Median	75th %ile	Max
8	10	28	67	90

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Results of planned/declared analyses:

- Starters matched to non-starters on site, #OUD Dx,
- Adjusted using high-dimensional self-harm risk score
- Compare starters to non-starters, regardless of actual use

Any Self-Harm Event			Any Injury or Poisoning			Opioid-Involved Overdose/Poisoning		
OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
1.01	(0.81, 1.24)	0.95	0.86	(0.77, 0.95)	0.004	1.09	(0.86, 1.38)	0.49

Oh Well…

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Oh Well…

Maybe…

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Oh Well…

Maybe…

What?!

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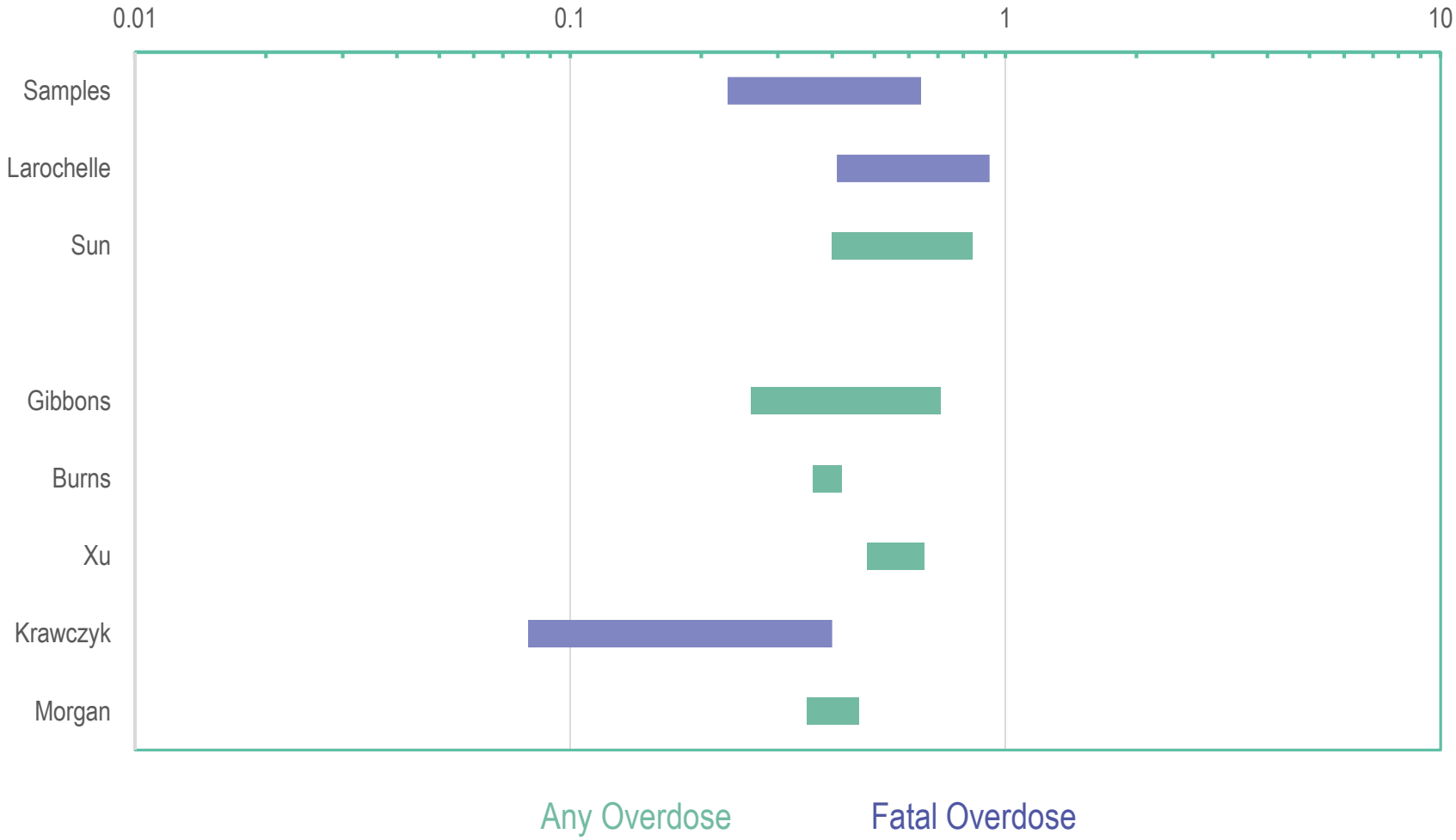
Prior studies of buprenorphine effect on opioid overdose

- Randomized trials – None (that we can find)
- Two types of observational studies:
  - Sample people with OUD (sometimes based on overdose or some other sentinel event) then compare risk during subsequent time "on" vs. time "off" buprenorphine over some defined period, with exposure and outcome usually assessed at month level
    - Samples (2023) – Medicare disability beneficiaries surviving opioid overdose
    - Larochelle (2018) – People without cancer who survived opioid overdose
    - Sun (2022) – Aged 18-64 with OUD diagnosis and no recent MOUD
  - Sample people starting buprenorphine (or any MOUD), then compare subsequent time "on" vs time "off" buprenorphine
    - Gibbons (2022) – Medicare beneficiaries with at least 2 buprenorphine fills
    - Burns (2022) - Medicaid beneficiaries with OUD diagnosis and MOUD dispensing
    - Xu (2022) – Age 12-64 with OUD diagnosis and use of buprenorphine or naltrexone
    - Krawczyk (2020) – Adults in outpatient specialty treatment for OUD
    - Morgan (2019) – Commercially insured adults starting MOUD

Observational studies of buprenorphine impact on overdose



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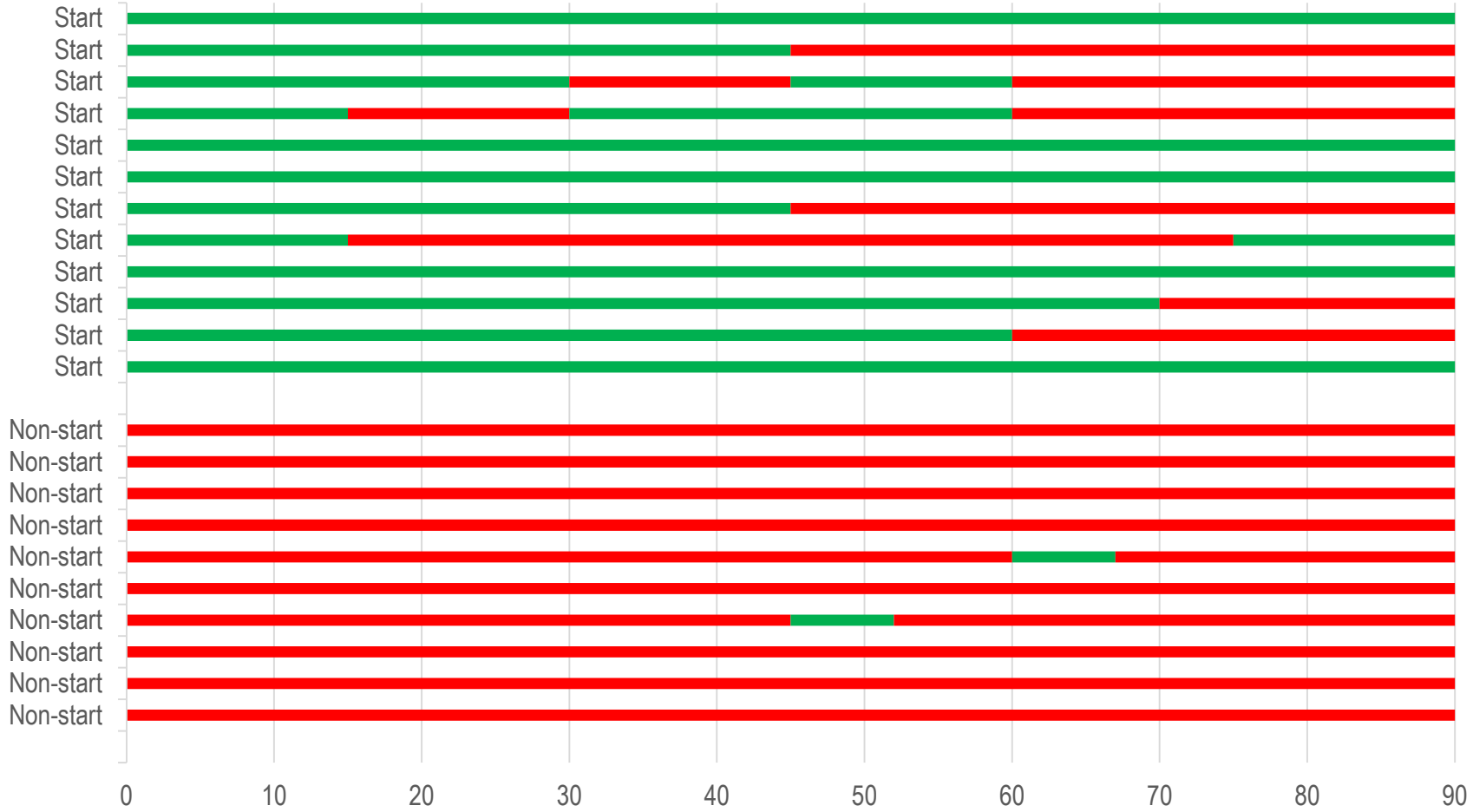
Our design: Starters vs. non-starters (regardless of subsequent use)



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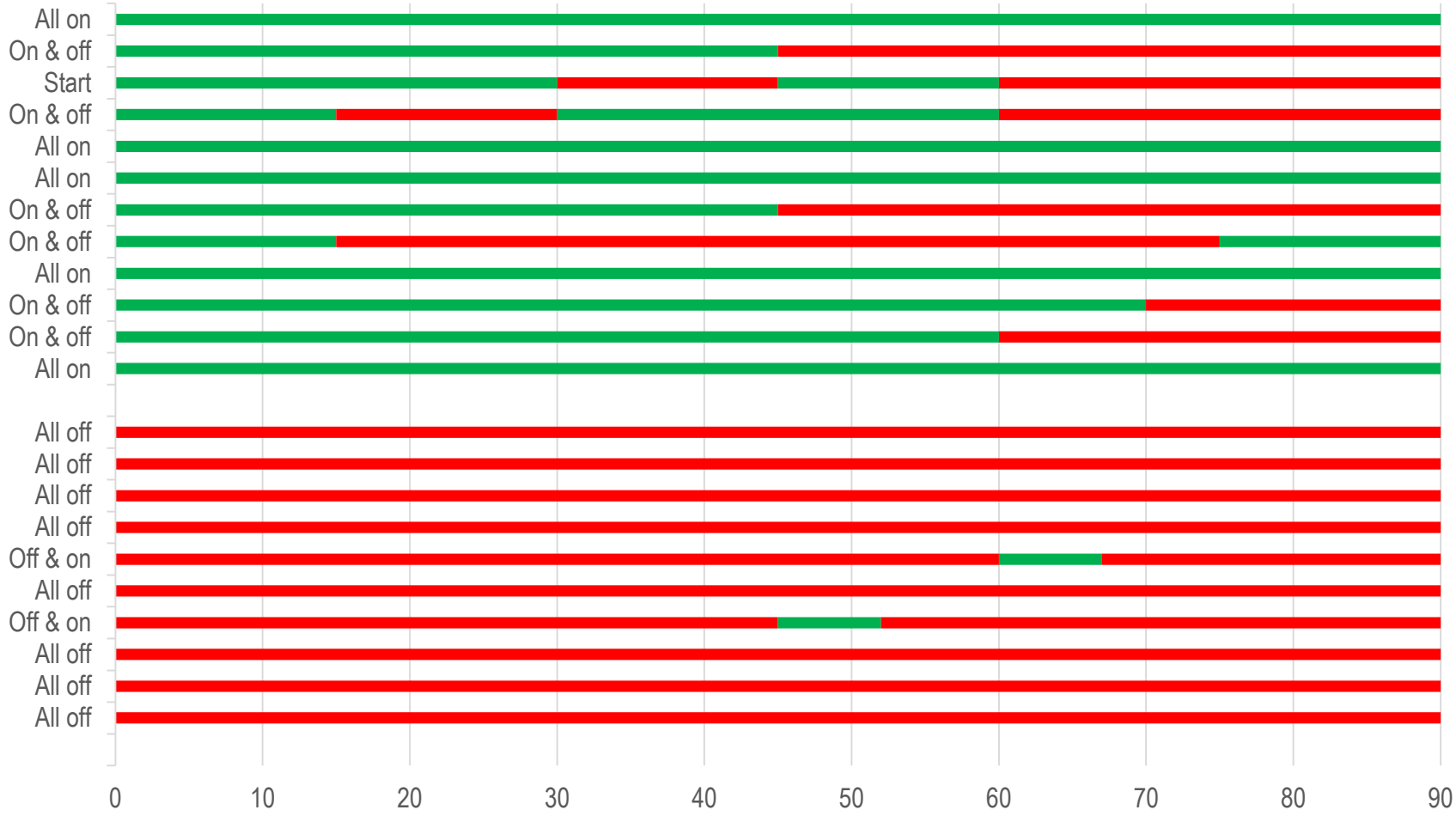
Some prior studies: Starters and non-starters, compare time on and time off



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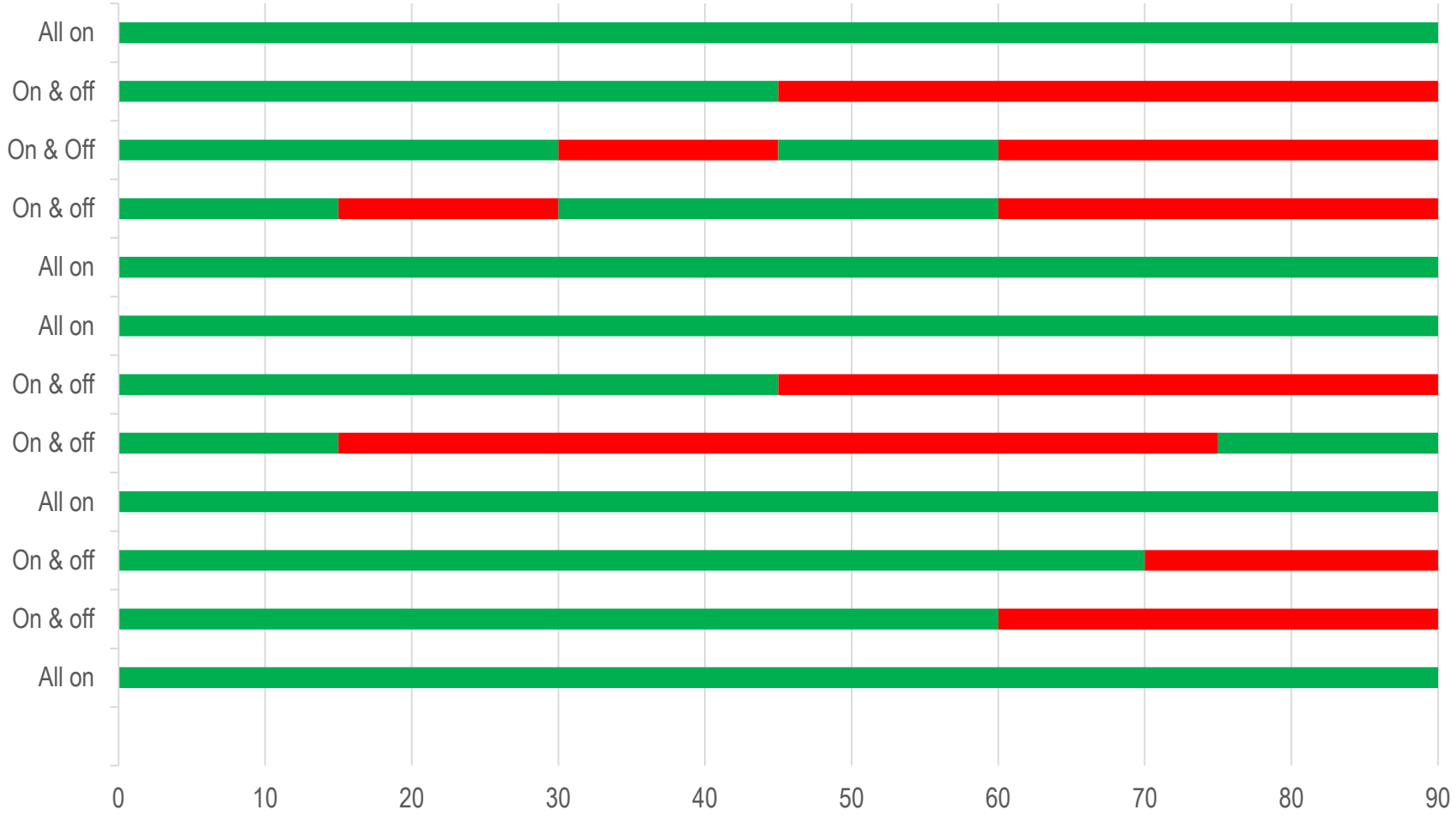
Other prior studies: Include only starters, time on vs. time off



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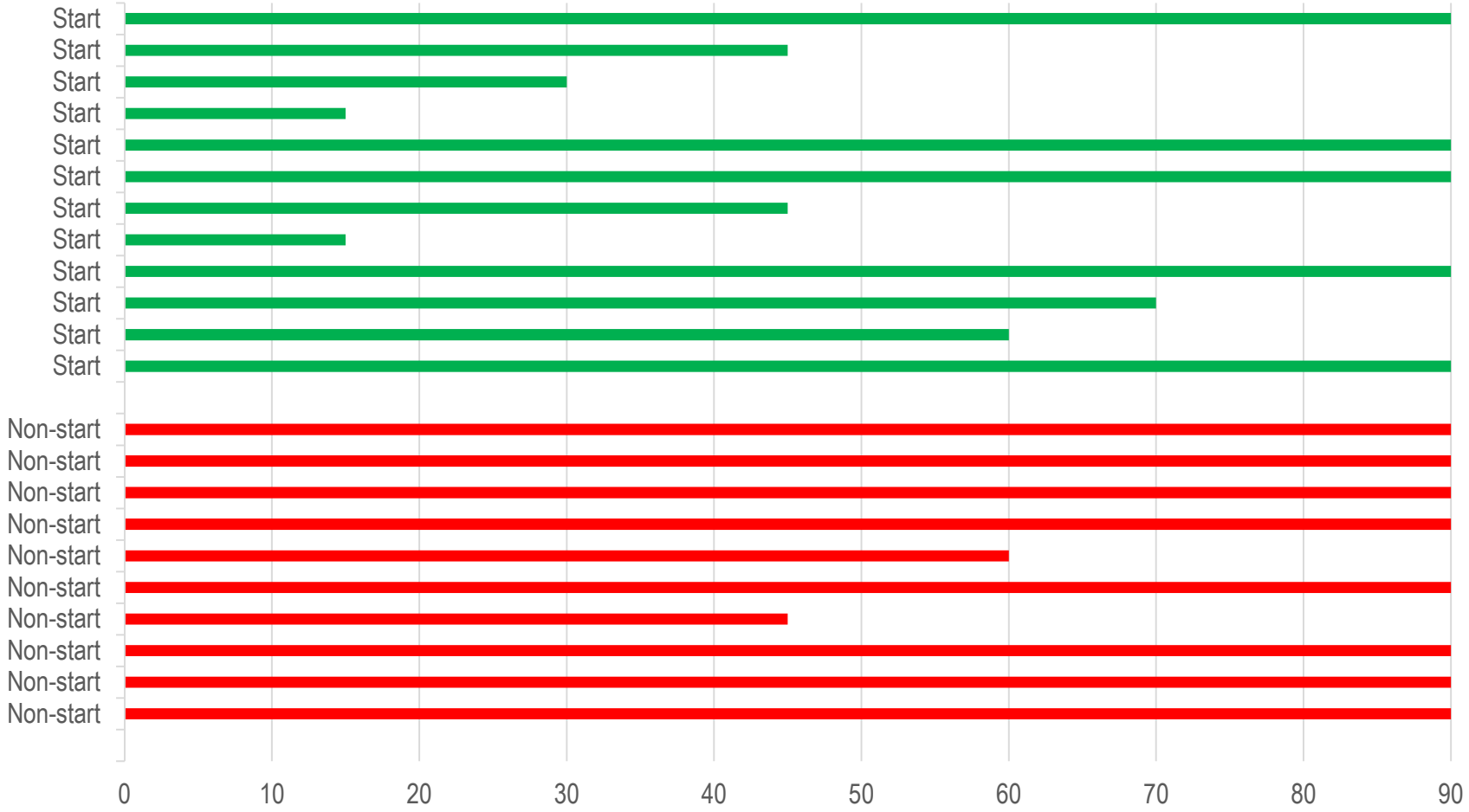
Our alternative analysis: Starters vs. non-starters with censoring at treatment change



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ITT vs “As treated” (censoring at discontinuation)

	Any Self-harm Event			Any Injury/Poisoning			Opioid –Involved Poisoning		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
No censoring (ITT)	1.18	(0.99, 1.40)	0.064	0.95	(0.88, 1.03)	0.226	1.19	(0.97, 1.45)	0.098
Censor at treatment change	0.74	(0.53, 1.02)	0.067	0.77	(0.67, 0.87)	<0.001	0.63	(0.43, 0.94)	0.022
Censor + added adjustment*	0.73	(0.52, 1.01)	0.054	0.77	(0.68, 0.88)	<0.001	0.61	(0.41, 0.90)	0.013

* - additional covariates associated with treatment change

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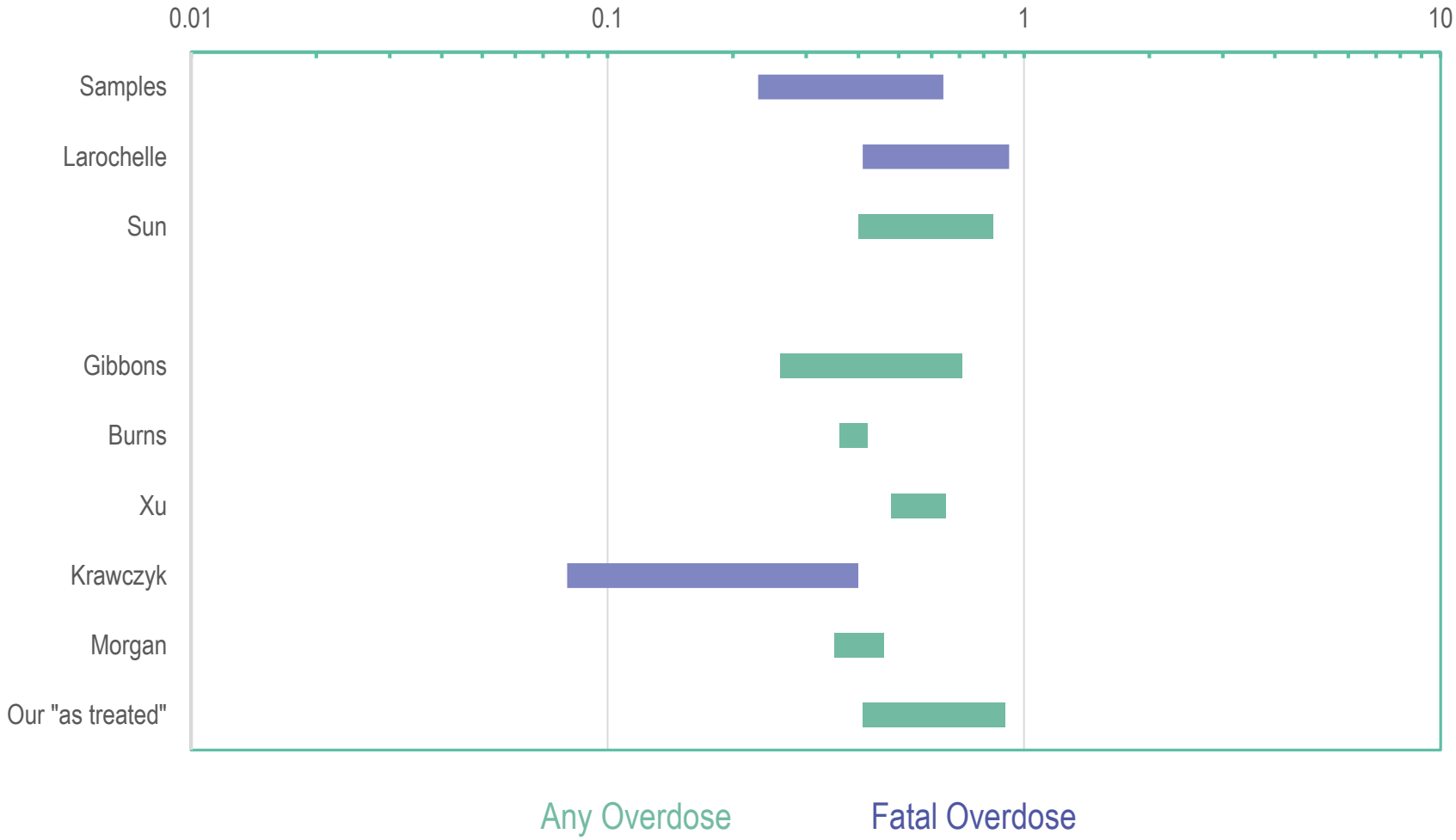
Observational studies of buprenorphine impact on overdose



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Increase in risk during 30 days after apparent discontinuation

	Self-harm Injury/Poisoning	Any Injury/Poisoning	Opioid Overdose/Poisoning
Before stopping	0.087/1000 person-days	0.57/1000 person-days	0.057/1000 person-days
30d after stopping	0.394/1000 person-days	1.58/1000 person-days	0.307/1000 person-days

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Limitations

- For starting vs. not starting, residual confounding is possible (or likely)
- Stopping/interrupting treatment is certainly not random

Our conclusions

- We do not find evidence that starting buprenorphine (vs. not starting) reduces risk of self-harm event over following 90 days
- These findings reinforce concerns about high risk of adverse outcomes soon after stopping or interrupting buprenorphine treatment

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What target trial should we be emulating?

- Questions about starting:
  - Randomly assigned to start vs. not start
  - Randomly assign policies/programs to increase start rates
- Questions about stopping:
  - Randomly assigned to continue vs. not continue
  - Randomly assign policies/programs to prevent stopping

What pragmatic trial should we be planning?

- Questions about starting:
  - Randomly assign encouragement/incentives to start buprenorphine
- Questions about stopping:
  - Randomly assign outreach/encouragement vs usual care among people who appear to have stopped
  - Randomized effectiveness comparison of oral vs. LAI buprenorphine

Questions?