Opioid Dose Reduction Trial Emulation

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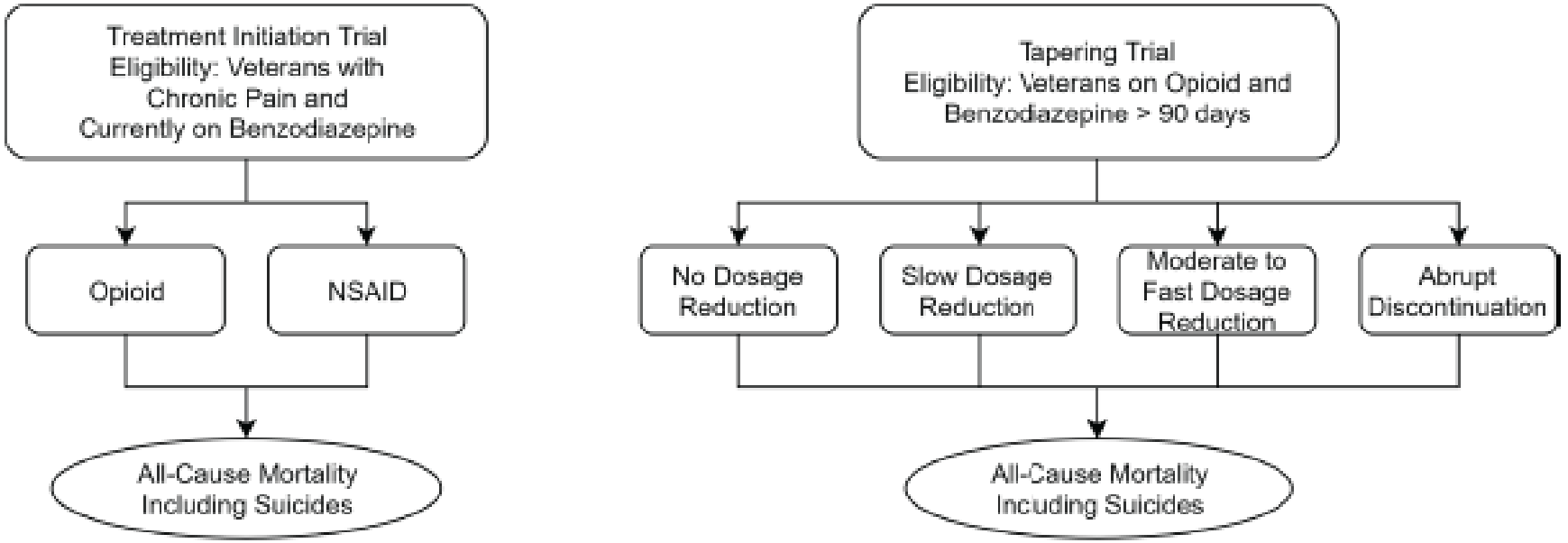
Disclosures

- I have no financial or other relationships with industry
- This project was funded by the VA Health Services Research and Development (HSR&D) Service as a supplement to an existing investigator-initiated study (#I01-HX001752, #I01-HX003063)
- Views expressed in this presentation are mine and do not reflect the position or policy of VA or the US government

Background: Previous National Academies Committee report

- Research question: In patients receiving benzodiazepines, what were effects of 1) opioid initiation and 2) opioid dosage reduction or discontinuation strategies on all-cause and suicide mortality?
- Emulated trial methodology: observational study design that uses existing data to try to approximate ("emulate") a hypothetical randomized trial



National Academies of Sciences, Engineering, and Medicine. 2019. An approach to evaluate the effects of concomitant prescribing of opioids and benzodiazepines on veteran deaths and suicides. Washington, DC: The National Academies Press. https://doi.org/10.17226/25532.

Objective

- To leverage an existing VA prospective observational cohort study to emulate an opioid tapering trial as proposed by the Committee

- Specific aims:
  1) To compare effects of each of two active opioid dose reduction strategies vs. no dose reduction control on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) in VA primary care patients receiving long-term opioid therapy (LTOT)
  2) To assess for varying treatment effects in subgroups defined by a) baseline opioid daily dose and b) baseline receipt of concomitant benzodiazepine treatment.

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Parent study: Effects of Prescription Opioid Changes in Veterans (EPOCH)

- Nationwide population cohort of VA patients receiving long-term opioid therapy (LTOT)
  - Electronic cohort of 271,892 VA patients
  - Representative survey panel of ~9000 VA patients
- EPOCH was established in 2016 to evaluate outcomes of changes in prescriber behavior following new opioid prescribing guidelines
  - Before 2016 CDC guidelines, prescribers rarely reduced or discontinued LTOT unless prompted by evidence of problems such as opioid misuse, diversion, or suicidal behavior
  - We anticipated that guidelines and policies would lead to more prescribers reducing or discontinuing LTOT
- Objective: To understand effects of changes in opioid prescribing on patient outcomes
  - Patient-reported outcomes in survey cohort (completed 5-year follow up in 2022)
  - Mortality and other outcomes in full population cohort

Krebs EE, Clothier B, Nugent S, et al. *PLoS One*. 2020;15(4):e0230751. doi:10.1371/journal.pone.0230751

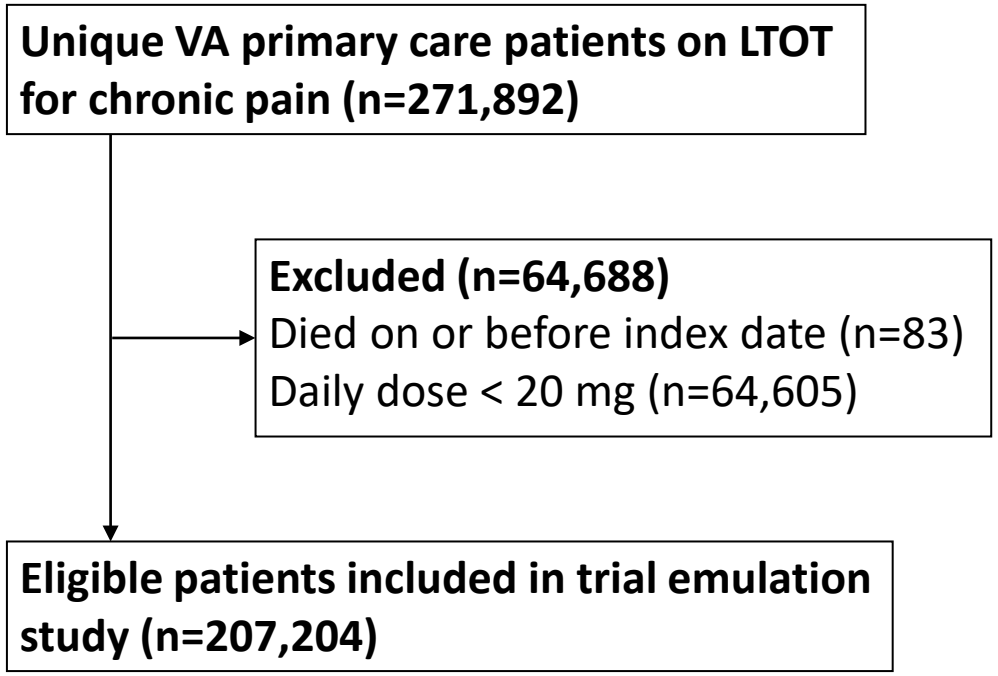
EPOCH eligibility

Primary care visit in the year before the 2016 index date

Current LTOT

- Qualifying opioid analgesic dispensed within 30 days, and
- ≥ 150 days' supply in the 180 days before the most recent dispensing date, and
- No gaps in supply > 40 days

Exclusions: Opioid use disorder treatment, dementia diagnosis or treatment, cancer treatment, end-of-life care, adult day care, nursing home residence



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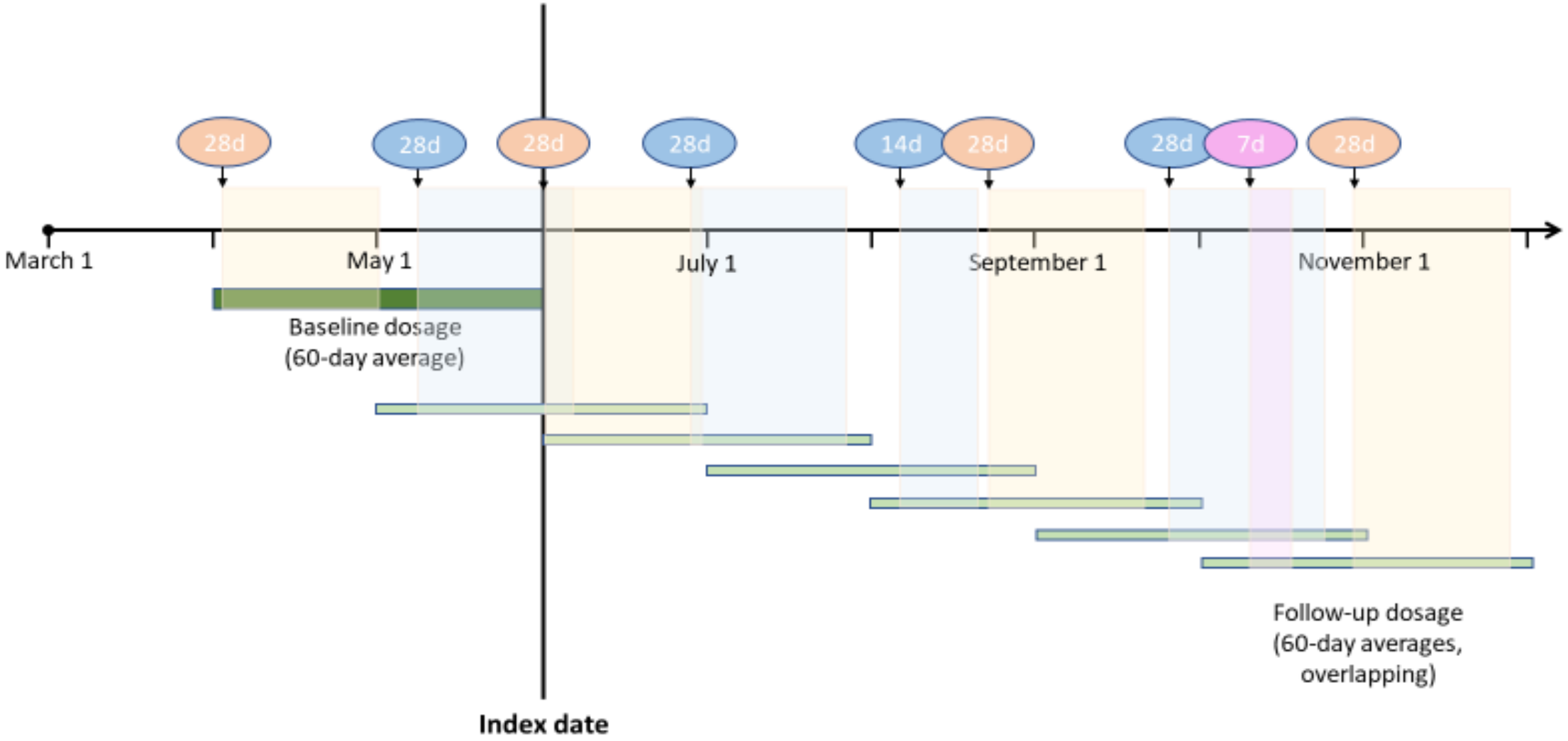
Emulated trial design

	Target trial design	Observational trial emulation design
Eligibility criteria	Inclusion: VA primary care patients receiving long-term opioid therapy for chronic pain with current daily dose of ≥ 20 mg. Exclusion: Opioid treatment for end-of-life care, active cancer, or opioid use disorder; dementia; nursing home residence	
Opioid treatment strategies	1) Taper goal of 15 to <50% reduction 2) Taper goal of ≥50% reduction 3) Control (no taper)	1) Small dose reduction (15 to <50%) 2) Large dose reduction (≥50%) 3) Control (<15% decrease)
Treatment assignment	Randomization to one of three treatment groups	Randomization emulated by cloning and censoring of patients
Treatment duration	Six months	
Follow-up duration	12 months (including treatment period)	
Outcome	Time to all-cause mortality (primary); time to suicide mortality (secondary)	

Key variables

- Opioid daily dose: CDW outpatient pharmacy
  - Dose was standardized by using CDC conversion factors to calculate morphine-equivalent mg
  - Dispensing data were used to calculate daily doses within 60-day windows
  - Baseline daily dose was categorized into 3 groups: 20 to <50 mg, 50 to <100 mg, ≥100 mg
- Baseline benzodiazepine use: Prescription dispensed in prior 60 days per CDW outpatient pharmacy data
- All-cause mortality: CDW patient table and vital status file
- Suicide mortality: ICD-10 codes X60-X84 and Y87.043 in National Death Index

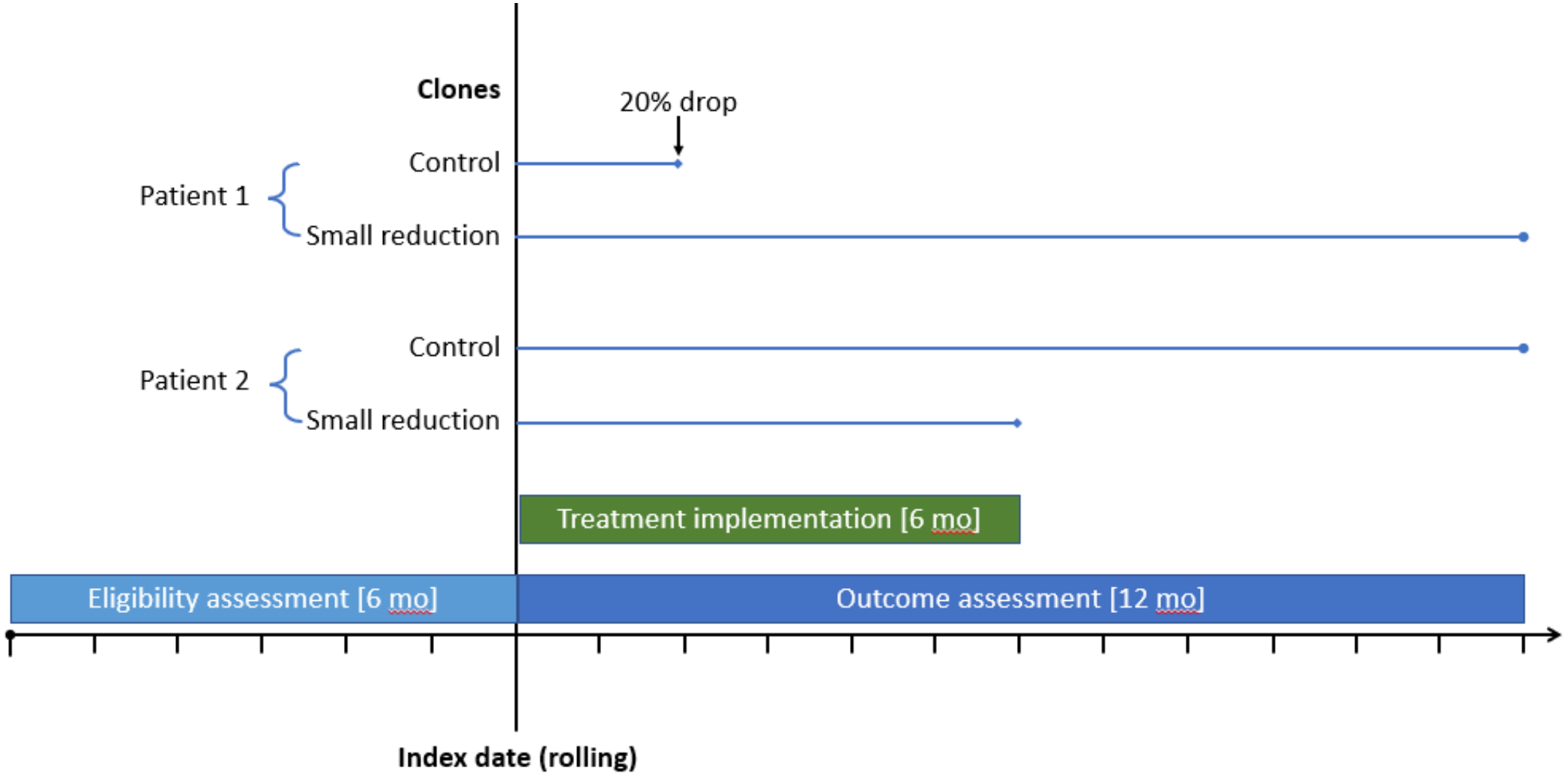
Illustration of daily dose calculation



Emulation methods

- First, we determined whether each patient received one of the two active mutually exclusive opioid treatment strategies (small reduction or large reduction) within the 6-month treatment implementation period. Those who received neither active strategy were in the control (no reduction) group.
- Next, we created two datasets corresponding to the two sets of analyses comparing 1) small dose reduction vs. control and 2) large dose reduction vs. control.
- Within each dataset, patient records were replicated at the index date, creating “clones” that were assigned to the alternate treatment group (active strategy or control). Clones were then censored at the time when the treatment the patient actually received was no longer compatible with the clone’s assigned treatment strategy

Illustration of cloning and censoring



Emulation methods

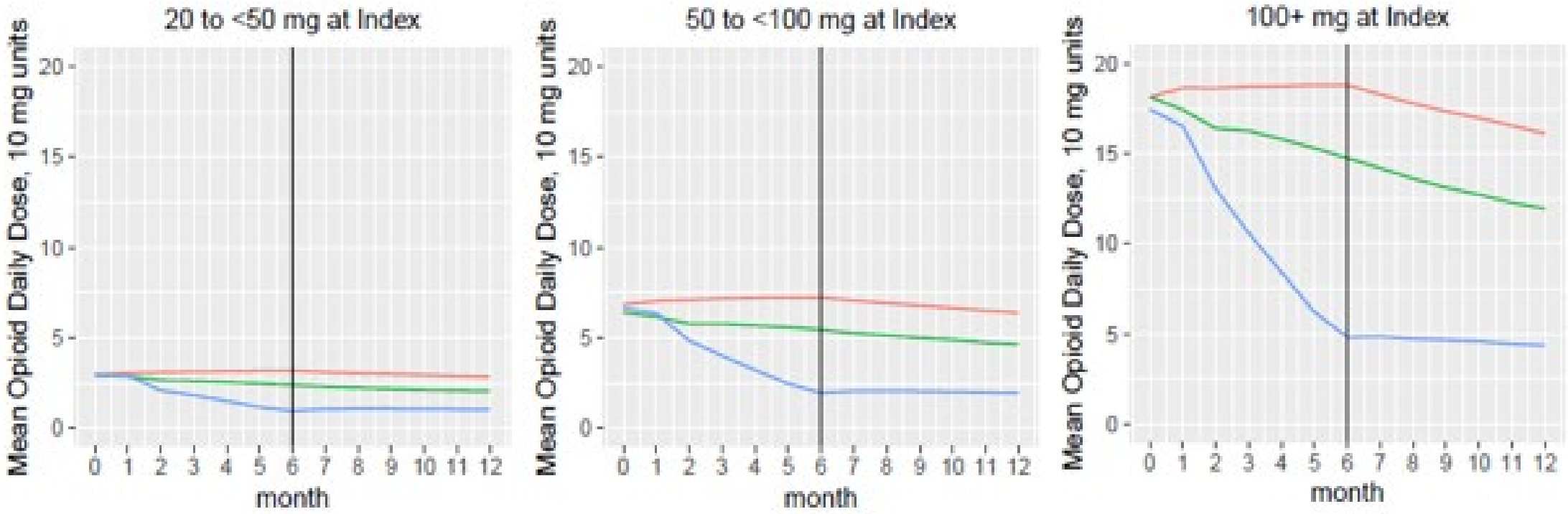
- To control for selection bias introduced by censoring of clones, we created inverse-probability-of-censoring weights (IPCW). We examined balance in potential confounding variables between active treatment and control in each dataset.
- Weighted Cox proportional hazards models were used for analysis of cloned data, to separately compare 1) small dose reduction vs. control and 2) large dose reduction vs. control.
- Pre-planned subgroup analyses
  - Baseline opioid daily dose categories (20 to <50 mg, 50-<100 mg, and 100+ mg)
  - Baseline benzodiazepine treatment (presence or absence of dispensing)

Baseline characteristics: opioid dose category and benzodiazepine treatment according to trial emulation treatment group assignment (N=206,353)*

	Small dose reduction n=29,835	Large dose reduction n=46,734	No dose reduction control n=129,784
Baseline opioid daily dose category			
20 to <50 mg	15055 (50.5%)	31269 (66.9%)	87964 (67.8%)
50 to <100 mg	8320 (27.9%)	9946 (21.3%)	26637 (20.5%)
100+ mg	6460 (21.7%)	5519 (11.8%)	15183 (11.7%)
Baseline benzodiazepine treatment	4998 (16.8%)	7660 (16.4%)	19433 (15.0%)

* Excludes 851 patients who survived <1 month because they could not be assigned to a treatment group

Average daily dosage over 12 months by trial emulation treatment group assignment, within baseline opioid dose categories



= *no reduction (control) group,* = *small reduction group,* = *large reduction group*

* Excludes 851 patients who survived <1 month because they could not be assigned to a treatment group

Unadjusted results: Deaths within one year according to trial emulation treatment group assignment (n=207,204)

	Patients with at least one follow-up month			Patients who survived less than one month n=851
	Small dose reduction n=29,835	Large dose reduction n=46,734	Control n=129,784	
All-cause death, n (column %)	1056 (3.5%)	2008 (4.3%)	5731 (4.4%)	851 (100%)
Suicide death, n (column %)	28 (0.09%)	30 (0.06%)	132 (0.10%)	18 (2.1%)
Median 1-year survival, months [range]	7 [1-12]	8 [2-12]	6 [2-12]	NA
Suicide death, % of all deaths	**2.7%**	**1.5%**	**2.3%**	**2.1%**

Results: Weighted estimates of the effect of dose reduction strategies vs. control on time to all-cause mortality (n=206,353)

	Small dose reduction n=29,835	Large dose reduction n=46,734
Overall, HR (95% CI)	**1.01 (0.98, 1.04)**	**1.23 (1.20, 1.27)**
Dose category, HR (95% CI)		
20 to < 50 mg	0.98 (0.94, 1.02)	1.22 (1.17,1.27)
50 to <100 mg	1.01 (0.95,1.08)	1.25 (1.18,1.33)
100+ mg	1.10 (1.02,1.19)	1.25 (1.16, 1.35)
Benzodiazepine treatment, HR (95% CI)		
Benzodiazepine	1.06 (0.98, 1.15)	1.22 (1.13, 1.31)
No benzodiazepine	1.01 (0.97, 1.04)	1.23 (1.19, 1.27)

* Excludes 851 patients who survived <1 month because they could not be assigned to a treatment group

Results: Weighted estimates of the effect of dose reduction strategies vs. control on time to suicide mortality (n=207,204)

	Small dose reduction n=29,835	Large dose reduction n=46,734
Hazard ratio (95% CI)	1.09 (0.89, 1.35)	1.01 (0.77, 1.33)

Risk of suicide cause of death among patients who died during 12-month follow-up (n=9,646)

	Small dose reduction n=1056	Large dose reduction n=2008
Hazard ratio (95% CI)	1.11 (0.89, 1.38)	0.88 (0.71, 1.09)

* Excludes 851 patients who survived <1 month because they could not be assigned to a treatment group

Post-hoc analysis

- By definition, the large dose reduction group included patients with a dose reduction to zero (i.e., no dispensed opioids in the 60-day window before a follow-up time point)
  - 30,802 (65.9%) of patients in the large dose reduction treatment group had “discontinuation”
  - 16,646 (53.7%) of patients with “discontinuation” subsequently filled an opioid prescription during the study period
    - 54% “restarted” within 1 month and 18% “restarted” within 2 months
- This suggests the large dose reduction group includes many patients with gaps in opioid dispensing, as well as patients with planned discontinuation and those with reduction to lower dose

Post-hoc analysis

- Split the large dose reduction treatment group into two subsets of patients
  - 15,932 patients who continued to fill opioid prescriptions (daily dose >0 mg)
  - 30,802 patients who had apparent discontinuation (dose = 0 mg)
- Repeated weighted Cox models for each subset of patients

Results: Weighted estimates of the effect of dose reduction strategies vs. control on time to all-cause mortality,

	Small dose reduction n=29,835	Large dose reduction n=46,734	
		Daily dose > 0 mg n=15,932	Daily dose = 0 mg n=30,802
Overall, HR (95% CI)	**1.01 (0.98, 1.04)**	**1.03 (0.97, 1.10)**	**1.33 (1.30, 1.38)**
Dose category, HR (95% CI)			
20 to < 50 mg	0.98 (0.94, 1.02)	1.03 (0.98, 1.07)	1.28 (1.23, 1.33)
50 to <100 mg	1.01 (0.95,1.08)	1.02 (0.95, 1.09)	1.41 (1.32, 1.50)
100+ mg	1.10 (1.02,1.19)	1.07 (0.98, 1.16)	1.46 (1.35, 1.58)

Limitations

- Results of this emulated tapering trial are dependent on design choices
  - For example, definitions of treatment groups, methods of calculating daily dose
- Target trial emulation requires assumption of treatment intent based on evidence of treatment delivery
  - May not be reasonable to assume tapering intent based on absence of evidence
- The trial emulation approach does not eliminate bias caused by unmeasured confounding
  - Common reasons for opioid dose reduction and discontinuation (e.g., evidence of opioid misuse) are not well captured in CDW data and are likely associated with outcomes

Limitations

- Follow-up duration not long enough to capture potential mortality *benefits* of dose reduction or discontinuation, which would accrue over time
- The tapering target trial emulated in this study may have limited relevance to clinical practice
  - Subjective, individual, and resource factors are highly relevant to decision-making
  - Tapering is a dynamic process involving multiple small decisions over time

Ongoing and future work

- Completion of additional analyses will provide context for interpretation
  - Original planned analyses of opioid dose reduction effects on patient outcomes
  - Sensitivity analyses for emulated trial (e.g., modifying treatment strategy definitions)

Comments about Opioid Initiation Trial Emulation Protocol

- Impossible to do with the EPOCH cohort of patients on established LTOT
- Proposed eligibility criterion: Chronic pain diagnosis
  - ICD-9 and ICD-10 lack good indicators of chronic pain
  - Fortunately, there are few indications other than chronic pain for extended-duration analgesic prescriptions
- Proposed eligibility criterion: No NSAIDS or opioids within prior 90 days
  - NSAIDs can be prescribed/dispensed with 90-day supply so a longer prescription-free window may be needed

Acknowledgements

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Thank you! Questions?