Target Trial Emulation

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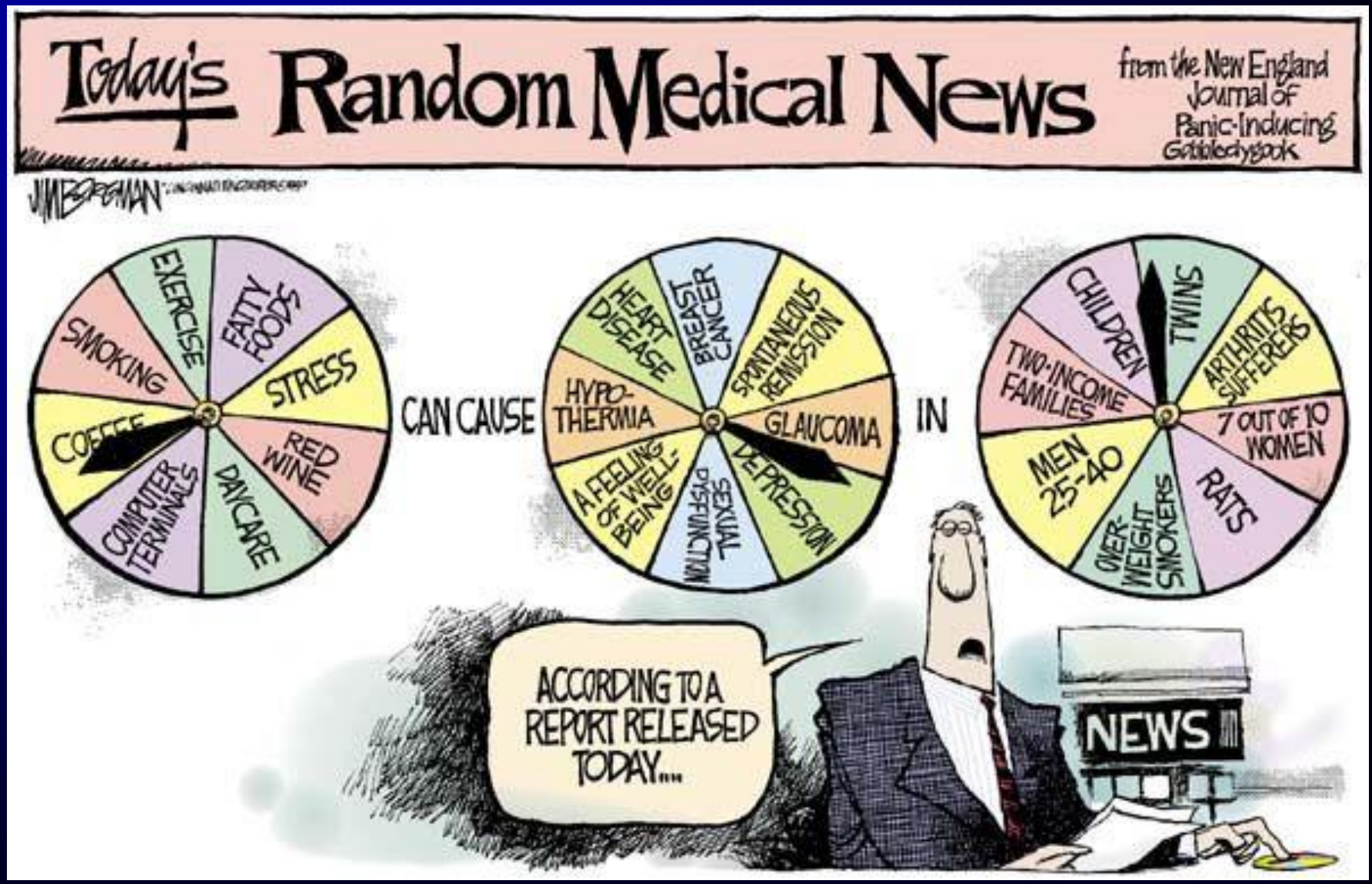
Disclosures

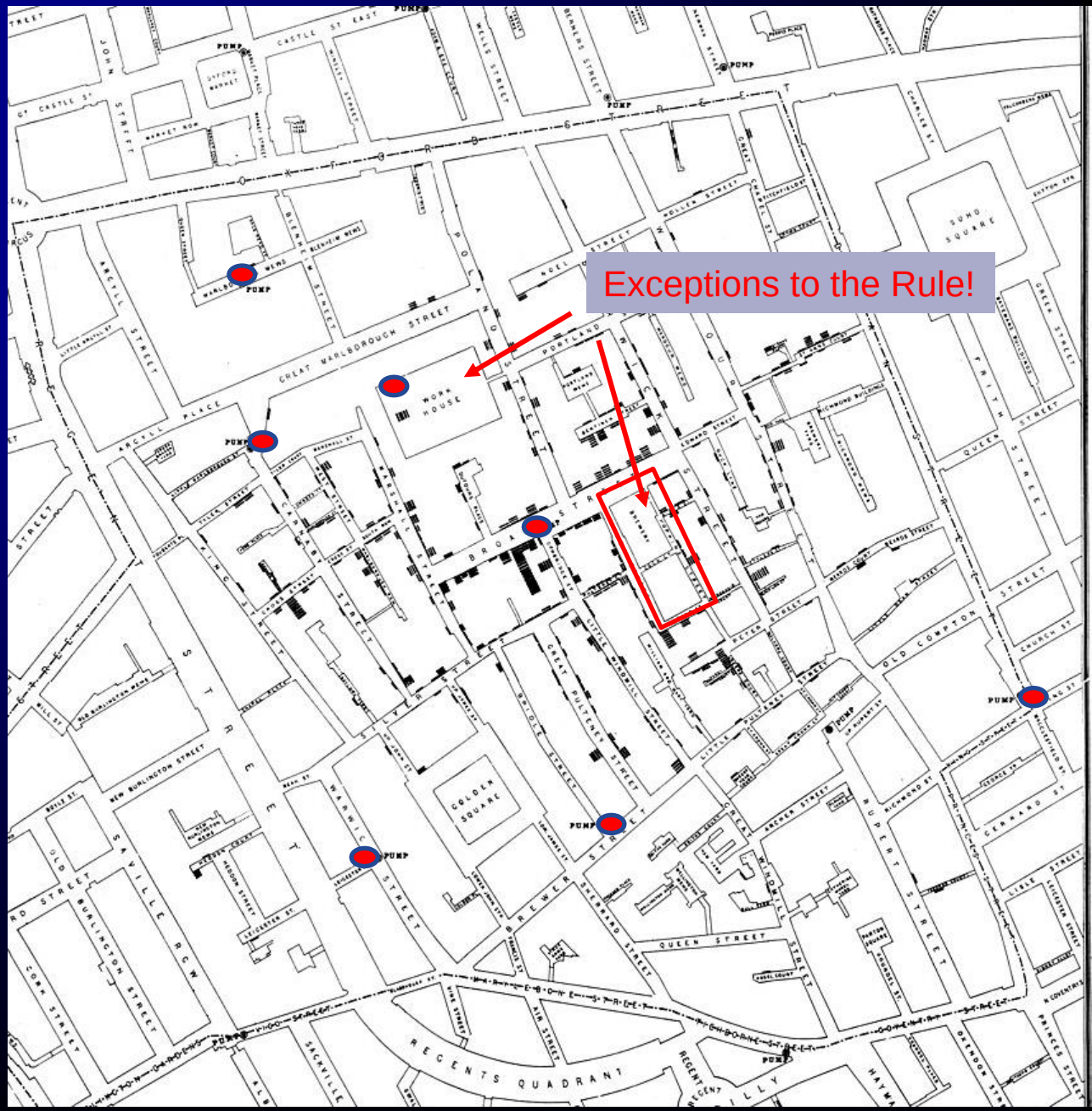
- NIH: NIAMS, NIA, NHLBI
- Rheumatology Research Foundation grant support
- Arthritis Foundation grant support
- CorEvitas, Epidemiologic Consultant
- Research grants/contracts: Amgen, Janssen, Novartis
- No personal financial relationship with any pharmaceutical company
- CARRA, Board of Directors
- UpToDate, royalties
- Member, FDA Arthritis Advisory Committee
- Editor in Chief, Arthritis & Rheumatology

Determining Cause

1. Principles of causation in clinical research
2. Improving causal inference
   a. Study designs
   b. Limiting bias


Today's Random Medical News
from the New England Journal of Panic-Inducing Gobbledygook
JIM BORGMAN
SMOKING
EXERCISE
FATTY FOODS
STRESS
COFFEE
RED WINE
COMPUTER TERMINALS
DAYCARE
CAN CAUSE
HEART DISEASE
BREAST CANCER
SPONTANEOUS REMISSION
HYPO-THERMIA
GLAUCOMA
A FEELING OF WELL-BEING
SEXUAL DYSFUNCTION
DEPRESSION
IN
CHILDREN
TWINS
TWO-INCOME FAMILIES
ARTHRITIS SUFFERERS
7 OUT OF 10 WOMEN
MEN 25-40
OVER-WEIGHT SMOKERS
RATS
ACCORDING TO A REPORT RELEASED TODAY...
NEWS

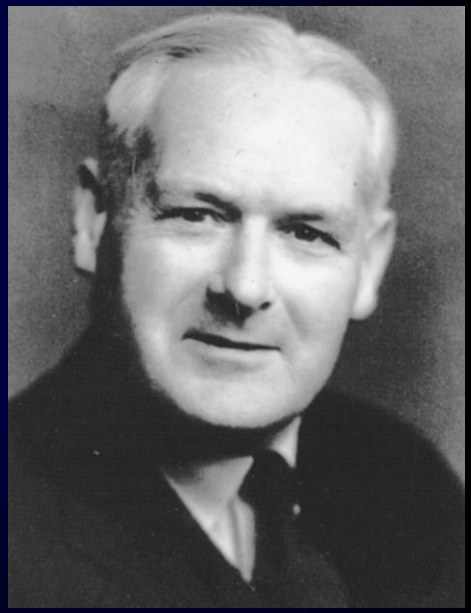
- John Snow
- 1854 Broad Street cholera outbreak
- Not miasma, but cholera likely a water-borne illness
- Mixing of infected fecal matter with drinking water



Hill's Criteria of Causation

1. Temporal relationship
2. Strength of effect size
3. Dose-response relationship

4. Consistency of effect across studies
5. Plausibility
6. Alternative explanations
7. Experimental proof
8. Specificity
9. Coherence



REF: AB Hill, 1965

Why do we want to know "what works"? Because decisions must be made NOW

- For clinical practice
  - Treat with A or with B?
  - Treat now or later?
  - Treat all individuals?
  - Stop all treatment?
- For public health
  - Implement a screening program?
  - At what age?
  - With what frequency?
  - Until what age?

- Decision making needs to be informed by causal knowledge about comparative effectiveness
  - and safety

Slide borrowed from M. Hernan

How do we learn what works and what harms? (How do we estimate causal effects?)

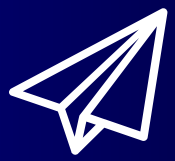
- The standard scientific answer:
  - Conduct a randomized experiment

A relevant randomized trial would, in principle, answer each causal question about comparative effectiveness and safety

But we rarely have randomized trials

expensive unethical impractical untimely






- And deferring decisions is not an option
  - no decision is a decision: “maintain status quo”
- What do we do?
  - We analyze observational data

Slide borrowed from M. Hernan

Types of observational data

Research data

- Data collected specifically for research
  - Cohort studies, case-control studies, and other epidemiologic studies
  - Biobanks
  - Disease registries
  - …

"Found" data

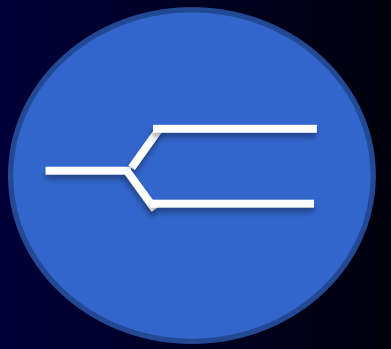
- Data generated for non-research purposes
  - Electronic health records
  - Insurance claims databases
  - National registers
  - …

"Real world data"

"Routinely collected data"

Observational analyses are **not** preferred. For each observational analysis for causal inference, we can imagine a hypothetical randomized trial that we would prefer to conduct. If only it were possible.

“Target” trial



- The (hypothetical) randomized trial that we would like to conduct to answer a causal question

- A causal analysis of observational data can be viewed as an attempt to emulate some target trial
  - If we cannot translate our causal question into a target trial, then the question is not well-defined

American Journal of Epidemiology

Vol. 1
DOI: 10.1093/aj
Advance Access pu
March

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

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* Correspondence to Dr. Miguel A. Hernán, Department of Epidemiology, 677 Huntington Avenue, Boston, MA 02115 (e-mail: miguel_hernan@post.harvard.edu).

1. Ask a causal question
   – Specify the protocol of the target trial
2. Answer the causal question

Option A:

Conduct the target trial

Option B:

Emulate the target trial

- **Draft study protocol**
- **Construct a causal framework**
- **Find the data**

A. What is the clinical question?

B. What is the target trial protocol?

C. How can we emulate it in observational data?

1. Eligibility criteria
2. Treatment strategies
3. Randomized assignment
4. Start and end follow-up
5. Outcomes
6. Causal contrast
7. Analysis plan

ORIGINAL RESEARCH

Annals of Internal Medicine

Delayed Denosumab Injections and Fracture Risk Among Patients With Osteoporosis

A Population-Based Cohort Study

Houchen Lyu, MD, PhD; Kazuki Yoshida, MD, ScD; Sizheng S. Zhao, MD; Jie Wei, MD, PhD; Chao Zeng, MD, PhD; Sara K. Tedeschi, MD, MPH; Benjamin Z. Leder, MD; Guanghua Lei, MD, PhD; Peifu Tang, MD, PhD; and Daniel H. Solomon, MD, MPH

QUESTION

- Is there increased fracture risk among patients who delay their denosumab?

METHODS

- UK primary care database (THIN), 2010 to 2019
- Persons aged 45 years or older who initiated denosumab therapy for osteoporosis.
- Observational data were used to emulate a hypothetical trial with 3 dosing intervals:
  - next dmab injection within 4 weeks after recommended date (“on time”),
  - delay by 4 to 16 weeks (“short delay”), and
  - delay by more than 16 weeks (“long delay”)
- Primary outcome was a composite of all fracture types at 6 months after the recommended date
- Secondary outcomes were major osteoporotic fracture, vertebral fracture, hip fracture, and nonvertebral fracture

Idealized Trial Design

Eligibility Criteria: Data source and study population

Inclusion criteria:

1. Found in THIN database which contains health information on approximately 17 million patients from 790 general practices in the UK;
2. Over 45 years of age;
3. Dmab between 2010-2019; and
4. Received at least 2 Dmab injections.

Exclusion criteria:

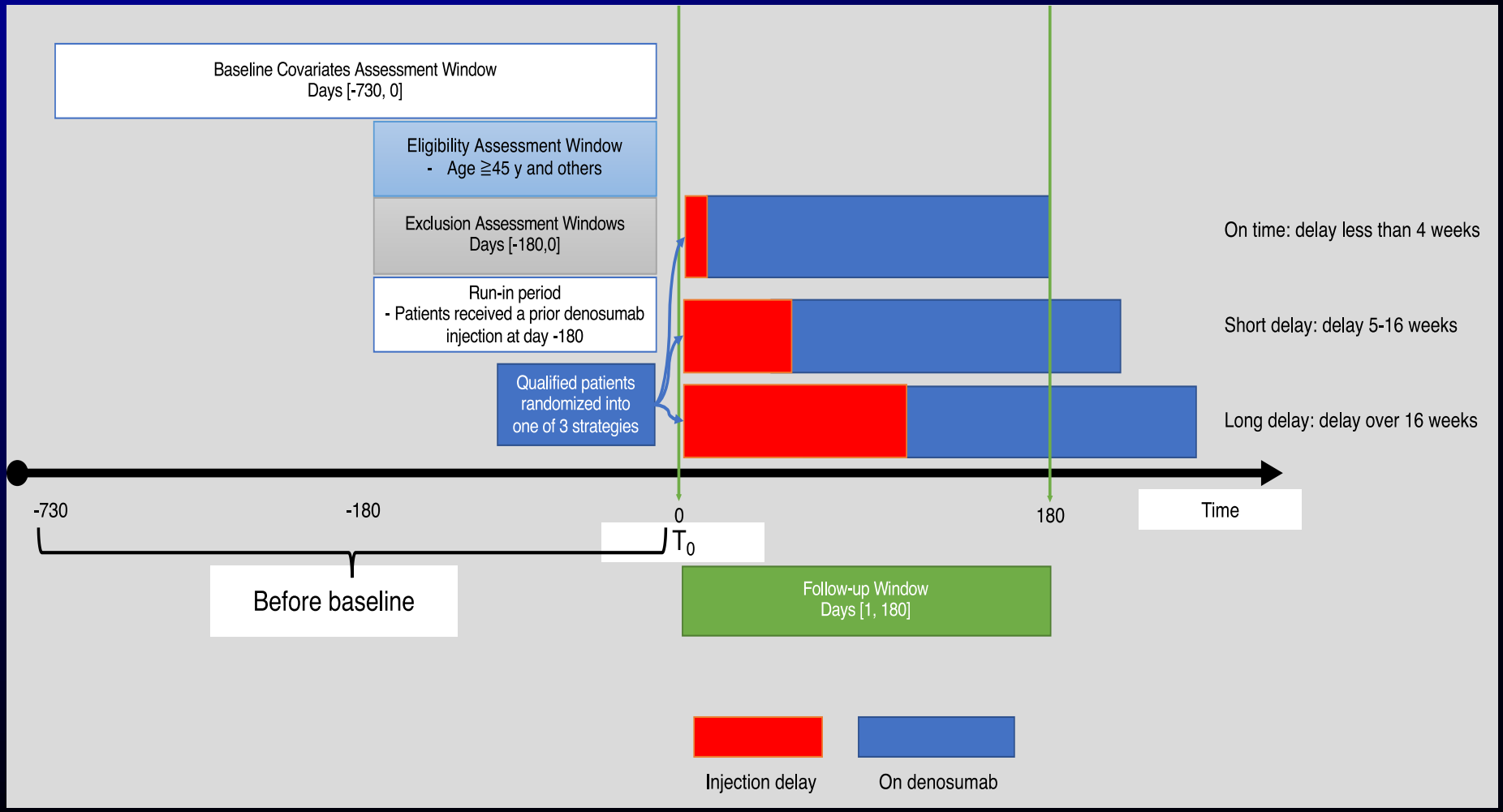
1. A history of Paget's disease or cancer;
2. Simultaneous use of teriparatide and/or bisphosphonates.

Major Design Challenges

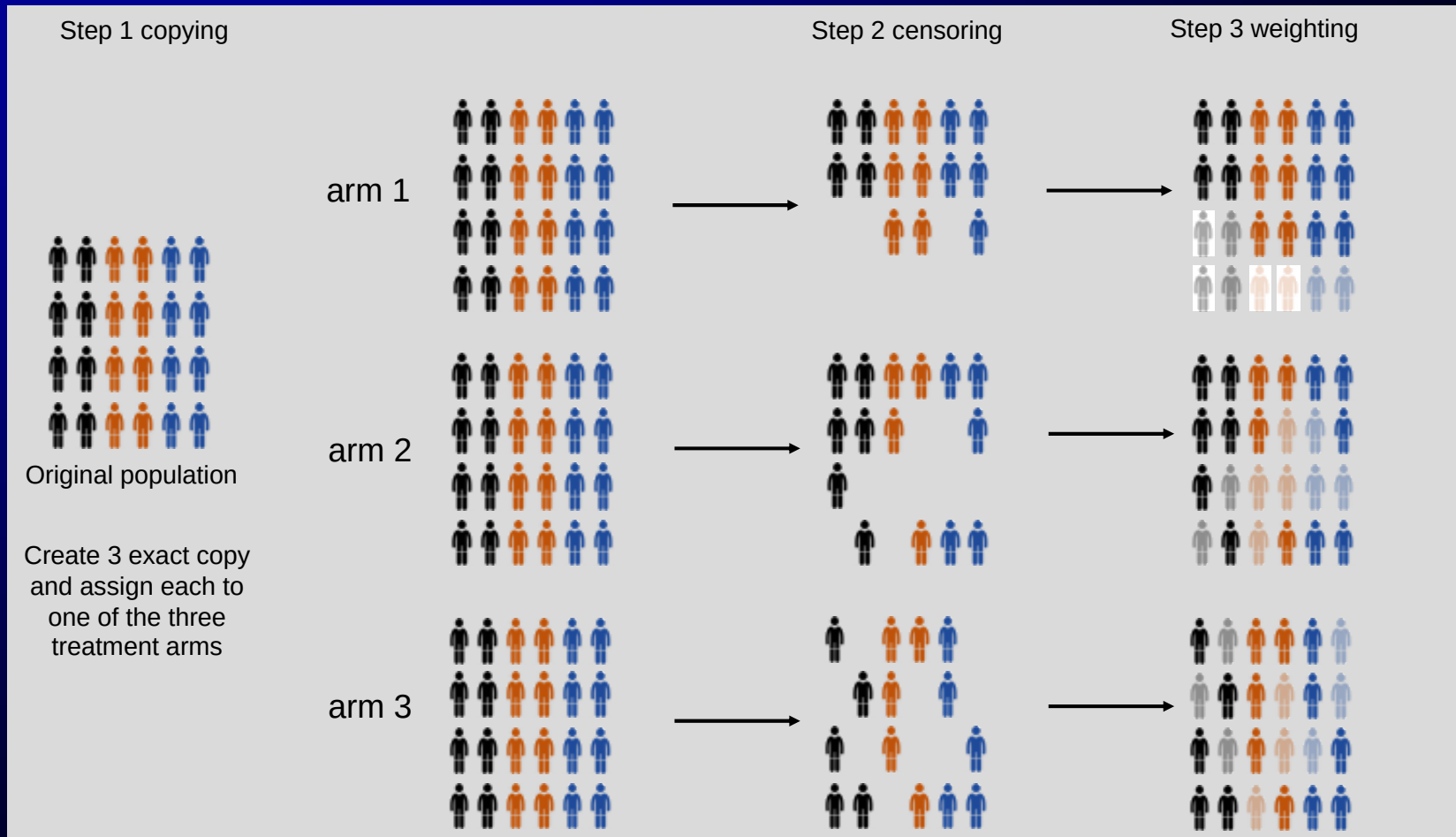
- Three treatment assignments that are impossible to determine at baseline
  - Correct assignment is only apparent over time
- Repeated cycles of treatment with changing assignments
  - Same patient can be in multiple treatment (delay) groups

Treatment Strategies

- On time injection: within 7 months of prior injection
- Short delay: 7 – 10 months after prior injection
- Long delay: > 10 months after prior injection



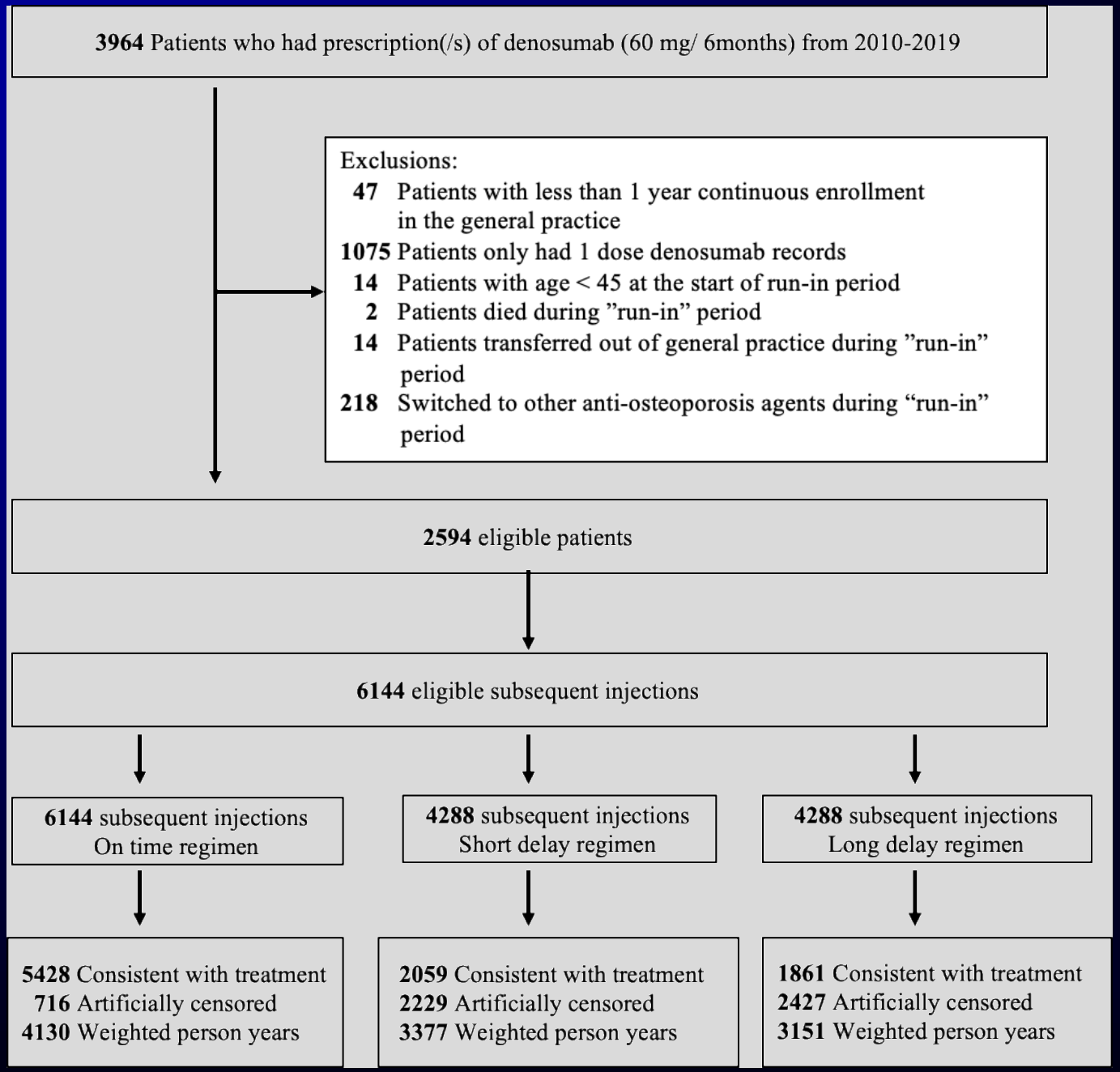
”Clone and Censor”



Outcomes

- Primary: composite of any fracture
- Major osteoporotic fracture (hip, vert, wrist, humerus, pelvis and rib)
- Vertebral fracture
- Hip fracture

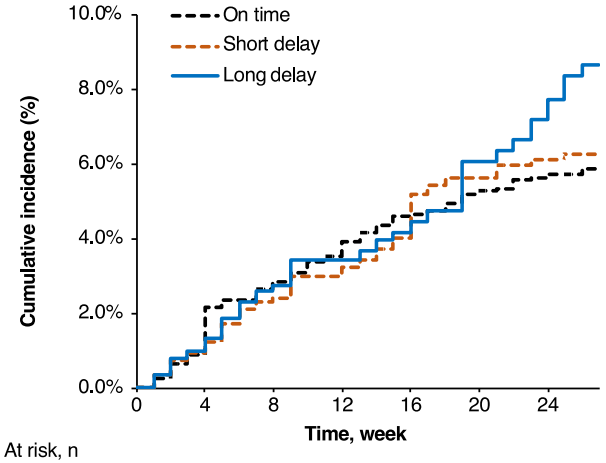
Cohort Assembly



Characteristic	On-Time* (n = 6144)	Short Delay* (n = 4288)	Long Delay* (n = 4288)	SMD
Mean age (SD), y	75.96 (9.42)	75.81 (9.52)	75.81 (9.52)	0.010
Women	5833 (94.9)	4071 (94.9)	4071 (94.9)	<0.001
Mean BMI (SD), kg/m2	24.45 (5.27)	24.55 (5.35)	24.55 (5.35)	0.013
Smoking status				0.012
Current	577 (9.4)	424 (9.9)	424 (9.9)	
None	3874 (63.2)	2702 (63.1)	2702 (63.1)	
Past	1677 (27.4)	1153 (26.9)	1153 (26.9)	
Chronic pulmonary disease	350 (5.7)	233 (5.4)	233 (5.4)	0.008
Dementia	164 (2.7)	115 (2.7)	115 (2.7)	0.001
Diabetes	187 (3.0)	127 (3.0)	127 (3.0)	0.003
Renal disease	264 (4.3)	181 (4.2)	181 (4.2)	0.003
Any cancer	131 (2.1)	90 (2.1)	90 (2.1)	0.002
Rheumatoid arthritis	79 (1.3)	57 (1.3)	57 (1.3)	0.003
Charlson Comorbidity Index (SD)	0.36 (0.76)	0.35 (0.77)	0.35 (0.77)	0.007
History of major osteoporotic fracture	3233 (52.6)	2250 (52.5)	2250 (52.5)	0.002
10-year risk of major OP fracture (SD), %	21.99 (15.27)	21.79 (15.32)	21.79 (15.32)	0.009
10-year risk of hip fracture (SD), %	18.66 (19.39)	18.49 (19.51)	18.49 (19.51)	0.006
Mean duration of bisphosphonates (SD), y	3.11 (3.61)	3.06 (3.56)	3.06 (3.56)	0.010
Intravenous bisphosphonates	12 (0.2)	9 (0.2)	9 (0.2)	0.002
Teriparatide	6 (0.1)	3 (0.1)	3 (0.1)	0.006
Systemic corticosteroids	1231 (20.0)	852 (19.9)	852 (19.9)	0.003
Benzodiazepine	968 (15.8)	655 (15.3)	655 (15.3)	0.009
Opioids	1874 (30.5)	1317 (30.7)	1317 (30.7)	0.003
PPI	3414 (55.6)	2400 (56.0)	2400 (56.0)	0.005
SSRI	868 (14.1)	627 (14.6)	627 (14.6)	0.009
Hospitalization (SD)	1.66 (2.56)	1.69 (2.65)	1.69 (2.65)	0.009
Mean number of primary care visits (SD)	18.29 (15.28)	18.02 (15.29)	18.02 (15.29)	0.012
Mean number of refer to hospitals (SD)	2.06 (2.34)	2.02 (2.32)	2.02 (2.32)	0.011

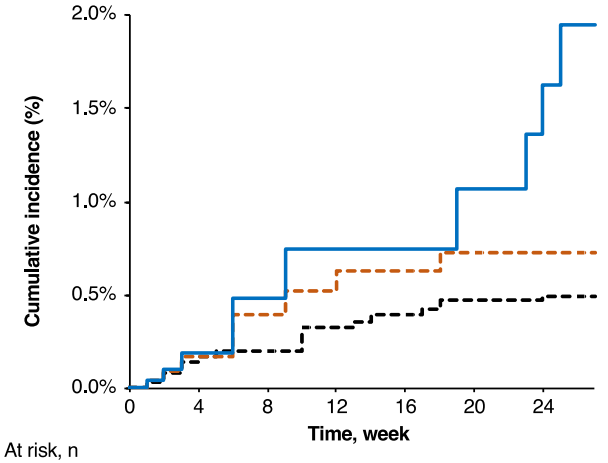
	On time	Short delay	Long delay	P for trend
Composite Fractures*				
Weighted persons years, n†	4130	3377	3151	-
Events, †	243	208	269	-
Rate (95% CI), Per 1000 person-years	58.9 (44.9, 76.4)	61.7 (41.9, 90.0)	85.4 (60.8, 117.3)	-
Unadjusted HR (95 %)	Reference	1.05 (0.62, 1.76)	1.45 (0.95, 2.21)	0.097
Full adjusted model HR (95% CI)‡	Reference	1.03 (0.63, 1.69)	1.44 (0.96, 2.17)	0.093
Weighted model HR (95% CI)‖	Reference	1.04 (0.64, 1.71)	1.46 (0.96, 2.20)	0.081
Sensitivity analysis HR (95% CI)§	Reference	1.07 (0.63, 1.82)	1.58 (1.04, 2.41)	0.040

A. Time to First Composite Fracture



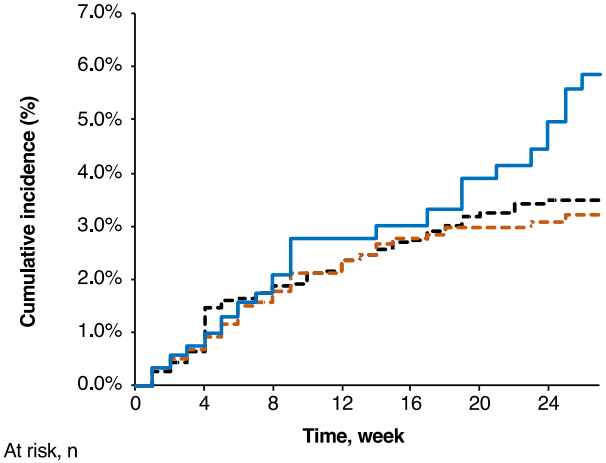
At risk, n							
On time	6144	4397	4262	4100	3962	3824	3680
Short delay	4288	1634	1606	1571	947	917	882
Long delay	4288	1631	993	740	573	565	556

B. Time to First Vertebral Fracture



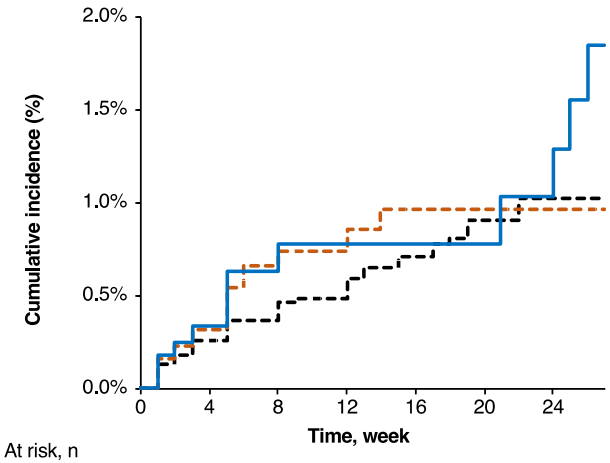
At risk, n							
On time	6144	4403	4279	4135	4020	3895	3756
Short delay	4288	1643	1626	1596	967	940	907
Long delay	4288	1643	1005	755	586	583	577

C. Time to First Major Osteoporotic Fracture



At risk, n							
On time	6144	4400	4271	4120	3995	3859	3717
Short delay	4288	1636	1613	1579	952	924	891
Long delay	4288	1634	998	744	579	574	567

D. Time to First Hip Fracture

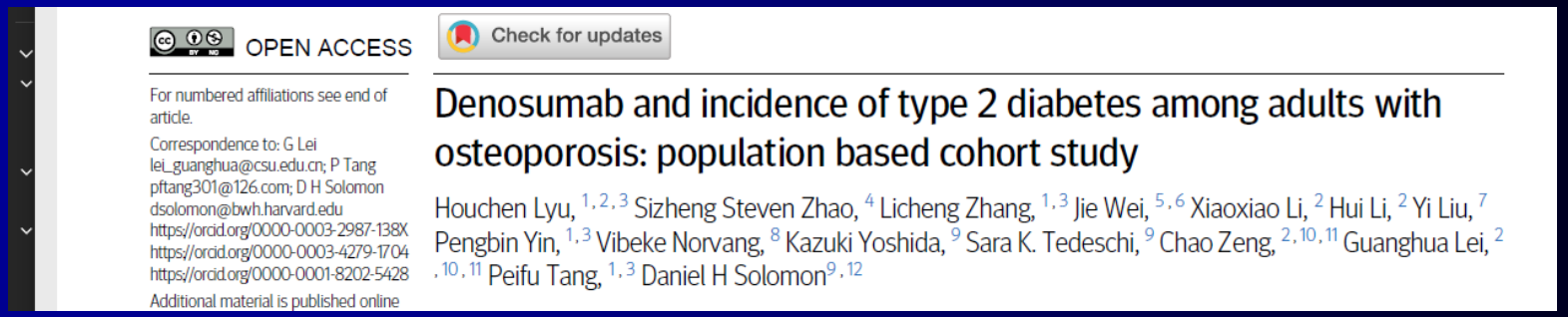


At risk, n							
On time	6144	4405	4281	4137	4019	3894	3753
Short delay	4288	1639	1620	1590	960	933	901
Long delay	4288	1639	1002	751	585	583	577

	On-time	Short delay	Long delay	p for trend
Composite fractures				
Stratified by age				
Age > 75 y	Reference	1.14 (0.58, 2.25)	1.58 (0.94, 2.64)	0.091
Age ≤ 75 y	Reference	0.96 (0.52, 1.80)	1.20 (0.59, 2.43)	0.630
Stratified by prior oral BP duration				
prior oral BP duration ≤ 3 y	Reference	1.18 (0.58, 2.38)	1.75 (1.01, 3.03)	0.053
prior oral BP duration > 3 y	Reference	0.96 (0.54, 1.70)	1.16 (0.61, 2.21)	0.668
Stratified by Q-fracture score*				
Fracture risk > 20 %	Reference	1.29 (0.66, 2.52)	1.64 (0.92, 2.90)	0.094
Fracture risk ≤ 20 %	Reference	0.72 (0.42, 1.25)	1.22 (0.67, 2.24)	0.568

Limitations

1. Delays are not randomized
2. Complicated methods
3. Relatively few patients followed for very long
4. UK primary care dataset



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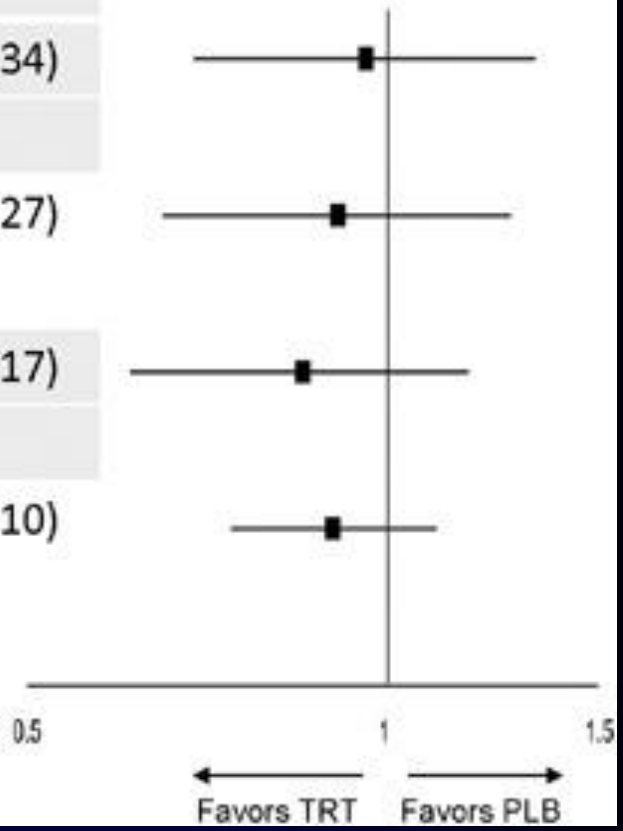
Denosumab and incidence of type 2 diabetes among adults with osteoporosis: population based cohort study

Houchen Lyu, [1,2,3] Sizheng Steven Zhao, [4] Licheng Zhang, [1,3] Jie Wei, [5,6] Xiaoxiao Li, [2] Hui Li, [2] Yi Liu, [7] Pengbin Yin, [1,3] Vibeke Norvang, [8] Kazuki Yoshida, [9] Sara K. Tedeschi, [9] Chao Zeng, [2,10,11] Guanghua Lei, [2,10,11] Peifu Tang, [1,3] Daniel H Solomon [9,12]

Objectives	To assess whether the use of denosumab is associated with a reduced risk of type 2 diabetes, compared to oral bisphosphonates, in individuals with osteoporosis.
Design	Population-based cohort study.
Setting	The IQVIA Medical Research Data United Kingdom primary care database (1995-2021).
Participants	Individuals aged 45 years or older who use denosumab or oral bisphosphonates therapy for osteoporosis.
Main outcomes	The primary outcome was incident type 2 diabetes, defined by diagnostic codes. Cox proportional hazards models were used to estimate the adjusted hazard ratio and 95% confidence intervals, comparing denosumab with oral bisphosphonates in an as-treated approach.

Effects of antiresorptive therapies on risk of diabetes: results from the FIT, HORIZON-PFT, and FREEDOM trials

	Treatment	No. of ppts	No. of cases	RR (95% CI)
FIT	ALN	3004	68	0.96 (0.69, 1.34)
	PLB	2973	70	
HORIZON-PFT	ZOL	3475	68	0.91 (0.65, 1.27)
	PLB	3498	75	
FREEDOM	DMAB	3447	66	0.85 (0.61, 1.17)
	PLB	3466	78	
Pooled	TMT	9926	202	0.90 (0.74, 1.10)
	PLB	9937	223	



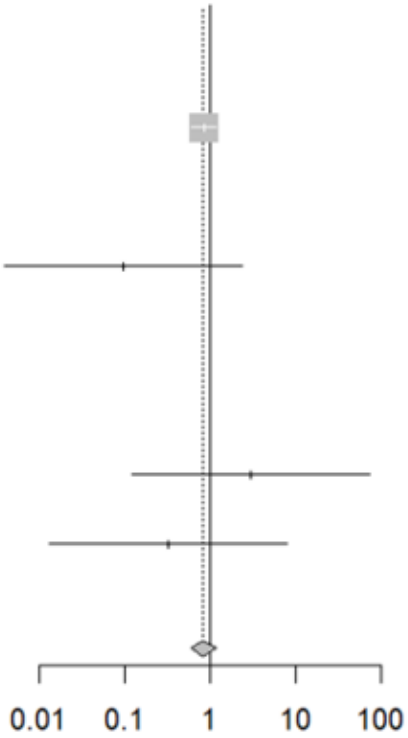
J of Bone & Mineral Res, Volume: 28, Issue: 6, Pages: 1348-1354, First published: 15 January 2013, DOI: (10.1002/jbmr.1865)

Meta-analysis of RCTs

A. All osteoporosis RCTs

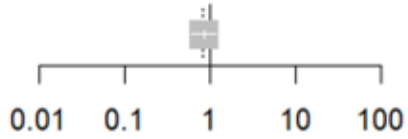
Study	Denosumab Events	Denosumab Total	Controls Events	Controls Total	RR	95%-CI	Weight
Anastasilakis 2015	0	32	0	26			0.0%
Bone 2008	0	166	0	166			0.0%
Brown 2009	0	594	0	595			0.0%
Cummings 2009	66	3447	78	3466	0.85	[0.62; 1.18]	97.0%
Kendler 2010	0	253	0	251			0.0%
Kendler 2011	0	125	0	117			0.0%
Koh 2016	0	64	0	64			0.0%
McClung 2006	0	314	1	92	0.10	[0.00; 2.39]	1.0%
Miller 2008	0	231	0	46			0.0%
Miller 2016	0	321	0	322			0.0%
Nakamura 2012	0	157	0	55			0.0%
Nakamura 2014	0	472	0	480			0.0%
Niimi 2018	0	100	0	100			0.0%
Recknor 2013	1	411	0	410	2.99	[0.12; 73.25]	1.0%
Roux 2014	0	429	0	429			0.0%
Saag 2019	0	394	1	385	0.33	[0.01; 7.97]	1.0%
Takeuchi 2019	0	221	0	224			0.0%
Random effects model		**7731**		**7228**	**0.84**	**[0.61; 1.15]**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.0001$, $p = 0.44$



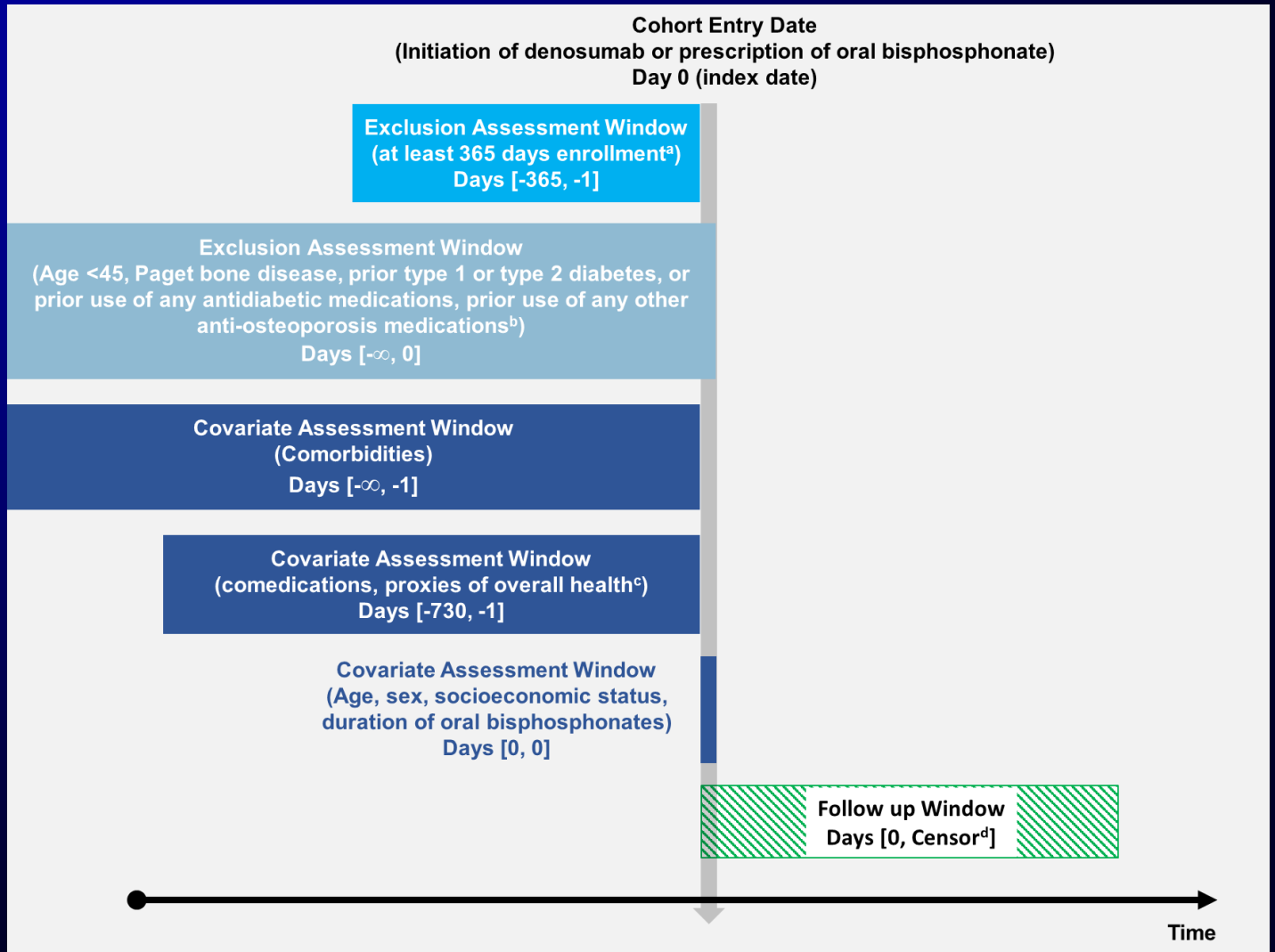
B. FREEDOM Study

Study	Denosumab Events	Denosumab Total	Controls Events	Controls Total	RR	95%-CI	Weight
Cummings 2009	66	3447	78	3466	0.85	[0.62; 1.18]	97.0%

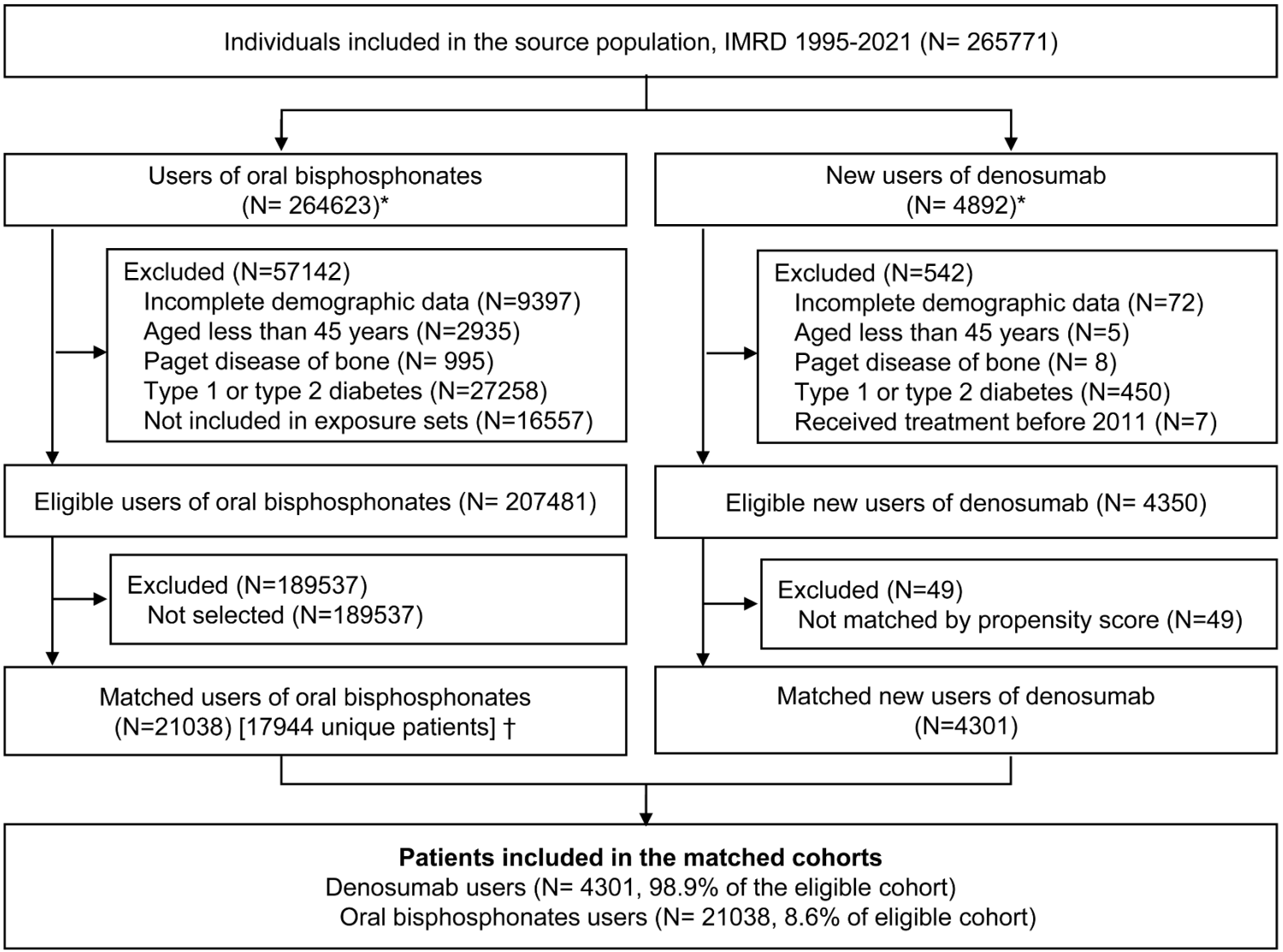


Protocol component	Target pragmatic trial specification (a hypothetical RCT that is ideal for answering this question)	Target trial emulation (using observational data to best approximate the RCT comparison)
Eligibility criteria	Age≥45, between 2011 and 2021; Patients using oral bisphosphonates or not yet receiving any anti-osteoporosis treatment; At least 1 year of up-to-standard data in a THIN primary care practice;	Same as the target trial;
Treatment strategies	(1) Denosumab treatment: initiating or switching to denosumab; (2) Oral bisphosphonate treatment: initiating or continuing with an oral bisphosphonate; Patients are not allowed to switch to any other anti-osteoporosis drug; patients are also not allowed to discontinue the initially assigned medication;	Same as for the target trial;
Treatment assignment	Eligible individuals are randomly assigned to one of the two “treatment strategies” stratified by duration of oral bisphosphonate (months) and are aware of the strategy to which they have been assigned;	We classify patients according to the strategy received at time zero and emulate randomization by propensity score matching; time zero is defined as the switch date or date of incident use for denosumab users and their matched oral bisphosphonate controls.
Outcomes	Incident type 2 diabetes;	Same as for the target trial but several different ways of defining
Follow-up	Starts at the time of assignment to a strategy and ends at the earliest of diagnosis of type 2 diabetes, death, 5 years after time zero or administrative end of follow-up;	Starts at the switch date or date of incident use for denosumab users and their matched oral bisphosphonate;
Casual contrasts	Per-protocol effect;	Observational analog of the per-protocol effect;
Statistical analysis	Intention-to-treat analysis; Per-protocol analysis;	Observational analog of the per-protocol analysis;

Study design



a. Patients were required to have at least 365 days enrollment.
b. Prior use of any other anti-osteoporosis medications included zoledronate, teriparatide, and raloxifene.
c. Proxies of overall health included number of hospitalization and physician visits.
d. Earliest of: outcome of interest (type 2 diabetes), discontinuation of drug of interests, death, transfer out of primary care clinic, 5-years follow-up, end of the study period


Individuals included in the source population, IMRD 1995-2021 (N= 265771)
Users of oral bisphosphonates (N= 264623)*
New users of denosumab (N= 4892)*
Excluded (N=57142)
Incomplete demographic data (N=9397)
Aged less than 45 years (N=2935)
Paget disease of bone (N= 995)
Type 1 or type 2 diabetes (N=27258)
Not included in exposure sets (N=16557)
Excluded (N=542)
Incomplete demographic data (N=72)
Aged less than 45 years (N=5)
Paget disease of bone (N= 8)
Type 1 or type 2 diabetes (N=450)
Received treatment before 2011 (N=7)
Eligible users of oral bisphosphonates (N= 207481)
Eligible new users of denosumab (N= 4350)
Excluded (N=189537)
Not selected (N=189537)
Excluded (N=49)
Not matched by propensity score (N=49)
Matched users of oral bisphosphonates (N=21038) [17944 unique patients] †
Matched new users of denosumab (N=4301)
Patients included in the matched cohorts
Denosumab users (N= 4301, 98.9% of the eligible cohort)
Oral bisphosphonates users (N= 21038, 8.6% of eligible cohort)

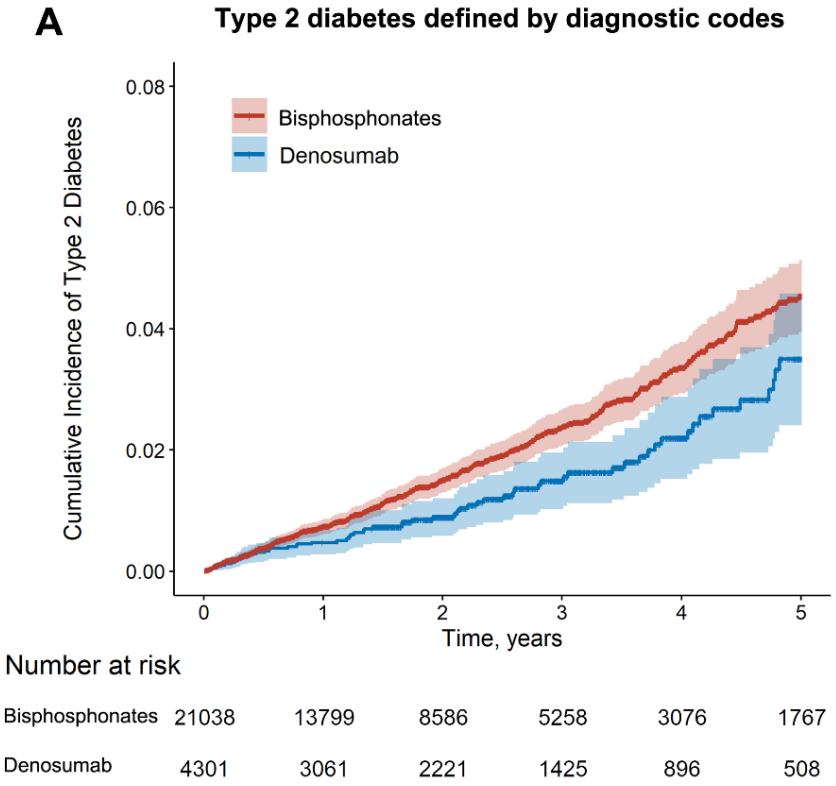
Characteristics	Oral bisphosphonate (n=21038)	Denosumab (n=4301)	Standardized difference
New user status, N (%)			
Incident new users	4802 (22.8)	961 (22.3)	
Oral bisphosphonate switched to denosumab	16236 (77.2)	3340 (77.7)	
Year of cohort entry, N (%)			0.01
2011-2013	3976 (18.9)	804 (18.7)	
2014-2016	8962 (42.6)	1819 (42.3)	
2017-2019	6101 (29.0)	1256 (29.2)	
2020-2021	1999 (9.5)	422 (9.8)	
Age at cohort entry, mean (SD)	75.7 (11.0)	75.7 (9.9)	0.007
Female sex, N (%)	19766 (94.0)	4055 (94.3)	0.01
Socioeconomic deprivation index, mean (SD)	2.19 (1.47)	2.19 (1.47)	0.001
BMI category, N (%)			0.02
Normal	8612 (40.9)	1766 (41.1)	
Obese	2224 (10.6)	450 (10.5)	
Overweight	5466 (26.0)	1109 (25.8)	
Underweight	3470 (16.5)	729 (16.9)	
Unknown	1266 (6.0)	247 (5.7)	
Major osteoporotic fracture history, N (%)	10457 (49.7)	2169 (50.4)	0.01
Comorbidity prior to cohort entry, N (%)			
Hypertension	10532 (50.1)	2147 (49.9)	0.003
Hypercholesterolemia	3346 (15.9)	670 (15.6)	0.009
Cerebrovascular disease	1831 (8.7)	369 (8.6)	0.004
Congestive heart disease	1007 (4.8)	217 (5.0)	0.01
Myocardial infarction	863 (4.1)	182 (4.2)	0.006
Venous thromboembolism	1494 (7.1)	297 (6.9)	0.008
Renal disease	4494 (21.4)	936 (21.8)	0.01
Cancer	3388 (16.1)	694 (16.1)	0.001
Medications in 2 years priors to cohort entry, N (%)			
Nonsteroidal anti-inflammatory drugs	11460 (54.5)	2361 (54.9)	0.008
Antihypertensive	12159 (57.8)	2497 (58.1)	0.005
Statin	6958 (33.1)	1417 (32.9)	0.003
Glucocorticoids	5700 (27.1)	1188 (27.6)	0.01
Benzodiazepines	3416 (16.2)	704 (16.4)	0.004
Proton pump inhibitors	11451 (54.4)	2322 (54.0)	0.009
SSRI	440 (2.1)	100 (2.3)	0.02
Healthcare utilization in 2 years priors to entry			
Hospitalizations, mean (SD)	2.1 (3.9)	2.1 (3.5)	0.008

Main Results

Table: Risk of incident type 2 diabetes among patients initiating denosumab compared with propensity score-matched controls

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
Primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	21038	347	41900	8.3 (7.4 to 9.2)	Reference
Denosumab	4301	60	10617	5.7 (4.3 to 7.3)	0.68 (0.52 to 0.89)
Secondary outcome: defined by diagnostic codes, antidiabetic medication, and lab results					
Oral bisphosphonate	21038	486	41827	11.6 (10.6 to 12.7)	Reference
Denosumab	4301	90	10598	8.5 (6.8 to 10.4)	0.73 (0.58 to 0.91)

Cumulative Incidence



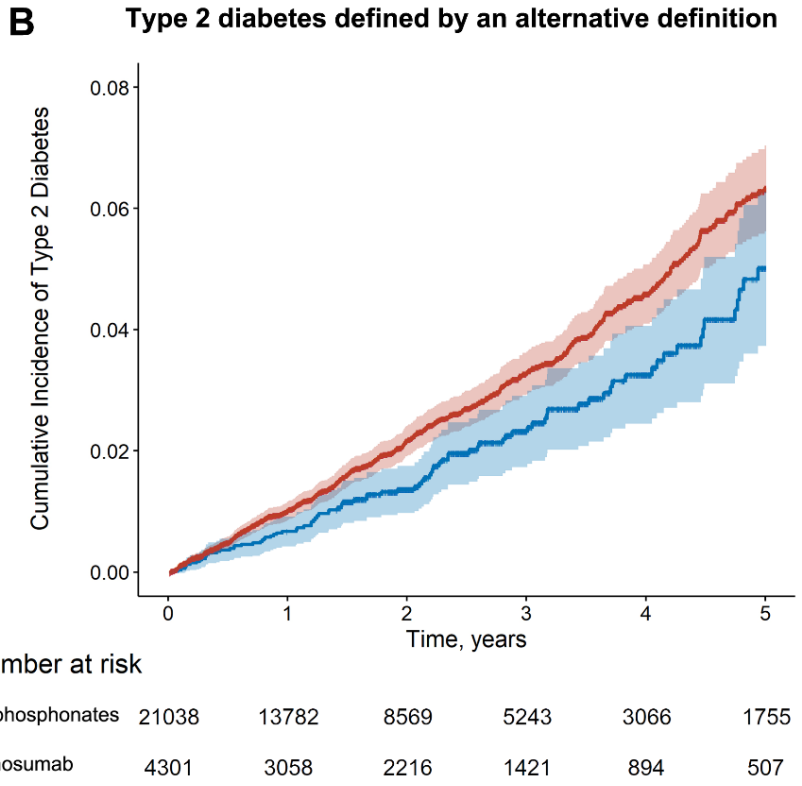


Table: Subgroup analysis stratified by risk factors for type 2 diabetes

Exposure	Number of patients, n	Number of events, n	Person-years	Incident rate* (95% CI)	HR (95% CI)
Subgroup analysis 1: stratified by prediabetes					
Prediabetes					
Oral bisphosphonate	4750	198	8951	22.1 (19.1 to 25.4)	Reference
Denosumab	868	24	2028	11.8 (7.6 to 17.6)	0.54 (0.35 to 0.82)
No prediabetes					
Oral bisphosphonate	16288	149	32949	4.5 (3.8 to 5.3)	Reference
Denosumab	3433	36	8589	4.2 (2.9 to 5.8)	0.92 (0.65 to 1.32)
Subgroup analysis 2: stratified by obesity					
Obesity					
Oral bisphosphonate	2224	116	4692	24.7 (20.4 to 29.7)	Reference
Denosumab	450	19	1172	16.2 (9.8 to 25.3)	0.65 (0.40 to 1.06)
No obesity					
Oral bisphosphonate	17548	218	34990	6.2 (5.4 to 7.1)	Reference
Denosumab	3604	41	8974	4.6 (3.3 to 6.2)	0.73 (0.53 to 1.01)

Notes: * per 1000 person-years. Prediabetes was defined by baseline impaired fasting glucose (fast blood glucose of 5.6 to 6.9 mmol/L) and/or impaired glucose tolerance (glucose tolerance test of 7.8-11.0 mmol/L) and/or HbA1c of 5.7% to 6.4%.

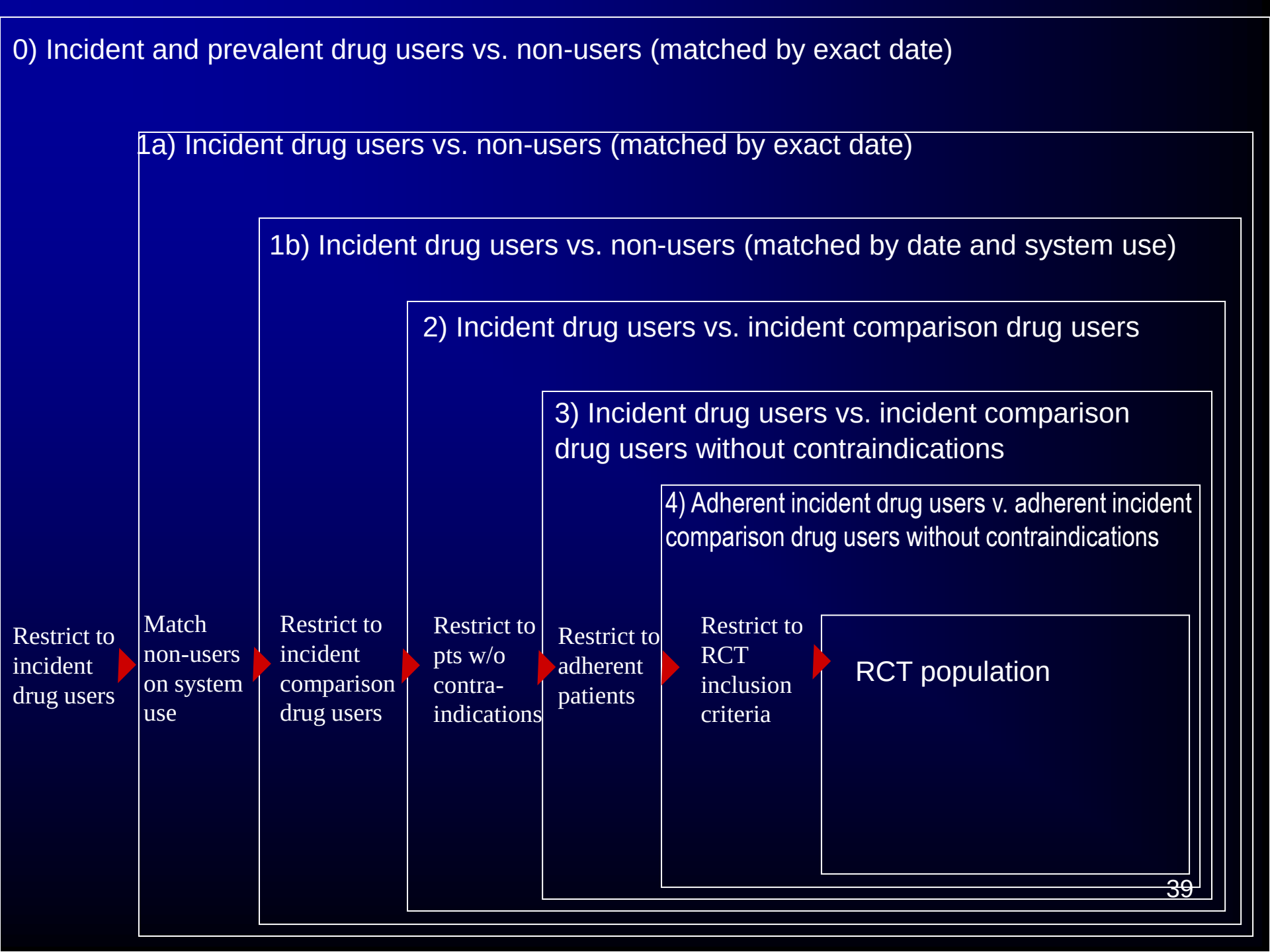
Table: Sensitivity analyses for risk of incident type 2 diabetes

Exposure	Number of patients, n	Number of events, n	Person-years	Incident rate* (95% CI)	HR (95% CI)
Sensitivity analysis 1: a subgroup of incident new users of denosumab and their oral bisphosphonate pairs					
Oral bisphosphonate	4802	89	10345	8.6 (6.9 to 10.6)	Reference
Denosumab	961	6	2036	3.0 (1.1 to 6.4)	0.35 (0.15 to 0.79)
Sensitivity analysis 2: asymmetric trimming of the propensity score					
Oral bisphosphonate	20015	326	39961	8.2 (7.3 to 9.1)	Reference
Denosumab	4056	56	10049	5.6 (4.2 to 7.2)	0.68 (0.52 to 0.90)
Sensitivity analysis 3: competing risk of death					
Oral bisphosphonate	21038	347	41900	8.3 (7.4 to 9.2)	Reference
Denosumab	4301	60	10617	5.7 (4.3 to 7.3)	0.68 (0.52 to 0.89)
Sensitivity analysis 4: lag six-month exposure time					
Oral bisphosphonate	21038	274	41900	6.5 (5.8 to 7.4)	Reference
Denosumab	4301	47	10617	4.4 (3.3 to 5.9)	0.65 (0.48 to 0.88)

* per 1000 person-years. HR, hazard ratio; CI, confidence interval.

Limitations

1. Mixing prevalent and incident users but sensitivity analyses suggest minimal bias
2. Residual confounding, e.g., diet and exercise
3. Misclassification of outcomes, but sensitivity analyses suggest minimal bias


0) Incident and prevalent drug users vs. non-users (matched by exact date)
1a) Incident drug users vs. non-users (matched by exact date)
1b) Incident drug users vs. non-users (matched by date and system use)
2) Incident drug users vs. incident comparison drug users
3) Incident drug users vs. incident comparison drug users without contraindications
4) Adherent incident drug users v. adherent incident comparison drug users without contraindications
Restrict to incident drug users
Match non-users on system use
Restrict to incident comparison drug users
Restrict to pts w/o contra-indications
Restrict to adherent patients
Restrict to RCT inclusion criteria
RCT population

Methodologic conclusions

- The “Target Trial” is an important concept in comparative effectiveness research.
- Carefully designed observational analyses can complement RCTs or may be the best substitute when RCTs are considered unethical.
- Having a large sample size can be very helpful, but it does not allow one to make stronger inferences about causation.
- Causal inference (“causal effect”) analyses can be useful but do not PROVE causation and cannot substitute for RCTs.

Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center

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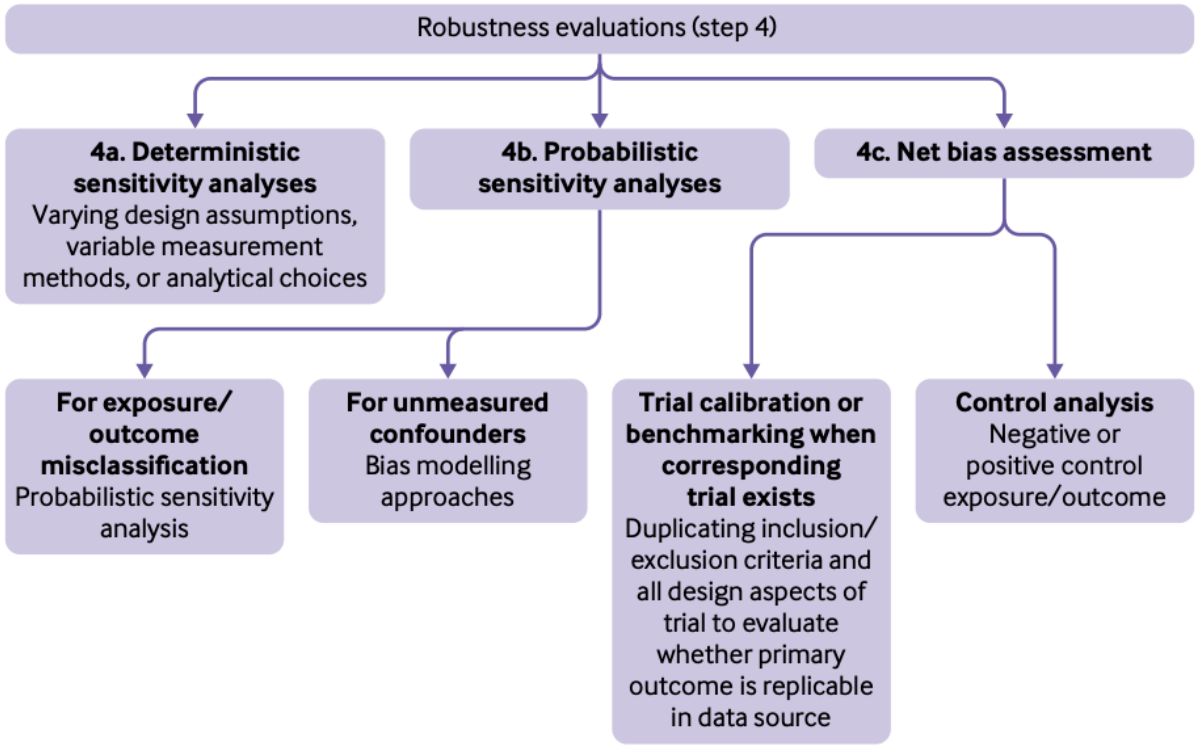

Robustness evaluations (step 4 of the process guide for inferential studies using healthcare data from routine clinical practice)

Thanks

Brigham and Women's Hospital
Founding Member, Mass General Brigham

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