

## Patterns of Initial Prescription Opioid Supply and Risk of Mortality Among Insured Adults in the United States

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### Online Supplement

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**eTable 1: A Summary of the Protocol of a Target Trial<sup>a</sup> to Estimate the Causal Effects of Initial pattern of Prescription Opioid Supply on the one-Year Risk of all-cause Mortality among Insured Adults in the United States, 2010-2015.**

Protocol Component	Description
Eligibility criteria	Opioid-naïve adults with no claims for cancer or hospice services in the past year (6 months before the first opioid prescription [baseline period] and 6 month after opioid initiation [index period]) and no opioid use disorder diagnosis at baseline.
Treatment strategies	Initiate and take prescription opioids daily versus non-daily as defined during the index period and remain on it during follow-up unless adverse events occur
Assignment procedures	Patients randomly assigned to either daily or nondaily opioid use during the index period and will be aware of the strategy to which they have been assigned.
Follow-up period	Starts at the end of the index period and ends with death, loss of enrolment or 5 years after index period, whichever occurs first
Outcome	All-cause mortality within 1 year as captured in the Social Security Administration Death Master file.
Causal contrast of interest	Intention-to-treat effect
Analysis plan	Intention-to-treat effect estimated via comparison of 1-year all-cause mortality risks among individuals assigned to each treatment strategy. All analyses were adjusted for baseline/index prognostic factors associated with exposure and outcome. Covariates included in the analysis were specified a priori.

<sup>a</sup>Hernán, M.A. and Robins, J.M. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *American Journal of Epidemiology*, 2016; 183(8): 758–764. <https://doi.org/10.1093/aje/kwv254>

**eTable 2. Current Procedural Terminology (CPT) and International Classification of Diseases, Ninth Revision (ICD-9) codes for surgical procedures**

Surgical procedures	CPT codes
Total Knee Arthroplasty	27447
Total Hip Arthroplasty	27130
Laparoscopic Cholecystectomy	47562, 47563, 47564
Open Cholecystectomy	47600, 47605, 47610
Laparoscopic Appendectomy	44970, 44979
Open Appendectomy	44950, 44960
Cesarean Section	59510, 59514, 59515
FESS	31237, 31240, 31254, 31255, 31256, 31267, 31276, 31287, 31288
Cataract Surgery	66982, 66983, 66984
TURP	52601, 52612, 52614, 52480, 52630
Simple Mastectomy	19301, 19302, 19303, 19180
Carpal tunnel release	64721
Parathyroidectomy	60500
Varicose veins	37785
Hemorrhoidectomy	46221, 46945, 46946, 46250, 46260, 46257, 46258, 46261, 46262, 46255
Thyroidectomy	60240
Surgical procedures	ICD-9codes
Gastric procedures	4498, 4464, 4495, 4438, 4468, 4382, 4439
Incisional hernia repair	5351, 5362, 5359
Esophagus	4495, 4466
Diaphragm	5362, 5371, 5383, 5372, 5361, 5384, 5369, 5363, 5375, 5380
Colon	4581, 4573, 4582, 4583
Uterus	6831, 6841, 6851, 6839, 6849, 689

FESS=Functional endoscopic sinus surgery, TURP=transurethral resection of the prostate

eTable 3. Pain diagnoses

Pain disorder category	ICD-9 codes
Headache/migraines	'3840', '3502', '34000', '346', '3460', '3461', '3462', '3463', '3464', '3465', '3466', '3467', '3468', '34600', '34601', '34602', '34603', '34610', '34611', '34612', '34613', '34620', '34621', '34622', '34623', '34630', '34631', '34632', '34633', '34640', '34641', '34642', '34643', '34650', '34651', '34652', '34653', '34660', '34661', '34662', '34663', '34670', '34671', '34672', '34673', '34680', '34681', '34682', '34683', '34690', '34691', '34692', '34693', '30781', '7840', '7238', '3469'
Neck/TMJ	'72231', '72271', '72281', '72291', '8390', '8391', '8470', '7210', '7211', '7220', '723', '52460', '52461', '52462', '52463', '52464', '52469'
Back	'72230', '72232', '72233', '72270', '72272', '72273', '72280', '72282', '72283', '72290', '72292', '72293', '7371', '7373', '7384', '7385', '7392', '7393', '7394', '75610', '75611', '75612', '75619', '8054', '8058', '8392', '83942', '846', '8460', '8471', '8472', '8473', '8479', '75613', '7222', '724', '7213' - '7219'
Abdominal pain	'7890', '78900', '78901', '78902', '78903', '78904', '78905', '78906', '78907', '78909', '78960', '78961', '78962', '78963', '78964', '78965', '78966', '78967', '78969', '5920', '5921', '5929', '5940', '5941', '5942', '5948', '5949', '7880', 'V1301'
Joint/arthritis pain	'710', '7101', '7103', '7104', '734', '725', '7105', '7108', '7109', '729', '7292', '7294', '7295', '7296', '737', '7378', '7379', '738', '7382', '7383', '7386', '7387', '7388', '7389', '739', '7391', '7395', '7396', '7397', '7398', '7399', '711', '712', '713', '714', '715', '716', '717', '718', '719', '726', '727', '728', '7293', '7297', '7298', '7299', '730', '731', '732', '733', '735', '736', '7372', '7374', '7381'
Fibromyalgia/CFS	'7291', '78071'
Chronic pain syndrome	'3380', '3382', '3384', '339', '346', '30781', '7840', '805', '806', '846', '847', '3502', '3540', '3544', '3555', '35571', '377', '3370' - '33719', '356', '357', '710' - '719', '720' - '724', '725' - '729', '731' - '738'
Other pain conditions	'78659', '5305', '5368', '7102', '3883', '5951', '564', '6257', '617'

TMJD=Temporal-mandibular joint disorder, CFS=Chronic fatigue syndrome, CPS=chronic pain syndrome; ICD-9= *International Classification of Diseases, Ninth Revision*

Adapted from: HCUP CCS. Healthcare Cost and Utilization Project (HCUP). March 2017. Agency for Healthcare Research and Quality, Rockville, MD. [www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp](http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). Accessed on 1/12/2018.

**eTable 4. Other pain conditions: ICD-9 codes for Fractures and Strains**

'81000'	'81001'	'81002'	'81003'	'81010'	'81011'	'81012'	'81013'	'81100'	'81101'	'81102'	'81103'	'81109'	'81110'
'81111'	'81112'	'81113'	'81119'	'81200'	'81201'	'81202'	'81203'	'81209'	'81210'	'81211'	'81212'	'81213'	'81219'
'81220'	'81221'	'81230'	'81231'	'81240'	'81241'	'81242'	'81243'	'81244'	'81249'	'81250'	'81251'	'81252'	'81253'
'81254'	'81259'	'81300'	'81301'	'81302'	'81303'	'81304'	'81305'	'81306'	'81307'	'81308'	'81310'	'81311'	'81312'
'81313'	'81314'	'81315'	'81316'	'81317'	'81318'	'81320'	'81321'	'81322'	'81323'	'81330'	'81331'	'81332'	'81333'
'81340'	'81341'	'81342'	'81343'	'81344'	'81345'	'81346'	'81347'	'81350'	'81351'	'81352'	'81353'	'81354'	'81380'
'81381'	'81382'	'81383'	'81390'	'81391'	'81392'	'81393'	'81400'	'81401'	'81402'	'81403'	'81404'	'81405'	'81406'
'81407'	'81408'	'81409'	'81410'	'81411'	'81412'	'81413'	'81414'	'81415'	'81416'	'81417'	'81418'	'81419'	'81500'
'81501'	'81502'	'81503'	'81504'	'81509'	'81510'	'81511'	'81512'	'81513'	'81514'	'81519'	'81600'	'81601'	'81602'
'81603'	'81610'	'81611'	'81612'	'81613'	'8170'	'8171'	'8180'	'8181'	'8190'	'8191'	'9052'	'82100'	'82101'
'82110'	'82111'	'82120'	'82121'	'82122'	'82123'	'82129'	'82130'	'82131'	'82132'	'82133'	'82139'	'8220'	'8221'
'82300'	'82301'	'82302'	'82310'	'82311'	'82312'	'82320'	'82321'	'82322'	'82330'	'82331'	'82332'	'82340'	'82341'
'82342'	'82380'	'82381'	'82382'	'82390'	'82391'	'82392'	'8240'	'8241'	'8242'	'8243'	'8244'	'8245'	'8246'
'8247'	'8248'	'8249'	'8250'	'8251'	'82520'	'82521'	'82522'	'82523'	'82524'	'82525'	'82529'	'82530'	'82531'
'82532'	'82533'	'82534'	'82535'	'82539'	'8260'	'8261'	'8270'	'8271'	'9054'	'80500'	'80501'	'80502'	'80503'
'80504'	'80505'	'80506'	'80507'	'80508'	'80510'	'80511'	'80512'	'80513'	'80514'	'80515'	'80516'	'80517'	'80518'
'8052'	'8053'	'8054'	'8055'	'8056'	'8057'	'8058'	'8059'	'80700'	'80701'	'80702'	'80703'	'80704'	'80705'
'80706'	'80707'	'80708'	'80709'	'80710'	'80711'	'80712'	'80713'	'80714'	'80715'	'80716'	'80717'	'80718'	'80719'
'8072'	'8073'	'8074'	'8075'	'8076'	'8080'	'8081'	'8082'	'8083'	'80841'	'80842'	'80843'	'80844'	'80849'
'80851'	'80852'	'80853'	'80854'	'80859'	'8088'	'8089'	'8090'	'8091'	'8280'	'8281'	'8290'	'8291'	'9051'
'9055'	'8400'	'8401'	'802'	'8403'	'8404'	'8405'	'8406'	'8407'	'8408'	'8409'	'8410'	'8411'	'8412'
'8413'	'8418'	'8419'	'84200'	'84201'	'84202'	'84209'	'84210'	'84211'	'84212'	'84213'	'84219'	'8430'	'8431'
'8431'	'8438'	'8439'	'8440'	'8441'	'8442'	'8443'	'8448'	'8449'	'84500'	'84501'	'84502'	'84503'	'84509'
'84510'	'84511'	'84512'	'84513'	'84519'	'8460'	'8461'	'8462'	'8463'	'8468'	'8469'	'8470'	'8471'	'8472'
'8473'	'8474'	'8479'	'8480'	'8481'	'8482'	'8483'	'84840'	'84841'	'84842'	'84849'	'8485'	'8488'	'8489'
'9057'	'V5414'	'V5415'	'V5416'	'V5424'	'V5425'	'V5426'	'V5410'	'V5411'	'V5412'	'V5420'	'V5421'	'V5422'	'V5417'
'V5419'	'V5427'	'V5429'	'V664'	'V674'	'V1352'	'V540'	'V5401'	'V5402'	'V5409'	'82000'	'82001'	'82002'	'82003'
'82009'	'82010'	'82011'	'82012'	'82013'	'82019'	'82020'	'82021'	'82022'	'82030'	'82031'	'82032'	'8208'	'8209'
'9053'	'V5413'	'V5423'	'80000'	'80001'	'80002'	'80003'	'80004'	'80005'	'80006'	'80009'	'80050'	'80051'	'80052'
'80053'	'80054'	'80055'	'80056'	'80059'	'80100'	'80101'	'80102'	'80103'	'80104'	'80105'	'80106'	'80109'	'80150'
'80151'	'80152'	'80153'	'80154'	'80155'	'80226'	'80227'	'80228'	'80229'	'80230'	'80231'	'80232'	'80233'	'80234'
'80235'	'80300'	'80301'	'80302'	'80303'	'80304'	'80305'	'80306'	'80309'	'80350'	'80351'	'80352'	'80353'	'80354'
'80355'	'80356'	'80359'	'80400'	'80401'	'80402'	'80403'	'80404'	'80405'	'80406'	'80409'	'80450'	'80451'	'80452'
'80453'	'80454'	'80455'	'80456'	'80459'	'9050'	'80236'	'80237'	'80238'	'80239'	'8024'	'8025'	'8026'	'8027'
'8028'	'8029'	'80156'	'80159'	'8020'	'8021'	'80220'	'80221'	'80222'	'80223'	'80224'	'80225'	34939'	'80600'
'80601'	'80602'	'80603'	'80604'	'80605'	'80606'	'80607'	'80618'	'80608'	'80609'	'80610'	'80611'	'80612'	'80613'
'80614'	'80615'	'80616'	'80617'	'80619'	'80620'	'80621'	'80622'	'80623'	'80624'	'80625'	'80626'	'80627'	'80628'
'80629'	'80630'	'80631'	'80632'	'80633'	'80634'	'80635'	'80636'	'80637'	'80638'	'80639'	'8064'	'8065'	'80660'
'80661'	'80662'	'80669'	'80670'	'80671'	'80672'	'80679'	'8068'	'8069'	'9072'	'95200'	'95201'	'95202'	'95203'
'95204'	'95205'	'95206'	'95207'	'95208'	'95209'	'95210'	'95211'	'95212'	'95213'	'95214'	'95215'	'95216'	'95217'
'95218'	'95219'	'9522'	'9523'	'9524'	'9528'	'9529'							

Adapted from: HCUP CCS. Healthcare Cost and Utilization Project (HCUP). March 2017. Agency for Healthcare Research and Quality, Rockville, MD. [www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp](http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). Accessed on 1/12/2018.

**eTable 5. Mental health disorders**

Mental health condition	CCS codes	ICD-9 codes
Adjustment disorders	650	3090 3091 30922 30923 30924 30928 30929 3093 3094 30982 30983 30989 3099
Anxiety disorders	651	29384 30000 30001 30002 30009 30010 30020 30021 30022 30023 30029 3003 3005 30089 3009 3080 3081 3082 3083 3084 3089 30981 3130 3131 31321 31322 3133 31382 31383
Conduct disorders	652	31200 31201 31202 31203 31210 31211 31212 31213 31220 31221 31222 31223 3124 3128 31281 31282 31289 3129 31381 31400 31401 3141 3142 3148 3149
Mood disorders	657	29383 29600 29601 29602 29603 29604 29605 29606 29610 29611 29612 29613 29614 29615 29616 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 29640 29641 29642 29643 29644 29645 29646 29650 29651 29652 29653 29654 29655 29656 29660 29661 29662 29663 29664 29665 29666 2967 29680 29681 29682 29689 29690 29699 3004 311
Schizophrenia & psychotic disorders	659	29381 29382 29500 29501 29502 29503 29504 29505 29510 29511 29512 29513 29514 29515 29520 29521 29522 29523 29524 29525 29530 29531 29532 29533 29534 29535 29540 29541 29542 29543 29544 29545 29550 29551 29552 29553 29554 29555 29560 29561 29562 29563 29564 29565 29570 29571 29572 29573 29574 29575 29580 29581 29582 29583 29584 29585 29590 29591 29592 29593 29594 29595 2970 2971 2972 2973 2978 2979 2980 2981 2982 2983 2984 2988 2989
Alcohol related disorders	660	2910 2911 2912 2913 2914 2915 2918 29181 29182 29189 2919 30300 30301 30302 30303 30390 30391 30392 30393 30500 30501 30502 30503 3575 4255 5353 53530 53531 5710 5711 5712 5713 76071 9800
Substance related disorders	661	2920 29211 29212 2922 29281 29282 29283 29284 29285 29289 2929 30400 30401 30402 30403 30410 30411 30412 30413 30420 30421 30422 30423 30430 30431 30432 30433 30440 30441 30442 30443 30450 30451 30452 30453 30460 30461 30462 30463 30470 30471 30472 30473 30480 30481 30482 30483 30490 30491 30492 30493 30520 30521 30522 30523 30530 30531 30532 30533 30540 30541 30542 30543 30550 30551 30552 30553 30560 30561 30562 30563 30570 30571 30572 30573 30580 30581 30582 30583 30590 30591 30592 30593 64830 64831 64832 64833 64834 65550 65551 65553 76072 76073 76075 7795 96500 96501 96502 96509 V6542
Miscellaneous mental health disorders	656 658 662 670	31230 31231 31232 31233 31234 31235 31239 3010 30110 30111 30112 30113 30120 30121 30122 3013 3014 30150 30151 30159 3016 3017 30181 30182 30183 30184 30189 3019 E9500 E9501 E9502 E9503 E9504 E9505 E9506 E9507 E9508 E9509 E9510 E9511 E9518 E9520 E9521 E9528 E9529 E9530 E9531 E9538 E9539 E954 E9550 E9551 E9552 E9553 E9554 E9555 E9556 E9557 E9559 E956 E9570 E9571 E9572 E9579 E9580 E9581 E9582 E9583 E9584 E9585 E9586 E9587 E9588 E9589 E959 V6284 29389 2939 30011 30012 30013 30014 30015 30016 30019 3006 3007 30081 30082 3021 3022 3023 3024 30250 30251 30252 30253 3026 30270 30271 30272 30273 30274 30275 30276 30279 30281 30282 30283 30284 30285 30289 3029 3060 3061 3062 3063 3064 30650 30651 30652 30653 30659 3066 3067 3068 3069 3071 30740 30741 30742 30743 30744 30745 30746 30747 30748 30749 30750 30751 30752 30753 30754 30759 30780 30781 30789 3101 316 64840 64841 64842 64843 64844 V402 V403 V4031 V4039 V409 V673

CCS=Clinical classification system code, ICD-9=International Classification of Diseases, Ninth Revision codes

Adapted from: HCUP CCS. Healthcare Cost and Utilization Project (HCUP). March 2017. Agency for Healthcare Research and Quality, Rockville, MD. [www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp](http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). Accessed on 1/12/2018.

**eTable 6. Substance use disorders**

Diagnoses	ICD-9 and ICD-10 codes
Drug abuse	'3040' '3041' '3046' '3046' '3047' '3048' '3049' '3054' '3055' '3058' 'F1120' 'F1121' 'F1320' 'F1321' 'F1920' 'F1921' 'F1310' 'F1110' 'F1910'
Overdose (others)	'9658' '9659' '967' '9691' '9692' '9693' '9694' '9695' '9697' '9698' '9699' '9752' '9753' '9778' '9779' 'T400X1A' 'T400X2A' 'T400X3A' 'T400X4A' 'T403X1A' 'T403X2A' 'T403X3A' 'T403X4A' 'T402X1A' 'T402X2A' 'T402X3A' 'T402X4A' 'T404X1A' 'T404X2A' 'T404X3A' 'T404X4A' 'T40601A' 'T40602A' 'T40603A' 'T40604A' 'T40691A' 'T40692A' 'T40693A' 'T40694A'
Opioid overdose	'96500' '96502' '96509' 'E8501' 'E8502'
Opioid use disorder	'30400' '30401' '30402' '30403' '30470' '30471' '30472' '30473' '30550' '30551' '30552' '30553'
Tobacco	'3051' 'V1582'
Alcohol	'3050' '3039' '2652' '3030' '3039' '3050' '3575' '4255' '5353' '980x' 'V113', '2911' - '2913', '2915' - '2919', '5710' - '5713'
Marijuana	'3043' '3052' '3043' '30430' '30431' '30432' '30433'
Cocaine	'3056' '3042' '30420' '30421' '30422' '30423'
Other substance use	'3053', '3054', '3057', '3058', '3059'

**eTable 7. List of Medical Comorbidities and ICD-9 Codes used to calculate the Charlson Co-morbidity index**

Medical Conditions	ICD-9 codes
Congestive Heart Failure	'39891', '4254', '4255', '4257', '4258', '4259', '428'
Myocardial infarction	'410' '412'
Peripheral Vascular Disease	'0930', '440', '441', '7854', 'V434', '4420'-'4428', '4431'-'4439', '44770'-'44773'
Chronic Obstructive Pulmonary Disease	'4168', '4169', '5064', '5191', '490' - '496', '500' - '505'
Diabetes Mellitus	'250' , '2500' - '2503'
Diabetes Mellitus with complications	'3620', '2504', '2509'
Chronic Kidney Disease	'40301', '40311', '40391', '40402', '40403', '40412', '40413', '40492', '40493', '582', '583', '585', '586', '588', 'V420', 'V451', 'V56'
Cardiovascular disease	'430' - '438'
Dementia	'290', '2910', '2911', '2912', '29282', '2941', '3310', '3311', '3312', '33182'
Liver Disease	'07022', '07023', '07044', 'V427', '4560' - '4562', '5722' - '5728'
Cirrhosis	'07032', '07033', '07054', '5712', '5714', '5715', '5716'
Ulcers	'531' - '534'
Rheumatoid arthritis	'7100', '7101', '7104', '71481', '725' , ('7140' - '7142'
Paralysis	'342', '3449', '3440' - '3446'
AIDS	'79571', 'V08', '042' - '044'

**eTable 8. Rates of selected conditions diagnosed within 6 months of death by initial pattern of prescription opioid supply among 15,630 decedents in the study cohort**

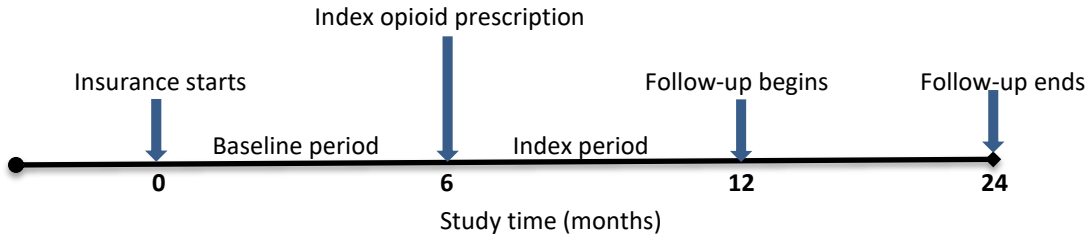
Condition	Total	Non-daily opioid supply (N=13,377)	Daily opioid supply (N=2,253)	p-value
Substance use disorder	37 (0.24)	27 (0.02)	10 (0.44)	0.0288
Overdose (others)	57 (0.36)	43 (0.32)	14 (0.62)	0.0289
Opioid overdose	14 (0.09)	11 (0.08)	12 (0.53)	< 0.001
Myocardial infarction	1,267 (8.11)	1,144 (8.55)	123 (5.46)	0.003
Cancer	897 (5.74)	743 (5.55)	154 (6.84)	0.0156
MOUD	6 (0.05)	6 (0.04)	1 (0.02)	0.3147
Hospice care	826 (5.28)	713 (5.33)	113 (5.02)	0.5370

MI= Myocardial infarction, MOUD=Medication-based treatment for opioid use disorder

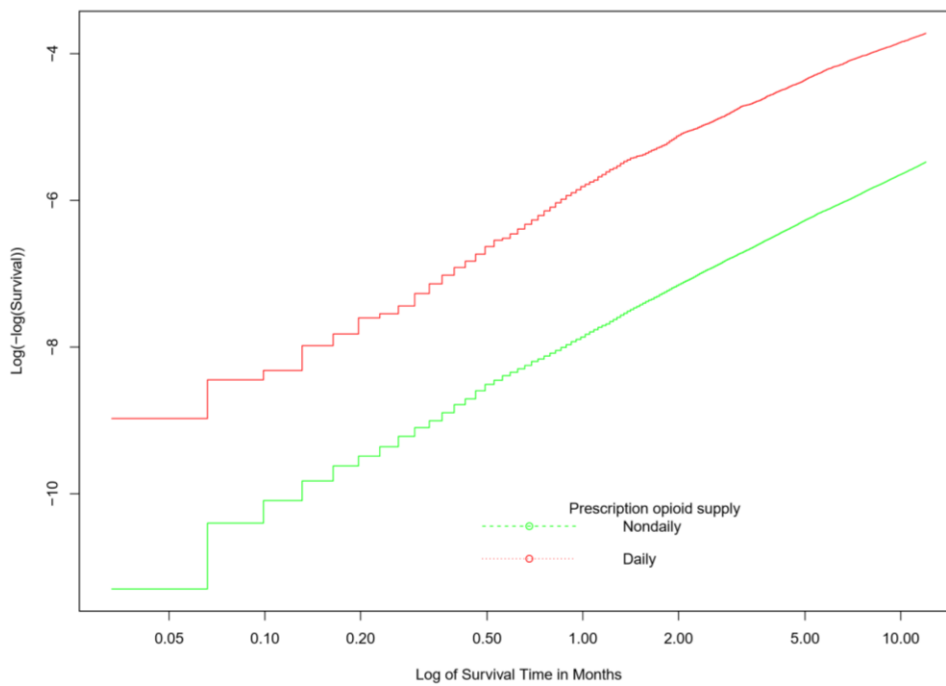
**eTable 9. Categories of last medical diagnosis during the 6 months prior to death among 15,630 decedents in the study cohort (Based on ICD-9/ICD-10 codes only)**

Medical Conditions	N (%)
Cardiac conditions	1,583 (17.38)
Cancer and cancer-related conditions	1,570 (17.16)
Respiratory disorders	1,505 (16.43)
Septicemia and other infections	1,179 (12.93)
Stroke and other CNS conditions	1,013 (11.18)
Others	702 (7.53)
Kidney failure/electrolytes problems	449 (5.03)
Gastrointestinal disorders	365 (4.59)
Fractures and other pain conditions	345 (4.23)
Hematologic disorders	129 (2.27)
<b>Total</b>	<b>8,840 (100%)</b>

CNS=Central nervous system



eFigure 1. Study timeline for patients selected into the study cohort



eFigure 2. Complementary log-log plot for the two patterns of prescription opioid supply showing parallel curves separated by a constant at all time points