

Laws Mandating Coprescription of Naloxone and Their Impact on Naloxone Prescription in Five US States, 2014–2018

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Objectives. To examine early impacts of laws that require naloxone to be prescribed to patients at increased overdose risk.

Methods. Using data from 2014 to 2018 from a large pharmacy chain, CVS Pharmacy, we examined the effects of naloxone-prescribing mandates 90 days before and after they took effect in Arizona, Florida, Rhode Island, Vermont, and Virginia. We compared the number of naloxone doses initiated directly by prescribers and by pharmacy standing order, prescriber specialty, pharmacies dispensing, and payor type by applying linear models and the χ^2 test.

Results. Naloxone-prescribing mandates increased pharmacy naloxone provision 255% from 90 days before to after implementation. This approach appeared to engage more prescribers (1028 before to 4285 after), complement ongoing naloxone provision under pharmacy standing orders, expand geographic reach (from 40% to 80% of pharmacies dispensing), and broaden the naloxone payor mix in 4 ($P < .05$) of 5 states.

Conclusions. Mandating the prescribing of naloxone quickly expands access to this life-saving medication for more people in more places. Other states should consider mandating the coprescription of naloxone to individuals at increased risk of overdose. (*Am J Public Health.* 2020;110:881–887. doi:10.2105/AJPH.2020.305620)

 See also Burris, p. 768.

A recent study¹ estimated that broader community uptake of naloxone could prevent 21 000 deaths over a 10-year period—more than restrictions on prescription opioids or expanding medications for addiction treatment. Naloxone has long been the first-line medication for treating respiratory depression brought on by opioids, which can progress to life-threatening overdose if untreated.² Since the 1990s, communities have trained laypersons to effectively respond to opioid overdose with naloxone^{3,4} and since the early 2010s have equipped uniformed first responders with the medication^{5,6} to more quickly restore breathing and prevent overdose-related morbidity and mortality.

After decades of advocacy, concerted community action, and the unprecedented toll of overdose deaths driven primarily now by fentanyl and its analogs,^{7–9} the Food and Drug Administration has recently taken steps

to increase naloxone access, including creating and testing a model drug facts label appropriate for an over-the-counter product to encourage over-the-counter applicants.¹⁰ Until an over-the-counter product advances to market, however, the coprescribing of naloxone to people who are at increased risk of opioid overdose can serve as a mechanism for expanding pharmacy access to naloxone to those at risk for future overdose and their social networks. In recognition of this fact, the

US Department of Health and Human Services issued guidance in December 2018 encouraging the coprescription of naloxone to people at risk for overdose.¹¹

Research and several scientific consensus guidance documents support the prescription of the rescue medication to people who might be at risk for experiencing opioid overdose.^{12–17} These include patients prescribed opioid medications at high doses (i.e., >50 daily morphine milligram equivalent [MME]),¹⁸ people taking opioids and sedating medications such as benzodiazepines concurrently,¹⁹ people with substance use disorders²⁰ and recent opioid overdose survivors,²¹ among others.²² Despite efforts to train and encourage prescribers²³ to prescribe naloxone to these patients at increased risk of overdose, stigma as well as a range of provider-specific^{24,25} and structural challenges such as naloxone stocking²⁶ have limited uptake of naloxone coprescribing. A recent study showed that only 1.5% of commercially insured patients at high risk of overdose from 2005 to 2016 received prescription naloxone, suggesting that regulatory efforts might be needed to bring pharmacy naloxone distribution in line with expert consensus and official guidelines.²⁷

Over the past 5 years, every state has passed at least 1 law designed to increase access to naloxone.²⁸ A key innovation of earlier versions of these laws is the ability for prescribers to issue a standing order for naloxone,

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This article was accepted February 6, 2020.

doi: 10.2105/AJPH.2020.305620

which permits the medication to be dispensed to any person who meets criteria specified in the standing order instead of to a specific, named patient of the prescriber.²⁹ All 5 states in this study have passed laws containing this provision.

The newest form of naloxone access law goes a step further, by requiring that naloxone be coprescribed to individuals that meet criteria, specified in the law, for being at increased risk for overdose. We examined the effect of these legal mandates on the pharmacy dispensing of naloxone.

METHODS

We used data from a large community pharmacy chain, CVS Pharmacy, to examine the effect of mandatory coprescription laws in the first 5 states that adopted mandatory coprescribing laws in the United States (Arizona, Florida, Rhode Island, Vermont, and Virginia). Specifically, we explored the impact of coprescribing mandates on the number of naloxone doses dispensed at pharmacy locations, the number and specialties of naloxone prescribers, the number and proportion of doses dispensed under a standing order, the number and proportion of CVS pharmacies dispensing naloxone, and the payment type, both public and private.

Each measure examined reflects important aspects of the coprescribing mandate's impact on naloxone availability to individuals at increased risk of overdose. The change in number of doses dispensed indicates the broad impact of the mandate on naloxone availability to those individuals. Examining changes in the medical specialty of providers prescribing naloxone suggests the differential impact of coprescribing mandates on different types of providers, as well as on the types of patients at risk for overdose who can obtain naloxone from a pharmacy. Changes in the number of standing order–dispensed naloxone doses indicate the accessibility of naloxone through nonprescriber pathways critical to friends and family of patients at risk, which may complement the mandate's effect. Measuring changes in the number and proportion of pharmacies dispensing naloxone within the chain reflects the geographic reach of the mandate. Finally, examining how payment types for naloxone prescriptions shift

suggests the economic impact and patient burden of the mandate.

To determine the presence and characteristics of naloxone mandates, a trained legal researcher (C. D.) systematically searched the Westlaw legal database for all laws containing the terms “opioid antagonist” or “naloxone” and “prescri” that went into effect on or before September 31, 2018. We examined all resulting laws to determine whether they met study criteria, which we set a priori to include all and only laws that require that naloxone be prescribed in at least some circumstances. We downloaded all laws that met study criteria for review and recorded their characteristics (enactment date, effective date, and circumstances in which coprescription is required).

Records of each naloxone prescription dispensed contained the unique national provider identifier, and we matched publicly available data elements from the Centers for Medicare and Medicaid National Plan and Provider Enumeration System³⁰ to indicate the provider's practice specialty. We calculated doses per capita by dividing the number of naloxone doses dispensed from October 2017 to September 2018 by the estimated 2018 state population.³¹ We also descriptively analyzed payment type for every prescription. We grouped payment types into cash, Medicaid, Medicare, workers' compensation, and commercial insurance. For each state, we identified naloxone prescriptions dispensed under standing orders by identifying and differentiating the national provider identifier associated with standing orders issued both by state officials and by prescribers affiliated with the pharmacy chain. All states had similar naloxone access laws in place during the study period.²⁸ Summary data characterizing standing order trends included naloxone prescriptions filled between 2014 and 2018.

To examine the short-term impacts of coprescribing mandates, we compared the number of naloxone doses dispensed, unique prescribers, pharmacies dispensing, and naloxone doses dispensed via standing order 90 days before compared with 90 days (i.e., in three 30-day increments) after the coprescription mandates went into effect. We used linear models and indicators of mandate implementation, controlling for state fixed effects. Data for the primary outcome analyses of the coprescription mandate pertained to naloxone doses dispensed from 2017 to 2018

(i.e., 90 days before the first enacted mandate in 2017). We also conducted a sensitivity analysis using Poisson regression on the count of naloxone doses. We used the χ^2 test to calculate differences in the distribution of payor mix and medical specialty provider type before compared with after the coprescription mandate. We conducted all statistical tests in SAS version 9.3 (SAS Institute, Cary, NC) at a *P* level of less than .05.

RESULTS

By September 2018, 5 states had implemented laws mandating that a prescription for naloxone be issued to certain patients (Table 1). The patient characteristics that trigger such a prescription vary by state. For example, the mandates in Arizona and Florida apply only to patients who are prescribed a schedule II opioid, whereas in other states the mandate applies regardless of the schedule of opioid prescribed. Arizona law³² requires that naloxone be coprescribed to a patient receiving greater than 90 MME, whereas in Florida coprescribing is required for those for whom the opioid was prescribed for pain related to a traumatic injury with an Injury Severity Score of 9 or greater, regardless of the MME prescribed.³³ Vermont requires the coprescribing of naloxone to any patient receiving greater than 90 MME per day and patients receiving both opioids and benzodiazepines,³⁴ whereas Virginia mandates that naloxone be prescribed to patients who are receiving greater than 120 MME per day, those receiving both benzodiazepines and opioids, and those with a history of overdose or substance misuse.³⁵ Finally, Rhode Island requires that naloxone be prescribed to any patient who is receiving 50 MME or higher, to any patient who has been prescribed both opioids and benzodiazepines in the past 30 days, and to patients with a history of opioid use disorder or overdose when they are prescribed an opioid.³⁶

Across the 5 states with mandated naloxone prescription laws, the total number of naloxone doses dispensed in the 90 days after implementation of the coprescription mandate grew 255%, from 6208 to 22 067 ($F = 29.45$; $P < .001$) compared with the 90 days before adoption of the mandate (Table 2). A sensitivity analysis using Poisson

TABLE 1—US States With Coprescription Mandates as of September 30, 2018

State	No. Study Pharmacies	Year Pharmacy Standing Order for Naloxone Implemented at Pharmacy Chain	When Naloxone Must Be Prescribed	Coprescription Mandate Effective Date
Arizona	199	2016	New Rx for schedule II opioid for >90 MME per d	April 25, 2018
Florida	861	2016	Rx for a schedule II opioid for pain related to a traumatic injury with an Injury Severity Score \geq 9	July 1, 2018
Rhode Island	64	2014	When any of the following exist: Rx opioid to patient receiving \geq 50 MME per d Rx for any dose of an opioid when a benzodiazepine has been prescribed in the past 30 days or will be prescribed at the visit Rx for any dose of an opioid to patient with a history of opioid use disorder or overdose	July 2, 2018
Vermont	10	2015	When any of the following exist: Rx to patient receiving > 90 MME per day All patients receiving concomitant opioid and benzodiazepine Rx	July 1, 2017
Virginia	347	2015	To any patient with any of the following risk factors: Opioid doses > 120 MME per day Concomitant opioid and benzodiazepine Rx Prior overdose or substance misuse history	March 15, 2017

Note. MME = morphine milligram equivalents; Rx = prescription.

regression yielded a similar consistent and significant before to after mandate increase in naloxone doses dispensed across the 5 states ($P < .001$). Overall, the mean number of doses dispensed per 30-day increment in the 5 states was 943 (median = 564; SD = 928; range = 10–3303 doses). The highest annual

rates of naloxone dispensing were in Rhode Island (540.8 doses per 100 000 population) and Virginia (182.4 doses per 100 000 population).

The amount and proportion of naloxone dispensed pursuant to pharmacy standing orders varied substantially across the 5 states

before the coprescription mandate, and that pattern continued subsequent to the mandate. The median proportion of standing order naloxone doses dispensed from the date the standing order law was implemented at the pharmacy chain up to the month preceding the date of mandated coprescribing was 29% (Arizona: 4%, Florida: 15%, Virginia: 29%, Rhode Island: 47%, Vermont: 76%). The change in the absolute number of naloxone doses dispensed under a standing order increased 50% from 795 to 1194 doses ($F = 2.74$; $P = .11$) after the mandate was implemented, but this change was not statistically significant. The number of doses dispensed via traditional prescription, however, increased significantly: from 5413 to 20 873 doses ($F = 28.87$; $P < .001$). Overall, the proportion of naloxone doses prescribed via standing order fell from 12.8% of all naloxone doses dispensed in the 90 days before to 5.4% of doses 90 days after the coprescription mandate ($\chi^2 = 405.2$; $df = 1$; $P < .001$).

During the 90 days before the mandate, the number of naloxone prescribers totaled 1028; this increased 317% in the 90 days after the mandate to 4285 ($F = 36.30$; $P < .001$). Before the mandate, medical specialties that

TABLE 2—Short-Term Impacts of Naloxone Coprescription Mandates in 5 US States: 2014–2018

	Virginia	Rhode Island	Arizona	Florida	Vermont	Overall
Change in total doses dispensed	7 660	5 083	4 760	10 540	232	28 275
Percentage change in total doses dispensed	+1116	+223	+241	+240	+187	+255 ^a
Percentage change in standing order doses dispensed	+19	-17	-32	+280	-17	+51
Annual ^c naloxone dose dispensing rate per 100 000 population	182.4	540.8	54.0	27.7	48.4	...
Standing order doses, %						
Before mandate	24.7	36.1	1.9	7.0	20.0	12.8
After mandate	2.4	9.2	0.9	7.8	2.3	5.4 ^b
Nonstanding order doses, %						
Before mandate	75.3	63.9	98.1	93.0	80.0	87.2
After mandate	97.6	90.8	99.1	92.2	97.7	94.6

^aStatistically significant change before to after mandate: $F = 29.45$; $df = 1$; $P < .001$.

^bStatistically significant change before to after mandate: $\chi^2 = 405.2$; $df = 1$; $P < .001$.

^cNaloxone doses dispensed October 2017 to September 2018.

prescribed most frequently were nurse practitioners, anesthesiology and pain medicine physicians, other providers, and family practice and general practice physicians (Table 3). After the mandate became effective, there was a significant shift in the specialty of those prescribing naloxone ($\chi^2 = 816.7$; $df = 12$; $P < .001$). Most notably, the proportion of naloxone prescribed by nurse practitioners decreased by nearly half, from 24.3% to 12.9%, whereas the percentage prescribed by anesthesiology and pain medicine physicians fell from 23.4% to 17.3%, and the percentage prescribed by infectious disease physicians fell from 7.0% to 1.8%. The greatest percentage increases in prescribing naloxone occurred among physician assistants (5.3% to 12.4%), internal medicine physicians (5.0% to 9.1%), family practice and general practice physicians (11.5% to 15.0%), and other providers (18.2% to 22.2%).

During the 90 days before adoption, the number of pharmacies dispensing naloxone was 1483. It increased 48% ($F = 17.58$; $P < .001$) in the 90 days after the coprescription to 3019. Of all study chain pharmacies in operation before the state's coprescription mandate, a median of 40% of stores dispensed at least 1 naloxone dose, and

after the coprescription mandate, a median of 80% of stores dispensed 1 or more naloxone doses (Arizona: 82%, Florida: 61%, Rhode Island: 97%, Vermont: 80%, Virginia: 78%).

Naloxone prescription mandates were associated with changes in the overall payor mix for the medication in 4 of the 5 study states ($\chi^2 = 102.7$; $df = 4$; $P < .001$; Table 4). There was a total of 13 831 naloxone prescriptions during the study period, payment for which was made by cash (3.3%; $n = 456$), by Medicaid (24.3%; $n = 3364$), Medicare (34.9%; $n = 4826$), commercial payors (35.5%; $n = 4912$), or workers' comprehensive (2.0%; $n = 273$). Payment for naloxone differed by prescription type ($\chi^2 = 2106.4$; $df = 4$; $P < .001$): standing order prescription payments were more likely to be by cash (22.6% standing order vs 3.1% nonstanding order) and less likely to be by Medicare (13.9% standing order vs 31.4% nonstanding order) than nonstanding order prescriptions. Across all states, the proportion of naloxone prescriptions paid for with cash decreased after the mandate from 5.4% to 2.7%, but the increases in other payor types differed by state. Arizona, Florida, Rhode Island, and Virginia all exhibited statistically significant changes in the naloxone payor mix comparing 90 days

before and after coprescription mandate, whereas Vermont exhibited no statistically significant changes. More than half of all naloxone dispensed through a pharmacy in the study states is paid for by Medicaid or Medicare, and that dominant role was unaffected by a coprescription mandate.

DISCUSSION

The hidden nature of some drug use and the changing nature of the opioid epidemic argue for multiple paths to the life-saving medication naloxone. Our analysis shows that naloxone coprescribing mandates greatly enhanced naloxone provision from pharmacies, engaged more prescribers, provided naloxone to more geographic areas, boosted naloxone provision to the point that nearly every pharmacy in a major chain dispensed at least 1 dose of naloxone, and reduced the burden on patient cash purchases. The particular changes on each of these metrics differed between states, suggesting that variation in the specifics of each state naloxone law may affect their effectiveness. There should be further research on this topic.

We found that standing order models appear to complement the prescriber-based naloxone dispensed through community pharmacies and remain an important source of naloxone for patients, even when coprescription mandates were in place. Because our analysis drew from the pharmacy chain's dispensing data that include prescribers' national provider identifier, it was possible to differentiate the state and pharmacy chain standing order prescribers from all other prescribers. Previous studies draw from vendor-based private insurance claims,²⁷ restrict to Medicaid claims databases,³⁷ or otherwise lack the specificity to distinguish among prescribers³⁸ and thus miss the impact of these legal mechanisms on pharmacy naloxone access. We found that the coprescription mandate was associated with a decrease in the proportion of naloxone dispensed via standing orders, which might suggest that standing orders are effective in reaching many of the same individuals targeted by coprescribing laws (i.e., those at higher risk for overdose).

Accessibility of pharmacy-acquired naloxone is highly dependent on several factors,

TABLE 3—Proportion of Naloxone Prescriptions Issued by Medical Provider Specialty, Before and After Naloxone Coprescription Mandate in 5 US States: 2014–2018

Specialty	Before, %	After, %
Nurse practitioners	24.3	12.9
Anesthesiology and pain medicine physicians	23.4	17.3
Other providers	18.2	22.2
Family practice/general practice physicians	11.5	15.0
Infectious disease physicians	7.0	1.8
Physician assistants	5.3	12.4
Internal medicine physicians	5.0	9.1
Emergency medicine physicians	2.1	1.9
Obstetricians/gynecologists	0.9	3.0
Psychiatrists	0.7	0.7
Pediatric adolescent specialists	0.7	0.3
Pharmacists ^a	0.6	0.1
Surgeons	0.4	3.7

Notes. Statistically significant change before to after mandate: $\chi^2 = 816.7$; $df = 12$; $P < .001$.

^aIn some states, pharmacists provide naloxone through prescriptive authority or dispense pursuant to a state protocol order. In Arizona, which initially had a protocol order model for naloxone provision that later became a state standing order, a pharmacist's national provider identifier was listed.

TABLE 4—Proportion Payment Type for Naloxone Prescriptions Dispensed 90 Days Before and After Implementation of Mandated Naloxone Coprescription: 5 US States, 2014–2018

Payment Type	Virginia		Rhode Island		Arizona		Florida		Vermont	
	Before, %	After, %	Before, %	After, %	Before, %	After, %	Before, %	After, %	Before, %	After, %
Cash	14.1	4.2	2.7	0.5	3.5	2.4	6.4	2.6	0.0	3.5
Medicaid	18.8	14.6	34.4	37.9	38.5	33.8	19.8	19.5	33.3	24.7
Medicare	22.4	32.2	19.8	21.9	32.3	34.9	40.4	45.9	20.0	30.6
Commercial	42.6	46.3	41.6	39.0	25.3	27.8	30.7	29.6	46.7	41.2
Workers' compensation	2.2	2.8	1.5	0.8	0.5	1.2	2.6	2.4	0.0	0.0
χ^2		63.10		28.38		10.66		44.04		2.72
<i>P</i>		<.001		<.001		.031		<.001		.44

including the medication's price. With numerous generic formulations as well as an intramuscular generic injectable, an intramuscular autoinjector branded product (Evzio), and an intranasal branded product (Narcan), there are more options than ever for patients—if they can afford them. Costs of naloxone have increased over the past few years,³⁹ and none of the cash-price options offered in pharmacies around the country (as low as \$40 for generic injectable and \$100–\$4000 for the branded products) are likely to be affordable to most patients. Our analysis showed that more than half of all naloxone dispensed through a pharmacy in the study states is paid for by Medicaid or Medicare, which corresponds well to public payor distributions for opioid use disorder diagnoses.⁴⁰ The prominence of Medicare payment for naloxone prescriptions in our analysis is consistent with another recent study of naloxone coprescription to Medicare beneficiaries,⁴¹ which reported similar state-specific dispensing patterns and further demonstrated that patients receiving naloxone were more likely to be concurrently prescribed an opioid and benzodiazepine or to be on a high daily MME dose.

The observed changes in payor mix, especially the reduction in cash-purchased naloxone, might be related to the post-mandate reduction in the proportion of standing order naloxone prescriptions obtained by friends and family. It also might reflect broader payor support for third-party billing of naloxone (i.e., patients' insurance pays for naloxone obtained for intended use on a third party)⁴² after mandates were

implemented. Beyond our study states, the number of states that have placed naloxone on their Medicaid formularies or that have mandated insurance coverage for naloxone is growing, and this is a sustainable pathway to low-cost and no-cost naloxone. Because the cost of naloxone will remain a key issue for other states considering coprescription mandates, we suggest future innovations to reduce patient cost burden, for example with copayment assistance vouchers.

Limitations

There are important limitations to our analysis. Based on published prescription information,³⁸ we estimate that the study pharmacy's data represents between 10% and 20% of the national US retail pharmacy sales of naloxone at the time of our analysis. The counts should therefore not be considered comprehensive or definitive of naloxone distributed through pharmacies. However, the legal changes we examined could be expected to affect all community pharmacies in our study states similarly, as prescribers are all required to abide by the mandate, with subsequent prescriptions filled in community pharmacies.

Thus, we believe that the detected associations remain valid and reliable estimates of the laws' effects. For instance, we note that the medical specialties involved with naloxone coprescription map largely onto the types of providers who prescribe the most schedule II opioids nationally⁴³ and catalog a growth in naloxone prescribing that corresponds to the rise in providers granted newly expanded

buprenorphine prescribing privileges⁴⁴ to treat opioid use disorder. Findings regarding the coprescription mandates enacted until 2017 are consistent with naloxone dispensing reported previously^{41,45} and can be further validated by data from states with naloxone reported to the prescription drug monitoring program, such as Rhode Island, where preliminary analysis suggests similar patterns of effects on naloxone dispensing following Rhode Island's coprescription mandate in July 2018.⁴⁶

We were not able to detail the complete opioid overdose risk profile for the individuals who received naloxone through the pharmacy, and the evidence for the life-saving impact of naloxone is based on observational studies in which naloxone was largely distributed to people who were using illicit heroin. The Naloxone for Opioid Safety Evaluation study of Coffin et al., for example, found reduced opioid-related emergency department visits in patients receiving chronic opioid therapy when naloxone was coprescribed compared with when naloxone was not coprescribed.¹⁴ Examining the risk profile of those receiving naloxone from the pharmacy warrants further study using a data set that includes those characteristics. However, because coprescribing laws largely target individuals with known overdose risk factors, they likely result in those with these risks receiving more naloxone than they did before. Although previous analyses indicate that provision of naloxone is extremely cost effective,⁴⁷ and our analysis considered changes to the type of payor for the naloxone, future studies should examine the cost effectiveness of expanded naloxone access under pharmacy access models. Finally, we considered only short-term impacts of coprescription; a comprehensive, longitudinal examination of these laws is warranted.

Public Health Implications

Mandating that naloxone be coprescribed to individuals at increased risk of overdose quickly and effectively expands the reach of naloxone to those individuals and addresses some economic and geographic disparities in naloxone provision. Our findings support the adoption of these types of mandates in all US states as 1 public health strategy to prevent fatal opioid overdose. State- and

pharmacy-based standing orders remain a key complement to prescriber-based naloxone even under a coprescription mandate and reflect the partnership among prescribers, pharmacists, and the community that is necessary to save lives and stem the tide of opioid overdose deaths. *AJPH*

CONTRIBUTORS

T. C. Green conceptualized and supervised the study. C. Davis contributed conceptual guidance, conducted the legal analysis, and assisted with data interpretation. Z. Xuan conducted the analyses and contributed to the methodology of the policy analysis. A. Y. Walley and J. Bratberg guided the concept and execution of the study. All authors contributed to the writing.

ACKNOWLEDGMENTS

Funding for this study was provided by the Agency for Healthcare Research and Quality (grant R18 HS024021) and the National Institute on Drug Abuse (grants R21 DA045848 and R01 DA045745).

We are grateful to Tyler Davis, Nicole Harrington, Tom Davis, and CVSHealth for their steadfast support of this analysis and pharmacy, public health, and naloxone research endeavors.

Note. The funding organizations had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the article. As part of the federally funded grants, CVSHealth provided the dispensed prescriptions data used in the analysis and reviewed the text describing the laws and data source for accuracy. CVSHealth had no role in the design and conduct of the study; in the analysis and interpretation of the data; or in the preparation or approval of the article.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

HUMAN PARTICIPANT PROTECTION

This study was reviewed and approved by the Boston University Medical Campus institutional review board.

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