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Study Protocol

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1. Summary of Changes to the Protocol and Statistical Analysis Plan

There were no changes made to the protocol or statistical analysis plan.

2. Final Study Protocol

A Randomized trial of behavioral economic approaches to reduce unnecessary opioid prescribing -

The REDUCE Trial

Study Protocol

June 2019

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1. Abstract

Opioid-related abuse and overdose represent a growing national epidemic in the United States. Clinician practice patterns play an important role: opioid prescriptions impact the likelihood that patients will misuse or become dependent on these medications, with longer prescriptions leading to greater sustained use. In this study, we will evaluate a Sutter Health System quality improvement initiative using monthly individual audit feedback and/or monthly peer comparison feedback to clinicians to change opioid prescribing patterns. In partnership with Sutter Health System, this will be conducted using randomization to evaluate its effect. We will also conduct a process evaluation to understand factors associated with better or worse performance at the clinician level.

2. Overall objectives

The objective of this research study is to evaluate the effect of a health system initiative aiming to change clinician opioid prescribing behaviors using two behavioral economic interventions – individual audit feedback and peer comparison feedback on performance to clinicians.

3. Aims

3.1 Primary outcome

The primary outcome measure is the change in the mean number of pills per opioid prescription.

3.2 Secondary outcome

The secondary outcome measure is the change in proportion of patient-visits that an opioid was prescribed.

3.3 Exploratory outcomes

We will explore several other outcomes of interest. We will evaluate the change in morphine milligram equivalents (MME) per opioid prescription. We will evaluate the change in the mean number of opioid pills per patient-visit, which represents a combination of the primary and secondary outcome measures, allowing us to evaluate both changes in prescription pill quantity and proportion of visits with an opioid prescription. We will evaluate changes in rates of prescriptions for non-narcotic prescription analgesics (e.g., ibuprofen, acetaminophen, celecoxib, or muscle relaxants such as cyclobenzaprine, baclofen or tizanidine) to explore if clinicians shifted to using these prescriptions.

4. Background

Drug overdose is the leading cause of injury-related death in the United States, with 91 Americans dying from opioid-related overdoses each day (1). Physician behavior and prescription patterns have played a particularly important role in the genesis and acceleration of this opioid epidemic: over the last two decades, the number of opioid prescriptions quadrupled while drug overdose deaths due to prescription opioids more than tripled (2,3). Moreover, the higher the pill burden in an individual opioid prescription, the more likely that the patient continues to use opioids at 1 and 3 years (4). Physicians who are higher-intensity opioid prescribers are more likely to have their patients using opioids for longer durations (5).

Despite the roll out of prescription drug monitoring programs (PDMPs) designed to curb opioid overprescribing, awareness, acceptance and adoption of PDMPs among prescribing physicians has been low, and the effect of these programs on opioid use and mortality remains inconsistent (6-14). To better address the national opioid epidemic, additional strategies are needed to change physician prescribing behavior (5).

One promising and largely unexplored strategy is to leverage the psychology of human decision-making by designing health care organization level interventions using behavioral economics. These principles have recently begun to be used to nudge physician prescribing in other settings, such as inappropriate antibiotics for upper respiratory infections (15, 16). Our team has worked with health plans serving patients at high risk for opioid misuse that have also embedded behavioral principles within plan design to reduce the number of new opioid prescriptions and/or the number of pills per prescription (17). Applying similar behavioral techniques within health care organizations could reduce opioid prescribing in clinically appropriate ways that minimize patient harm. Interventions based on feedback to clinicians delivered by email could be scaled more easily and cost efficiently than personnel-intensive approaches. However, to our knowledge, there have been few randomized trials at this scale testing these approaches to reduce opioid prescription pill burden.

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5. Study design

5.1 Design

This research study will analyze results from a Sutter Health System initiative that uses a four-arm, factorial randomized trial. Emergency departments and urgent care centers at Sutter will be randomly assigned at the site level approximately 48 emergency department or urgent care sites) to have all their clinicians receive either individual audit feedback, peer comparison feedback, both, or none. The intervention period will be 6 months in duration. Our research study will evaluate the results of this study.

We will also conduct additional qualitative evaluations to inform interpretation of findings. We will conduct pre- and post-intervention surveys with all clinicians. After the intervention period, we will invite some clinicians to participate in interviews to evaluate the experience and perspectives of both clinicians who reduced opioid prescribing pill burden and those who did not.

5.2 Study duration

The study is expected to take 3 years to conduct including planning, the six-month active phase of trial, and then analysis and dissemination of results.

5.3 Target population

Clinicians practicing at emergency medicine departments and urgent care centers at Sutter Health System.

5.4 Accrual

This is an evaluation of a health system intervention of approximately 451 clinicians at approximately 48 sites at Sutter Health System.

5.5 Key inclusion criteria

Clinicians that practice primarily at emergency departments and urgent care centers at Sutter Health System that are included in the quality improvement initiative will be included in the evaluation.

In research study analysis, patients will be included in the primary sample if they are age 18 years or older, present to a participating emergency department or urgent care center during the study period, and are discharged to home from the visit. For the main analysis, we will include only the patient's first visit in the one year before or during the intervention period.

In a secondary, subgroup analysis, we will evaluate only opioid naïve patients who have no record in the Sutter Health System of an opioid prescription in the 6 months prior to presentation.

5.6 Key exclusion criteria

In research study analysis, clinicians will be excluded if they: 1) saw less than 100 patients in the prior year; 2) practiced primarily at another site that is not in the main trial; 3) did not practice at Sutter Health System in the prior 90 days.

In research study analysis, patients will be excluded if 1) they are less than 18 years of age or 2) are pregnant.

6. Subject recruitment

Since this is an evaluation of a health system intervention, clinicians and patients will not be recruited or enrolled individually but instead an analysis will be conducted based on encounters in the health system. We estimate that the sample will include approximately 451 clinicians and 250,000 patients.

7. Subject compensation

No compensation will be offered in this study.

8. Study procedures

8.1 Consent

A waiver of informed consent is requested from both clinicians and patients. This is a health system initiative that will be implemented with or without the proposed research study. The study is an evaluation of that implementation which has support from leadership at Sutter Health System. Therefore, clinicians and their patients will not be consented as this is the standard of practice within the context of the health system initiative. Without a waiver of the consent, the initiative would still be implemented by the health system, but the study would be infeasible. There are several additional reasons why we feel a waiver of consent should be granted. First, it is not feasible to consent every clinician and patient at the 30+ health system sites including

those that do not prescribe or receive opioids. Second, if clinicians in the control group were consented, they would know they were being monitored and this could influence their behavior. This could potentially disrupt the design of the evaluation and make interpretation of the findings challenging. Third, clinicians are not being forced to prescribe opioids in a specific manner. Instead, they are being guided toward evidence-based prescribing practices but maintain their autonomy to practice as they feel is necessary. This is no different than standard of care in which a clinician would review the same information and decide how to prescribe.

Written consent will be acquired for the clinician surveys and verbal consent will be acquired for the clinician interviews.

8.2 Procedures

The following procedure will be used at Sutter to randomize clinicians informed by research study team input. Sites with less than 8 eligible clinicians will be combined to meet the minimum number of clinicians needed for the block and stratification methods. Practice sites will be randomly assigned using an electronic random number generator, block sizes of 4, and stratified on site (emergency department or urgent care), mean number of pills per opioid prescription (above or below mean), and proportion of visits with an opioid prescription (above or below mean). Practice sites randomly assigned to have one of the feedback interventions will be sent information by email to each clinician at the site each month for 6 months. We will work with the local sites to deliver the information from the leadership or communications director at each site.

Individual audit feedback will inform the clinician that the health system is doing monthly audits and providing them the number of patients in the last month for whom they prescribed 30 opioid pills per prescription or higher.

Peer comparison feedback will use data on the mean number of opioid pills per prescription and the proportion of visits with an opioid prescription will be delivered using a 3-month rolling average as follows: a) If clinician is above median: informed how their data compares to the median; b) If clinician is below median but above 10^{th} percentile: informed how their data compares to the 10^{th} percentile; c) If clinician is 10^{th} percentile or below: informed of their data and commended for being a "low prescriber." Data will be compared to peer clinicians.

Data on clinicians and their patients at Sutter Health System will be obtained from the electronic medical record and then sent securely to the University of Pennsylvania for analysis on secure, encrypted server. Clinician data includes practice site and clinician characteristics as available and prescription data. Patient data includes demographic information, medical history and conditions, reasons for the visit, and prior prescription data specifically for opioids and other pain medications. We will also obtain additional information as available through prescription drug monitor programs (PDMPs).

The process evaluation will include surveys to clinicians administered through an online platform both before and after the trial. Pre-trial surveys will assess clinicians' knowledge, attitudes, norms, and behavioral intent related to prescribing opioids for acute conditions. Post-trial surveys will systematically assess acceptability of the study and its various components, as well as possible effects in other domains.

We will conduct a series of clinician interviews among 1) 15 (5 per intervention arm) clinician participants who successfully improved opioid prescribing post-hoc and 2) 15 (5 per intervention arm) participants who were not successful in improving opioid prescribing. We will examine how participation in study interventions influenced interactions with practice administration and patients and solicit narratives describing patient experiences that provide a deeper understanding of the impact of trial arms on provider-patient interactions. We will examine the perceived impact of the interventions, how the intervention could be modified to increase likelihood of success, barriers faced in changing behaviors, benefits and barriers clinicians or health systems would face in program implementation, and perceptions by patients, staff, and colleagues. We will also discuss unanticipated effects, such as how participation may have changed the clinician-patient relationship or elements of health behaviors outside of the health care context. All clinician interviews will be audio-taped and transcribed.

9. Analysis plan

We will perform an intention-to-treat analysis comparing a 6-month pre-intervention period to a 6-month intervention period, excluding any needed washout period to roll out the intervention to full scale.

In the primary analysis, we will fit a linear multivariate mixed effects model adjusting for available patient, clinician, and site characteristics including a clinician's pre-intervention opioid prescribing. Analyses will be adjusted for clustering at the level of the clinician and site by using clinician and site random effects. For the secondary binary outcome measure of proportion of patient-visits an opioid was prescribed, we will conduct chi-square tests of unadjusted data and fit a logistic multivariate mixed effects model using the same adjustments as the main model.

For all patients in the trial, we will evaluate their first visit during each period. In secondary analyses, we will evaluate subsequent visits and in a subgroup analysis evaluate only opioid naïve patients. For the primary outcome variable, we will focus on prescriptions for short-acting opioids in tablet form that include one of the following: pain medications with codeine, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, tapentadol, tramadol. We will exclude long-acting opioids because these are not likely to be prescribed for acute pain conditions. In a secondary outcome variable, we will include both short-acting and long-acting opioids.

We will control for multiple testing using a structured testing approach that is designed for a 2x2 factorial trial in which we will prioritize testing for main effects, followed by interaction effects. We will first test the null hypothesis of either a main effect of individual audit feedback or peer comparison feedback at an alpha level of 0.05; if this test is rejected, we will test (i) the null hypothesis of no main effect of individual audit feedback; (ii) the null hypothesis of no main effect of peer comparison feedback at an alpha level of 0.05; if both of these tests are rejected, we will test for an interaction at an alpha level of 0.05. This sequential structured testing procedure controls the familywise Type I error rate at a level of 0.05 and has greater power for testing main effects than a Bonferroni approach.

Survey data will be captured via online platforms (e.g., SurveyMonkey) and analyzed in statistical software packages (e.g., STATA, SAS). Interview content will be analyzed based on the grounded theory approach. We will use NVivo 8.0 to manage interview data. Two independent reviewers will code the transcripts.

10. Investigators

--University of Pennsylvania--

Dr. Amol Navathe, MD, PhD, (MPI) is Associate Director of CHIBE, Assistant Professor of Medicine and Health Policy at the Perelman School of Medicine (PSOM), and founding co-Editor-in-Chief of the peer-review journal Healthcare: the Journal of Delivery Science and Innovation. He is a general internist and health economist with a research portfolio focusing on physician behavior and response to incentives. His expertise includes large-scale policy trial design in multiple health plans and health care organizations around physician incentives and high-value practice.

Dr. Mitesh Patel (MPI) is the Director of the Penn Medicine Nudge Unit and an Assistant Professor of Medicine and Health Care Management at PSOM and The Wharton School at the University of Pennsylvania. He is a general internist who conducts research focused on studying how to leverage technology to test and scale approaches from behavioral economics. He has extensive experience leading clinical trials including more than 15 randomized trials that have used insights from behavioral economics to change clinician and patient behaviors.

Dr. Kevin Volpp (Co-I) is the Director of CHIBE and the NIA-funded Penn-CMU Roybal P30 Center on Behavioral Economics and Health. He is the Janet and John Haas President's Distinguished Professor of Medicine and Health Care Management at PSOM and the Wharton School at UPENN, a well-known authority in the field of behavioral economics and health who has led numerous studies on incentives and choice architecture focused on changing clinician and patient behavior, and an elected member of the National Academy of Medicine (NAM) (formerly the Institute of Medicine).

Professor Dylan Small (Co-I) is a Professor of Statistics at The Wharton School at UPENN. He is an expert on causal inference and has extensive experience leading the statistical design and analysis for large-scale randomized controlled trials including pragmatic trials within the health system.

Dr. M. Kit Delgado (Co-I) is an Assistant Professor of Emergency Medicine. His research is focused on discovering innovative approaches to improve the outcomes of acutely ill and injured patients and also reduce the occurrence of injuries and the shortsighted behaviors that cause them in the first place. He has experience with interventions that change opioid prescription settings to influence clinician prescribing behaviors.

--University of Washington--

Dr. Joshua Liao (Co-I) is an Assistant Professor of Medicine at the University of Washington where he is Associate Medical Director of Contracting and Value-Based Care. His work focuses on organizational strategy related to value-based care transformation and innovation. He has collaborated with Drs. Navathe and Patel in the past.

--Sutter Health System--

Professor Xiaowei (Sherry) Yan (Co-I, Sutter Site Co-PI) is a Statistician Investigator at Sutter Health with extensive experience in obtaining and analyzing health care data on physician and patient behavior. She has led several innovative pilot programs at Sutter.

Dr. William Isenberg (Co-I) is the Enterprise Vice President for Patient Safety. He leads operational initiatives for Sutter Health System related to health information technology, quality of care, and patient safety.

11. Human research protection

11.1 Data confidentiality

Data on clinicians, patients, patient diagnoses, and opioid prescriptions will be obtained from Sutter Health System. This will be conducted at Sutter Research, Development & Dissemination (RDD) under supervision by Co-I, Dr. Yan, who has experience regularly obtaining these data in the past. Data will be transferred and then stored, managed, and analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. This server was created for projects conducted by the Penn Medicine Nudge Unit related to clinician and patient behavior. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and the CITI human subjects research. Data access will be password protected. Whenever possible, data will be de-identified for analysis.

Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information. Precautions are already in place to ensure the data are secure by using passwords and HIPAA-compliant encryption.

11.2 Subject confidentiality

Data on clinicians and patients will be obtained from Sutter Health System. Any information that is obtained will be used for research purposes only. Information on patients will only be disclosed within the study team. The feedback messages will only provide aggregate numbers of opioids prescribed and no individual patient information. All study staff will be reminded of the confidential nature of the data collected and contained in these databases. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and the CITI human subjects research. Data access will be password protected. Whenever possible, data will be de-identified for analysis.

11.3 Subject privacy

All efforts will be made by study staff to ensure subject privacy. Data will be evaluated in a de-identified manner whenever possible.

11.4 Data disclosure

Information on clinicians and patients will not be disclosed to anyone outside of the study team.

11.5 Data safety and monitoring

The investigators from both Sutter Health System and University of Pennsylvania will provide oversight for the study evaluation of this health system initiative. Clinician practices will follow their standards of care to manage patients initiated on opioids.

11.6 Risk/benefit

11.6.1 Potential study risks

The potential risks associated with this study are minimal given the research is focused on a evaluation of health system initiative. Breach of data is a potential risk that will be mitigated by using HIPAA compliant and secure data platforms for analysis a previously described.

11.6.2 Potential study benefits

The main potential benefit is knowledge gained on approaches that could reduce unnecessary opioid prescribing. Patients may benefit from less exposure to unnecessary amounts of opioids as a result. However, it is possible that patients will receive no benefit from this study.

11.6.3 Risk/benefit assessment

The risk/benefit ratio is favorable given the potential benefit of scientific knowledge that could be gained on how to change clinician and patient behavior to reduce unnecessary opioid prescribing. Efforts have been put into place to minimize the risk of breach of data. If favorable outcomes are found, then there is a potential to leverage the insights scale successful interventions across the entire network of health care organizations and broadly disseminate findings to other health systems.

Appendix Table 1. List of short-acting opioids included in the study

Short-Acting Oral Opioids	
ACETAMINOPHEN-CODEINE #2 300-15 MG PO TABS	HYDROMORPHONE HCL 2 MG PO TABS
ACETAMINOPHEN-CODEINE #3 300-30 MG PO TABS	HYDROMORPHONE HCL 4 MG PO TABS
ACETAMINOPHEN-CODEINE #4 300-60 MG PO TABS	HYDROMORPHONE HCL 8 MG PO TABS
ACETAMINOPHEN-CODEINE 300-15 MG PO TABS	MEPERIDINE HCL 100 MG PO TABS
ACETAMINOPHEN-CODEINE 300-30 MG PO TABS	MEPERIDINE HCL 50 MG PO TABS
ACETAMINOPHEN-CODEINE 300-60 MG PO TABS	MORPHINE SULFATE 15 MG PO TABS
BUTALBITAL-ASA-CAFF-CODEINE 50-325-40-30 MG PO CAPS	MORPHINE SULFATE 30 MG PO TABS
CODEINE SULFATE 15 MG PO TABS	OXYCODONE HCL 10 MG PO TABS
CODEINE SULFATE 30 MG PO TABS	OXYCODONE HCL 15 MG PO TABS
CODEINE SULFATE 60 MG PO TABS	OXYCODONE HCL 20 MG PO TABS
HOMEPACK ACETAMINOPHEN-CODEINE 300-30 MG PO TABS #4	OXYCODONE HCL 30 MG PO TABS
HOMEPACK APAP/CODEINE 300MG-30MG TAB	OXYCODONE HCL 5 MG PO CAPS
HOMEPACK HYDROCODONE/APAP 5/325MG #4 TABS	OXYCODONE HCL 5 MG PO TABA
HOMEPACK HYDROCODONE/APAP 5/325MG #6 TABS	OXYCODONE HCL 5 MG PO TABS
HOMEPACK HYDROCODONE/APAP 5MG/325MG #2 TABS	OXYCODONE HCL 7.5 MG PO TABA
HOMEPACK OXYCODONE HCL 5MG PO TABS	OXYCODONE-ACETAMINOPHEN 10-300 MG PO TABS
HOMEPACK OXYCODONE-ACETAMINOPHEN 5-325 MG PO #2 TABS	OXYCODONE-ACETAMINOPHEN 10-325 MG PO TABS
HOMEPACK OXYCODONE-ACETAMINOPHEN 5-325MG #3 TABS	OXYCODONE-ACETAMINOPHEN 2.5-325 MG PO TABS
HOMEPACK OXYCODONE-ACETAMINOPHEN 5-325MG #4 TABS	OXYCODONE-ACETAMINOPHEN 5-325 MG PO TABS
HOMEPACK TRAMADOL HCL 50 MG PO TABS	OXYCODONE-ACETAMINOPHEN 7.5-300 MG PO TABS
HOMEPACK TRAMADOL HCL 50MG PO #4 TABS	OXYCODONE-ACETAMINOPHEN 7.5-325 MG PO TABS
HYDROCODONE-ACETAMINOPHEN 10-300 MG PO TABS	OXYCODONE-ASPIRIN 4.8355-325 MG PO TABS
HYDROCODONE-ACETAMINOPHEN 10-325 MG PO TABS	TAPENTADOL HCL 100 MG PO TABS
HYDROCODONE-ACETAMINOPHEN 2.5-325 MG PO TABS	TAPENTADOL HCL 50 MG PO TABS
HYDROCODONE-ACETAMINOPHEN 5-300 MG PO TABS	TRAMADOL HCL 50 MG PO TABS
HYDROCODONE-ACETAMINOPHEN 5-325 MG PO TABS	TRAMADOL HCL 50 MG PO TBDP
HYDROCODONE-ACETAMINOPHEN 7.5-300 MG PO TABS	TRAMADOL-ACETAMINOPHEN 37.5-325 MG PO TABS
HYDROCODONE-ACETAMINOPHEN 7.5-325 MG PO TABS	
HYDROCODONE-IBUPROFEN 5-200 MG PO TABS	
HYDROCODONE-IBUPROFEN 7.5-200 MG PO TABS	

*This list of opioids was used for the following outcome measures: pills per opioid prescription, morphine milligram equivalents (MME) per opioid prescription

Appendix Table 2. List of 'all opioids' included in the study

All Opioids	
ACETAMINOPHEN-CODEINE 120-12 MG/5ML PO SOLN	MORPHINE SULFATE ER 15 MG PO T12A
ACETAMINOPHEN-CODEINE 120-12 MG/5ML PO SUSP	MORPHINE SULFATE ER 15 MG PO TBCR
ACETAMINOPHEN-CODEINE 120-12MG/5ML ORAL LIQD (PEDIATRIC) SH	MORPHINE SULFATE ER 15 MG PO TBEA
CHLORPHENIRAMINE-CODEINE 2-10 MG/5ML PO LIQD	MORPHINE SULFATE ER 150 MG PO CP24
CODEINE POLT-CHLORPHEN POLT ER 14.7-2.8 MG/5ML PO SUER	MORPHINE SULFATE ER 20 MG PO CP24
CODEINE SULFATE 30 MG/5ML PO SOLN	MORPHINE SULFATE ER 200 MG PO TBCR
GUAIFENESIN-CODEINE 100-10 MG/5ML PO SOLN	MORPHINE SULFATE ER 30 MG PO CP24
GUAIFENESIN-CODEINE 100-10 MG/5ML PO SYRP	MORPHINE SULFATE ER 30 MG PO T12A
GUAIFENESIN-CODEINE 100-6.3 MG/5ML PO SOLN	MORPHINE SULFATE ER 30 MG PO TBCR
GUAIFENESIN-CODEINE 200-10 MG/5ML PO LIQD	MORPHINE SULFATE ER 30 MG PO TBEA
GUAIFENESIN-CODEINE 200-8 MG/5ML PO LIQD	MORPHINE SULFATE ER 50 MG PO CP24
HOMEPACK APAP/CODEINE 120MG-12MG/5ML SUSP	MORPHINE SULFATE ER 60 MG PO CP24
HOMEPACK PROMETHAZINE/CODEINE 6.25MG-10MG/5ML SYRUP	MORPHINE SULFATE ER 60 MG PO T12A
HOMEPACK STCH PROMETHAZINE/CODEINE 6.25MG-10MG/5ML SYRUP 20ML	MORPHINE SULFATE ER 60 MG PO TBCR
HOMEPACK WBLK GUAIFENESIN-CODEINE 100-10 MG/5ML PO SOLN 30ML	OXYCODONE HCL 100 MG/5ML PO CONC
HYDROCODONE-ACETAMINOPHEN 10-300 MG/15ML PO SOLN	OXYCODONE HCL 5 MG/5ML PO SOLN
HYDROCODONE-ACETAMINOPHEN 10-325 MG/15ML PO SOLN	OXYCODONE HCL ER 10 MG PO T12A
HYDROCODONE-ACETAMINOPHEN 10-500 MG/15ML PO SOLN	OXYCODONE HCL ER 15 MG PO T12A
HYDROCODONE-ACETAMINOPHEN 2.5-108 MG/5ML PO SOLN	OXYCODONE HCL ER 30 MG PO T12A
HYDROCODONE-ACETAMINOPHEN 5-217 MG/10ML PO SOLN	OXYCODONE HCL ER 40 MG PO T12A
HYDROCODONE-ACETAMINOPHEN 7.5-325 MG/15ML PO SOLN	OXYCODONE HCL ER 60 MG PO T12A
HYDROMORPHONE 1MG/ML ORAL LIQD (PEDIATRIC) SH	OXYCODONE HCL ER 80 MG PO T12A
HYDROMORPHONE HCL 1 MG/ML IJ SOLN	OXYCODONE-ACETAMINOPHEN 5-325 MG/5ML PO SOLN
HYDROMORPHONE HCL 1 MG/ML PO LIQD	PHENYLEPHRINE-BROMPHEN-CODEINE 10-4-10 MG/5ML PO LIQD
HYDROMORPHONE HCL 2 MG/ML IJ SOLN	PHENYLEPHRINE-BROMPHEN-CODEINE 7.5-4-10 MG/5ML PO LIQD
HYDROMORPHONE HCL 3 MG PR SUPP	PROMETHAZINE VC/CODEINE 6.25-5-10 MG/5ML PO SYRP
HYDROMORPHONE VARIABLE DOSE INJ	PROMETHAZINE-CODEINE 6.25-10 MG/5ML PO SYRP
MORPHINE SULFATE (CONCENTRATE) 10 MG/0.5ML PO SOLN	PROMETHAZINE-PHENYLEPH-CODEINE 6.25-5-10 MG/5ML PO SYRP
MORPHINE SULFATE (CONCENTRATE) 100 MG/5ML PO SOLN	PSEUDOEPHEDRINE-CODEINE-GG 30-10-100 MG/5ML PO SOLN
MORPHINE SULFATE (CONCENTRATE) 20 MG/ML PO SOLN	TRAMADOL HCL ER (BIPHASIC) 100 MG PO TB24
MORPHINE SULFATE 10 MG/5ML PO SOLN	TRAMADOL HCL ER 100 MG PO CP24
MORPHINE SULFATE 10 MG/ML IJ SOLN	TRAMADOL HCL ER 100 MG PO TB24
MORPHINE SULFATE 20 MG/5ML PO SOLN	TRAMADOL HCL ER 150 MG PO CP24
MORPHINE SULFATE 5 MG PR SUPP	TRAMADOL HCL ER 200 MG PO CP24
MORPHINE SULFATE ER 10 MG PO CP24	TRAMADOL HCL ER 200 MG PO TB24
MORPHINE SULFATE ER 100 MG PO CP24	TRAMADOL HCL ER 300 MG PO TB24
MORPHINE SULFATE ER 100 MG PO T12A	
MORPHINE SULFATE ER 100 MG PO TBCR	

*This list of opioids was used for the following outcome measures: proportion of patient encounters with an opioid prescription

Appendix Table 3. Characteristics of the Patient Sample during the Pre-Intervention Period

Characteristic	Usual Care (N = 73,489)	Individual Audit Feedback	Peer Comparison Feedback	Combined Feedback (N = 79,767)
Age, Mean (SD)	49.5 (19.7)	49.1 (19.5)	48.3 (19.2)	48.5 (19.4)
Gender, No. (%)				
Male	32085 (43.7)	31563 (43.9)	38234 (44.5)	34370 (43.1)
Female	41399 (56.3)	40369 (56.1)	47770 (55.5)	45395 (56.9)
Unknown	5 (0.0)	5 (0.0)	6 (0.0)	2 (0.0)
Race/Ethnicity, No. (%)				
White non-Hispanic	43597 (59.3)	34753 (48.3)	37614 (43.7)	36297 (45.5)
Black non-Hispanic	5071 (6.9)	5948 (8.3)	9936 (11.6)	8429 (10.6)
Asian non-Hispanic	4277 (5.8)	5687 (7.9)	8549 (9.9)	9167 (11.5)
Hispanic	11793 (16.0)	17334 (24.1)	19994 (23.2)	16197 (20.3)
Other	8751 (11.9)	8215 (11.4)	9917 (11.5)	9677 (12.1)
Insurance, No. (%)				
Commercial	39802 (54.2)	37477 (52.1)	46852 (54.5)	42775 (53.6)
Medicare	20626 (28.1)	18262 (25.4)	20882 (24.3)	19665 (24.7)
Medicaid	13061 (17.8)	16198 (22.5)	18276 (21.2)	17327 (21.7)
Annual household income, No. (%)				
Less than $50,000	14806 (20.1)	5064 (7.0)	14784 (17.2)	9389 (11.8)
$50,000 to $100,000	45248 (61.6)	41563 (57.8)	43563 (50.6)	45032 (56.5)
Greater than $100,000	11516 (15.7)	23565 (32.8)	24941 (29.0)	23988 (30.1)
Missing	1919 (2.6)	1745 (2.4)	2722 (3.2)	1358 (1.7)
Site type, No. (%)				
Emergency Department	38599 (52.5)	41398 (57.5)	48590 (56.5)	47427 (59.5)
Urgent Care Clinic	34890 (47.5)	30539 (42.5)	37420 (43.5)	32340 (40.5)
Substance Use				
Current tobacco use, No. (%)	10556 (14.4)	10003 (13.9)	13172 (15.3)	9527 (11.9)
Current alcohol use, No. (%)	30472 (41.5)	29734 (41.3)	35964 (41.8)	29486 (37.0)
Charlson Comorbidity Index, Mean (SD)	0.5 (1.4)	0.4 (1.3)	0.5 (1.4)	0.5 (1.5)

*Data is during the pre-intervention period from 03/03/2019 to 09/02/2019

Appendix Table 4. Characteristics of the Patient Sample during the Follow-Up Period

Characteristic	Usual Care (N = 47,493)	Individual Audit Feedback (N = 47,442)	Peer Comparison Feedback (N = 56,709)	Combined Feedback (N = 54,311)
Age, Mean (SD)	49 (19.3)	48.2 (19.1)	47.8 (18.8)	47.7 (19.3)
Gender, No. (%)				
Male	21763 (45.8%)	21908 (46.2%)	26716 (47.1%)	24591 (45.3%)
Female	25727 (54.2%)	25534 (53.8%)	29990 (52.9%)	29719 (54.7%)
Unknown	3 (0%)	0 (0%)	3 (0%)	1 (0%)
Race/Ethnicity, No. (%)				
White non-Hispanic	27995 (58.9%)	21960 (46.3%)	24808 (43.7%)	25203 (46.4%)
Black non-Hispanic	3235 (6.8%)	4114 (8.7%)	6535 (11.5%)	5591 (10.3%)
Asian non-Hispanic	2327 (4.9%)	3283 (6.9%)	4622 (8.2%)	4544 (8.4%)
Hispanic	8358 (17.6%)	13062 (27.5%)	14405 (25.4%)	12860 (23.7%)
Other	5578 (11.7%)	5023 (10.6%)	6339 (11.2%)	6113 (11.3%)
Insurance, No. (%)				
Commercial	25820 (54.4%)	25400 (53.5%)	30931 (54.5%)	28844 (53.1%)
Medicare	12367 (26%)	11066 (23.3%)	13088 (23.1%)	12600 (23.2%)
Medicaid	9306 (19.6%)	10976 (23.1%)	12690 (22.4%)	12867 (23.7%)
Annual household income, No. (%)				
Less than $50,000	9838 (20.7%)	4319 (9.1%)	10396 (18.3%)	7912 (14.6%)
$50,000 to $100,000	30197 (63.6%)	29308 (61.8%)	29878 (52.7%)	32650 (60.1%)
Greater than $100,000	6170 (13%)	12601 (26.6%)	14325 (25.3%)	12716 (23.4%)
Missing	1288 (2.7%)	1214 (2.6%)	2110 (3.7%)	1033 (1.9%)
Site type, No. (%)				
Emergency Department	26582 (56.0)	28496 (60.1)	33140 (58.4)	35244 (64.9)
Urgent Care Clinic	20911 (44.0)	18946 (39.9)	23569 (41.6)	19067 (35.1)
Substance Use				
Current tobacco use, No. (%)	7473 (15.7%)	7055 (14.9%)	9473 (16.7%)	7081 (13%)
Current alcohol use, No. (%)	19199 (40.4%)	19254 (40.6%)	23180 (40.9%)	19751 (36.4%)
Charlson Comorbidity Index, Mean (SD)	0.5 (1.4)	0.4 (1.3)	0.5 (1.4)	0.5 (1.5)

*Data is during the follow-up period from 03/03/2020 to 09/02/2020

Appendix Table 5. Distribution of Message Types by Study Arm At Clinician-Month Level.

Both (Individual Audit + Peer) Intervention Arm		Number of clinicians with each message	Total clinician-months	Percentage of messages in arm
Higher than Avg in #pills per prescription	Higher than Avg in opioid prescription rate	135	587	23.00%
	Higher than low prescriber in opioid prescription rate	93	587	15.84%
	Low prescriber in opioid prescription rate	28	587	4.77%
Higher than Low Prescriber in #pills per prescription	Higher than Avg in opioid prescription rate	79	587	13.46%
	Hither than Low Prescriber in opioid prescription rate	81	587	13.80%
	Low Prescriber in opioid prescription rate	37	587	6.30%
Low Prescriber in #pills per prescription	Higher than Avg in opioid prescription rate	28	587	4.77%
	Hitgher than Low Prescriber in opioid prescription rate	41	587	6.98%
	Low Prescriber in opioid prescription rate	23	587	3.92%
No opioid prescription		42	587	7.16%

Peer Comparison Arm		Number of clinicians with each message	Total clinician-months	Percentage of messages in arm
Higher than Avg in #pills per prescription	Higher than Avg in opioid prescription rate	196	662	29.61%
	Higher than Low Prescriber in opioid prescription rate	92	662	13.90%
	Low Prescriber in opioid prescription rate	27	662	4.08%
Higher than Low Prescriber in #pills per prescription	Higher than Avg in opioid prescription rate	82	662	12.39%
	Higher than Low Prescriber in opioid prescription rate	89	662	13.44%
	Low Prescriber in opioid prescription rate	37	662	5.59%

Low Prescriber in #pills per prescription	Higher than Avg in opioid prescription rate	13	662	1.96%
	Higher than Low Prescriber in opioid prescription rate	46	662	6.95%
	Low Prescriber in opioid prescription rate	26	662	3.93%
Zero Prescription		54	662	8.16%

Individual Audit Feedback Arm	**Number of clinicians with each message**	**Total clinician-months**	**Percentage of messages in arm**
Had at least one # greater than 30 pills per prescription	66	710	9.30%

*Terms: *Clinician-month*; *Total clinician-month for each arm*: defined as total active clinician (who practice in that month and eligible to receive the intervention email) person-month across 6-month intervention period. Opt-out clinicians were excluded. *Number of clinicians with each message*; Sum across 6 intervention months of providers who received each template in the assigned intervention arm, with opted-out ones excluded. *Percentage of messages in arm*; # providers each template/total person-month in each

Appendix Table 6. Adjusted Analysis of Study Outcomes Using First Encounters

Outcome Measure			Usual Care	Individual Audit Feedback	Peer Comparison Feedback	Combined Feedback
Pills per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	15.3 (6.6)	15.4 (5.7)	15.7 (6.3)	14.9 (5.7)
		Intervention, Mean (SD)	15 (5.9)	14.6 (5.7)	14.7 (5.9)	13.5 (5.8)
		Follow-up, Mean (SD)	15 (5.9)	14.3 (5.6)	14 (5.6)	13.1 (5.1)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-0.3 (-0.9, 0.2)	**-0.8 (-1.4, -0.3)**	**-1.2 (-1.8, -0.7)**
		P Value	NA	0.27	**0.003**	**<0.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-0.4 (-0.8, 0.1)	**-0.9 (-1.3, -0.5)**	NA
		P Value	NA	0.16	**<0.001**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	0.0 (-0.7, 0.8)	**-1 (-1.8, -0.3)**	**-1.1 (-1.9, -0.3)**
		P Value	NA	0.9	**0.007**	**0.008**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.1 (-0.5, 0.8)	**-1.1 (-1.6, -0.5)**	NA
		P Value	NA	0.75	**<0.001**	NA
Encounters with an Opioid Prescription	Unadjusted	Pre-Internvention, No. (%)	7360 (10.0)	6076 (8.4)	8363 (9.7)	8030 (10.1)
		Intervention, No. (%)	6853 (10.0)	5968 (8.7)	7645 (9.4)	7353 (9.6)
		Follow-up, No. (%)	4300 (9.1)	3540 (7.5)	4449 (7.8)	4694 (8.6)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	0.98 (0.76, 1.26)	0.89 (0.69, 1.15)	0.84 (0.64, 1.10)
		P Value	NA	0.88	0.38	0.21
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.97 (0.80, 1.17)	0.88 (0.73, 1.05)	NA
		P Value	NA	0.74	0.16	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	0.98 (0.77, 1.25)	0.92 (0.72, 1.17)	0.74 (0.57, 0.96)
		P Value	NA	0.88	0.5	0.02
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.9 (0.75, 1.09)	0.84 (0.71, 1.01)	NA
		P Value	NA	0.29	0.06	NA
MME per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	80.9 (62.6)	86.6 (47.0)	86.6 (47.9)	84.5 (48.6)
		Intervention, Mean (SD)	91 (67.9)	82.2 (45.1)	82.3 (46.1)	77.7 (47.6)
		Follow-up, Mean (SD)	90 (55.4)	81.4 (45.9)	76.8 (38.8)	75.3 (43.6)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-3.4 (-7.3, 0.4)	**-5.1 (-8.9, -1.3)**	**-7.1 (-11.1, -3.2)**
		P Value	NA	0.08	**0.009**	**<0.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-2.7 (-5.8, 0.4)	**-4.5 (-7.4, -1.6)**	NA
		P Value	NA	0.09	**0.003**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	-2.2 (-6.1, 1.8)	**-6.7 (-10.5, -2.8)**	**-6.2 (-10.2, -2.2)**
		P Value	NA	0.29	**<0.001**	**0.003**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-0.3 (-3.7, 3.1)	**-5.3 (-8.1, -2.5)**	NA
		P Value	NA	0.86	**<0.001**	NA

*Abbreviations: SD=standard deviation; CI=confidence interval; MME=Morphine Milligram Equivalent

**Unadjusted data are at the encounter level; models are adjusted at the clinician level; data includes each patient's first encounter in each period

***Bold values indicate statistical significance using a p-value threshold for statistical significance of 0.05 for main effects and <0.017 for comparison between each intervention arm and control

****The "Adjusted difference for main effects relative to usual care" estimates reflect the effect of each intervention type alone, *including the effect it has in the factorial arm in which participants received both interventions.* This was a pre-specified statistical testing approach that first tested for main effects of each intervention. We then used the pairwise testing "Adjusted difference relative to usual care" estimates to compare the effect of each intervention arm with usual care – these are the study outcomes of most interest.

Appendix Table 7. Adjusted Outcomes Using First Encounters and Clustered Standard Errors at Site Without Site Random Effects

Outcome Measure			Usual Care	Individual Audit Feedback	Peer Comparison Feedback	Combined Feedback
Pills per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	15.3 (6.6)	15.4 (5.7)	15.7 (6.3)	14.9 (5.7)
		Intervention, Mean (SD)	15 (5.9)	14.6 (5.7)	14.7 (5.9)	13.5 (5.8)
		Follow-up, Mean (SD)	15 (5.9)	14.3 (5.6)	14 (5.6)	13.1 (5.1)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-0.5 (-0.9,0)	**-0.8 (-1.3,-0.3)**	**-1.6 (-2.3,-0.9)**
		P Value	NA	0.05	**0.002**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	**-0.6 (-1.1,-0.04)**	**-1.0 (-1.4,-0.5)**	NA
		P Value	NA	**0.04**	**<.001**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	-0.2 (-0.9,0.5)	**-1.2 (-2,-0.4)**	**-1.5 (-2.5,-0.5)**
		P Value	NA	0.57	**0.002**	**0.005**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-0.1 (-0.8, 0.6)	**-1.2 (-1.8, -0.6)**	NA
		P Value	NA	0.76	**<.001**	NA
Encounters with an Opioid Prescription	Unadjusted	Pre-Internvention, No. (%)	7360 (10.0)	6076 (8.4)	8363 (9.7)	8030 (10.1)
		Intervention, No. (%)	6853 (10.0)	5968 (8.7)	7645 (9.4)	7353 (9.6)
		Follow-up, No. (%)	4300 (9.1)	3540 (7.5)	4449 (7.8)	4694 (8.6)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	1.26 (0.86,1.86)	1.04 (0.65,1.67)	0.68 (0.23,2.06)
		P Value	NA	0.24	0.87	0.50
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.91 (0.49,1.69)	0.79 (0.48,1.29)	NA
		P Value	NA	0.77	0.34	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	0.99 (0.84,1.16)	0.96 (0.76,1.2)	0.80 (0.66,0.97)
		P Value	NA	0.91	0.71	0.03
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.92 (0.8, 1.06)	0.89 (0.78, 1.02)	NA
		P Value	NA	0.25	0.09	NA
MME per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	80.9 (62.6)	86.6 (47.0)	86.6 (47.9)	84.5 (48.6)
		Intervention, Mean (SD)	91 (67.9)	82.2 (45.1)	82.3 (46.1)	77.7 (47.6)
		Follow-up, Mean (SD)	90 (55.4)	81.4 (45.9)	76.8 (38.8)	75.3 (43.6)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-4.2 (-8.6,0.2)	**-5.5 (-9.8,-1.3)**	**-8.4 (-13.3,-3.5)**
		P Value	NA	0.06	**0.010**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	**-3.5 (-6.8,-0.3)**	**-5.0 (-8.1,-1.9)**	NA
		P Value	NA	**0.03**	**0.001**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	-2.9 (-7.6,1.9)	**-8.1 (-12.9,-3.3)**	**-7.0 (-12.4,-1.6)**
		P Value	NA	0.24	**<.001**	**0.011**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-0.4 (-4.4, 3.5)	**-6.3 (-9.6, -2.9)**	NA
		P Value	NA	0.83	**<.001**	NA

*Abbreviations: SD=standard deviation, CI=confidence interval, MME=morphine milligram equivalent

**Unadjusted data are at the encounter level; models are adjusted at site level; data includes each patient's first encounter in each period

***Bold values indicate statistical significance using a p-value threshold for statistical significance of 0.05 for main effects and <0.017 for comparison between each intervention arm and control

****The "Adjusted difference for main effects relative to usual care" estimates reflect the effect of each intervention type alone, *including the effect it has in the factorial arm in which participants received both interventions.* This was a pre-specified statistical testing approach that first tested for main effects of each intervention. We then used the pairwise testing "Adjusted difference relative to usual care" estimates to compare the effect of each intervention arm with usual care – these are the study outcomes of most interest.

Appendix Table 8. Adjusted Outcomes Using All Patient Encounters

Outcome Measure			Usual Care	Individual Audit Feedback	Peer Comparison Feedback	Combined Feedback
Pills per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	15.2 (6.7)	15.4 (6.0)	15.6 (6.4)	14.8 (5.7)
		Intervention, Mean (SD)	15.0 (6.0)	14.6 (5.7)	14.7 (5.9)	13.4 (5.6)
		Follow-up, Mean (SD)	15.1 (6.0)	14.3 (5.5)	14 (5.6)	13.1 (5.2)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-0.4 (-1.0, 0.2)	**-1.0 (-1.6, -0.4)**	**-1.4 (-2.0, -0.8)**
		P Value	NA	0.21	**0.002**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-0.4 (-0.9, 0.1)	**-1.0 (-1.4, -0.6)**	NA
		P Value	NA	0.14	**<0.001**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	-0.1 (-0.8, 0.6)	**-1.2 (-1.9, -0.4)**	**-1.2 (-1.9, -0.4)**
		P Value	NA	0.76	**0.002**	**0.003**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.0 (-0.6, 0.7)	**-1.1 (-1.6, -0.6)**	NA
		P Value	NA	0.92	**<.001**	NA
Encounters with an Opioid Prescription	Unadjusted	Pre-Internvention, No. (%)	9488 (9.7)	7570 (8.0)	10706 (9.2)	10026 (9.5)
		Intervention, No. (%)	8816 (9.7)	7453 (8.3)	9800 (9.0)	9095 (9.2)
		Follow-up, No. (%)	5344 (8.8)	4270 (7.1)	5661 (7.6)	5959 (8.5)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	0.95 (0.73, 1.24)	0.87 (0.66, 1.13)	0.81 (0.61, 1.07)
		P Value	NA	0.71	0.29	0.13
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.95 (0.78, 1.16)	0.86 (0.71, 1.04)	NA
		P Value	NA	0.59	0.13	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	0.96 (0.75, 1.23)	0.91 (0.71, 1.16)	0.72 (0.55, 0.95)
		P Value	NA	0.74	0.43	0.018
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.89 (0.74, 1.08)	0.84 (0.70, 1.01)	NA
		P Value	NA	0.23	0.06	NA
MME per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	91.4 (64.8)	87.3 (50.4)	87.2 (57.4)	84.4 (48.4)
		Intervention, Mean (SD)	92.2 (67.6)	83 (46.4)	82.7 (55.4)	77.5 (47.4)
		Follow-up, Mean (SD)	92 (59.4)	81.5 (45.8)	77.7 (50.0)	76.3 (50.0)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-3.8 (-7.7, 0.2)	**-5.7 (-9.7, -1.8)**	**-8.2 (-12.3, -4.2)**
		P Value	NA	0.06	**0.004**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-3 (-6.2, 0.2)	**-5.2 (-8.3, -2.2)**	NA
		P Value	NA	0.07	**<.001**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	-4 (-7.9, -0.1)	**-7.7 (-11.4, -3.9)**	**-7.2 (-11.1, -3.3)**
		P Value	NA	0.04	**<.001**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-1.3 (-4.6, 1.9)	**-5.4 (-8.1, -2.7)**	NA
		P Value	NA	0.42	**<.001**	NA

*Abbreviations: SD=standard deviation, CI=confidence interval, MME=morphine milligram equivalent
**Unadjusted data are at the encounter level; models are adjusted at the clinician level; data includes all patient encounters in each period
***Bold values indicate statistical significance using a p-value threshold for statistical significance of 0.05 for main effects and <0.017 for comparison between each intervention arm and control

****The "Adjusted difference for main effects relative to usual care" estimates reflect the effect of each intervention type alone, *including the effect it has in the factorial arm in which participants received both interventions.* This was a pre-specified statistical testing approach that first tested for main effects of each intervention. We then used the pairwise testing "Adjusted difference relative to usual care" estimates to compare the effect of each intervention arm with usual care – these are the study outcomes of most interest.

Appendix Table 9. Adjusted Outcomes Using All Encounters and Clustered Standard Errors at Site Without Site Random Effects

Outcome Measure			Usual Care	Individual Audit Feedback	Peer Comparison Feedback	Combined Feedback
Pills per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	15.2 (6.7)	15.4 (6.0)	15.6 (6.4)	14.8 (5.7)
		Intervention, Mean (SD)	15.0 (6.0)	14.6 (5.7)	14.7 (5.9)	13.4 (5.6)
		Follow-up, Mean (SD)	15.1 (6.0)	14.3 (5.5)	14 (5.6)	13.1 (5.2)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-0.5 (-1,0)	**-0.9 (-1.5,-0.4)**	**-1.8 (-2.6,-1)**
		P Value	NA	0.05	**0.001**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	**-0.6 (-1.2,-0.04)**	**-1.1 (-1.6,-0.6)**	NA
		P Value	NA	**0.04**	**<.001**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	-0.3 (-1,0.4)	**-1.3 (-2.1,-0.5)**	**-1.6 (-2.6,-0.6)**
		P Value	NA	0.38	**<.001**	**0.002**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-0.2 (-0.9, 0.6)	**-1.3 (-1.9, -0.7)**	NA
		P Value	NA	0.65	**<.001**	NA
Encounters with an Opioid Prescription	Unadjusted	Pre-Internvention, No. (%)	9488 (9.7)	7570 (8.0)	10706 (9.2)	10026 (9.5)
		Intervention, No. (%)	8816 (9.7)	7453 (8.3)	9800 (9.0)	9095 (9.2)
		Follow-up, No. (%)	5344 (8.8)	4270 (7.1)	5661 (7.6)	5959 (8.5)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	1.28 (0.93,1.78)	1.13 (0.75,1.7)	0.77 (0.29,2.01)
		P Value	NA	0.13	0.56	0.59
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.93 (0.54,1.6)	0.86 (0.57,1.31)	NA
		P Value	NA	0.79	0.50	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	0.96 (0.83,1.12)	0.96 (0.77,1.19)	0.79 (0.67,0.92)
		P Value	NA	0.63	0.69	0.003
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	0.90 (0.8, 1.02)	0.90 (0.8, 1.01)	NA
		P Value	NA	0.11	0.07	NA
MME per Opioid Prescription	Unadjusted	Pre-Internvention, Mean (SD)	91.4 (64.8)	87.3 (50.4)	87.2 (57.4)	84.4 (48.4)
		Intervention, Mean (SD)	92.2 (67.6)	83 (46.4)	82.7 (55.4)	77.5 (47.4)
		Follow-up, Mean (SD)	92 (59.4)	81.5 (45.8)	77.7 (50.0)	76.3 (50.0)
	Intervention	Adjusted difference relative to Usual Care (95% CI)	NA	-4.5 (-8.7,-0.2)	**-6.4 (-10.5,-2.3)**	**-9.8 (-15,-4.7)**
		P Value	NA	0.04	**0.002**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	**-3.8 (-7.2,-0.3)**	**-6.1 (-9.4,-2.9)**	NA
		P Value	NA	**0.03**	**<.001**	NA
	Follow-up	Adjusted difference relative to Usual Care (95% CI)	NA	-4.8 (-9.3,-0.3)	**-9.1 (-13.2,-5.1)**	**-8.2 (-12.6,-3.8)**
		P Value	NA	0.04	**<.001**	**<.001**
		Adjusted difference for main effects relative to Usual Care, (95% CI)	NA	-1.5 (-5.2, 2.2)	**-6.5 (-9.6, -3.4)**	NA
		P Value	NA	0.43	**<.001**	NA

*Abbreviations: SD=standard deviation, CI=confidence interval, MME=morphine milligram equivalent
**Unadjusted data are at the encounter level; models are adjusted at site level; data includes all patient encounters in each period
***Bold values indicate statistical significance using a p-value threshold for statistical significance of 0.05 for main effects and <0.017 for comparison between each intervention arm and control

****The "Adjusted difference for main effects relative to usual care" estimates reflect the effect of each intervention type alone, *including the effect it has in the factorial arm in which participants received both interventions.* This was a pre-specified statistical testing approach that first tested for main effects of each intervention. We then used the pairwise testing "Adjusted difference relative to usual care" estimates to compare the effect of each intervention arm with usual care – these are the study outcomes of most interest.

Appendix Exhibit 1. Example of a Peer Comparison Feedback Email

Sutter Health

DOE, JOHN

Dear Colleague,

As part of its opioid stewardship efforts, Sutter Health's Office of Patient Experience is reviewing opioid prescriptions with a high number of pills. The following information is about adult patients you provided care for at XX Emergency Department/Urgent Care.

Over the last 3 months:

- You prescribed opioids to X% of your patients. This is ***higher than the low prescriber OR higher than the average*** among your peer UC/ED clinicians at XX who prescribed opioids to X% of their patients.

OR

- You prescribed opioids to X% of your patients. ***Great work, you are a low prescriber.***

- You prescribed an average of X pills per opioid prescription for your patients. This is ***higher than the low prescribers OR higher than average*** among your peer UC/ED clinicians at XX who prescribed X% pills per opioid prescription.

OR

- You prescribed an average of X pills per opioid prescription for your patient. ***Great work, you are a low prescriber.***

While Sutter Health recognizes that some of these prescriptions may be appropriate, this is a reminder to prescribe the minimum clinically necessary number of opioid pills to maximize patient safety.

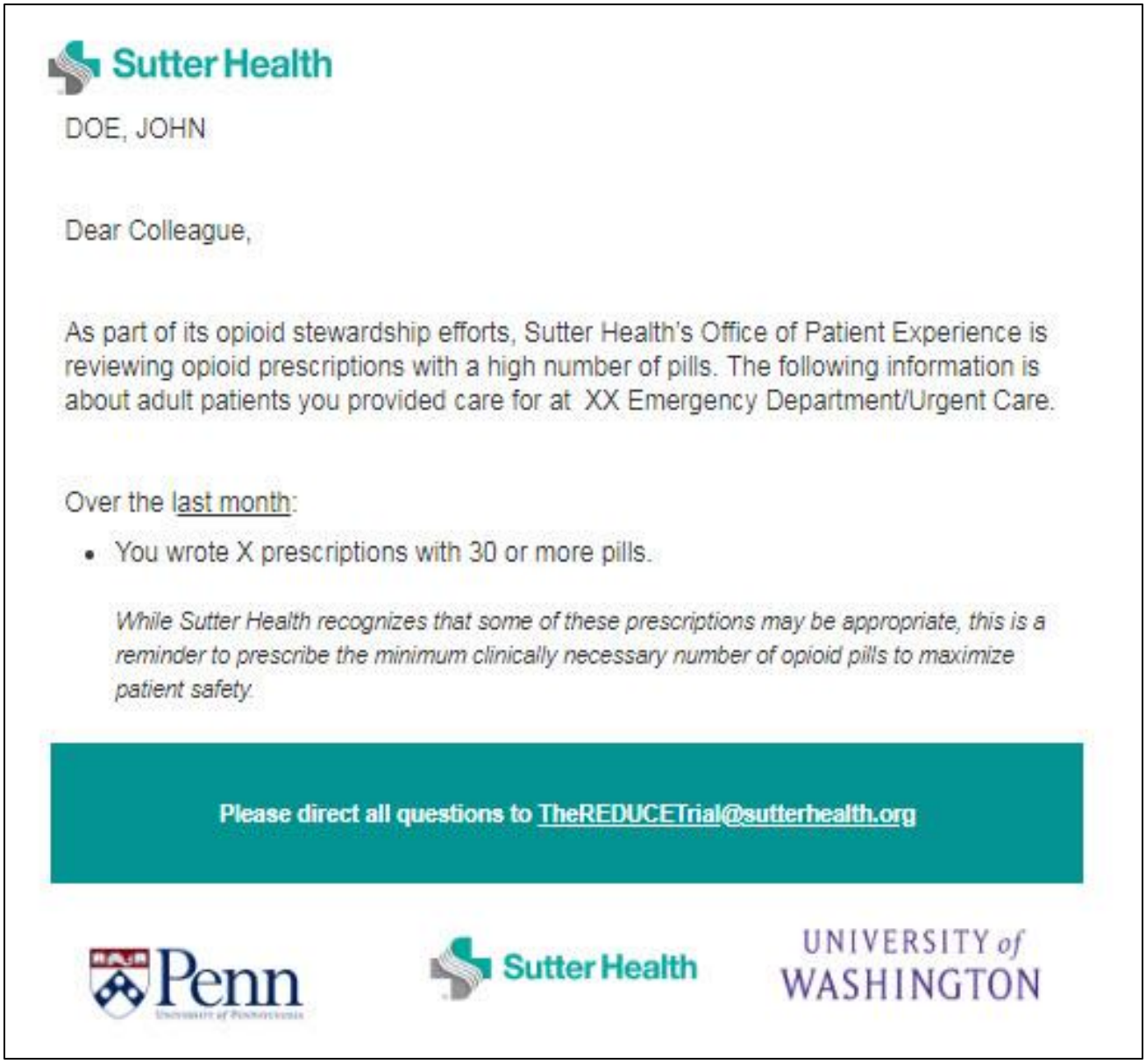
Please direct all questions to TheREDUCETrial@sutterhealth.org

Penn

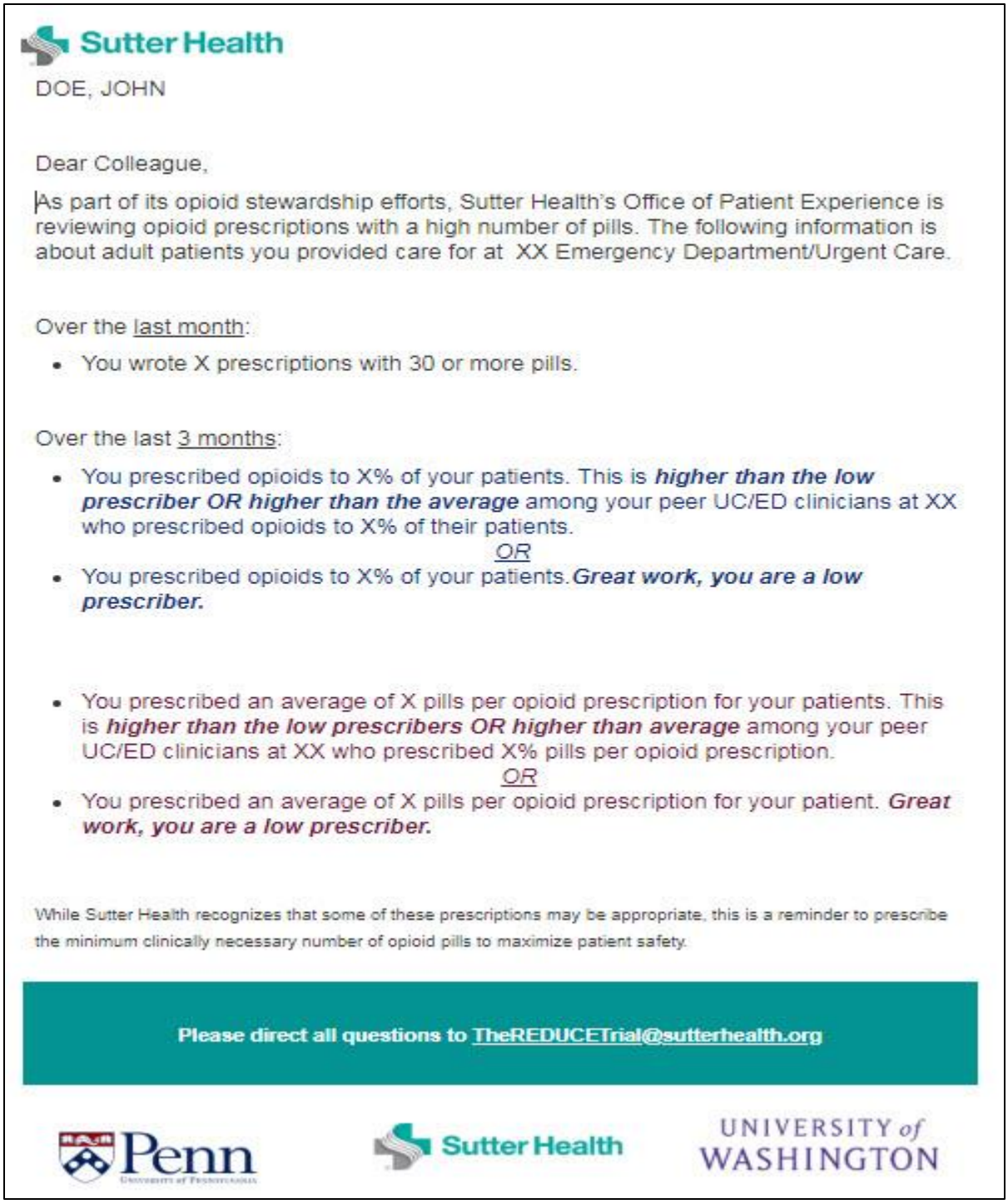
Sutter Health

UNIVERSITY of WASHINGTON

Appendix Exhibit 2. Example of an Individual Audit Feedback Email



Appendix Exhibit 3. Example of a Combined Feedback Email



Sutter Health

DOE, JOHN

Dear Colleague,

As part of its opioid stewardship efforts, Sutter Health's Office of Patient Experience is reviewing opioid prescriptions with a high number of pills. The following information is about adult patients you provided care for at XX Emergency Department/Urgent Care.

Over the last month:

- You wrote X prescriptions with 30 or more pills.

Over the last 3 months:

- You prescribed opioids to X% of your patients. This is ***higher than the low prescriber OR higher than the average*** among your peer UC/ED clinicians at XX who prescribed opioids to X% of their patients.

OR

- You prescribed opioids to X% of your patients. ***Great work, you are a low prescriber.***

- You prescribed an average of X pills per opioid prescription for your patients. This is ***higher than the low prescribers OR higher than average*** among your peer UC/ED clinicians at XX who prescribed X% pills per opioid prescription.

OR

- You prescribed an average of X pills per opioid prescription for your patient. ***Great work, you are a low prescriber.***

While Sutter Health recognizes that some of these prescriptions may be appropriate, this is a reminder to prescribe the minimum clinically necessary number of opioid pills to maximize patient safety.

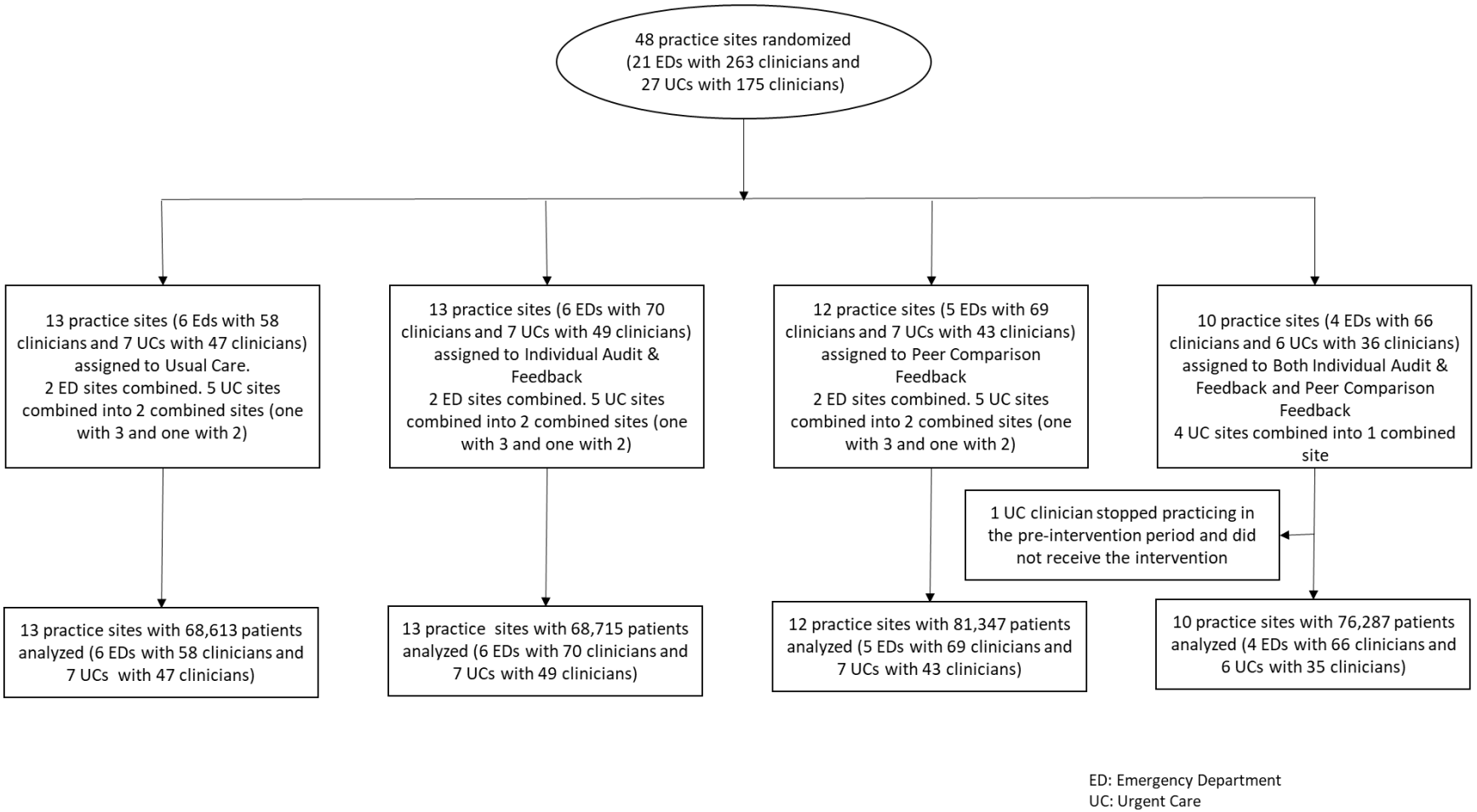
Please direct all questions to TheREDUCETrial@sutterhealth.org

Penn

Sutter Health

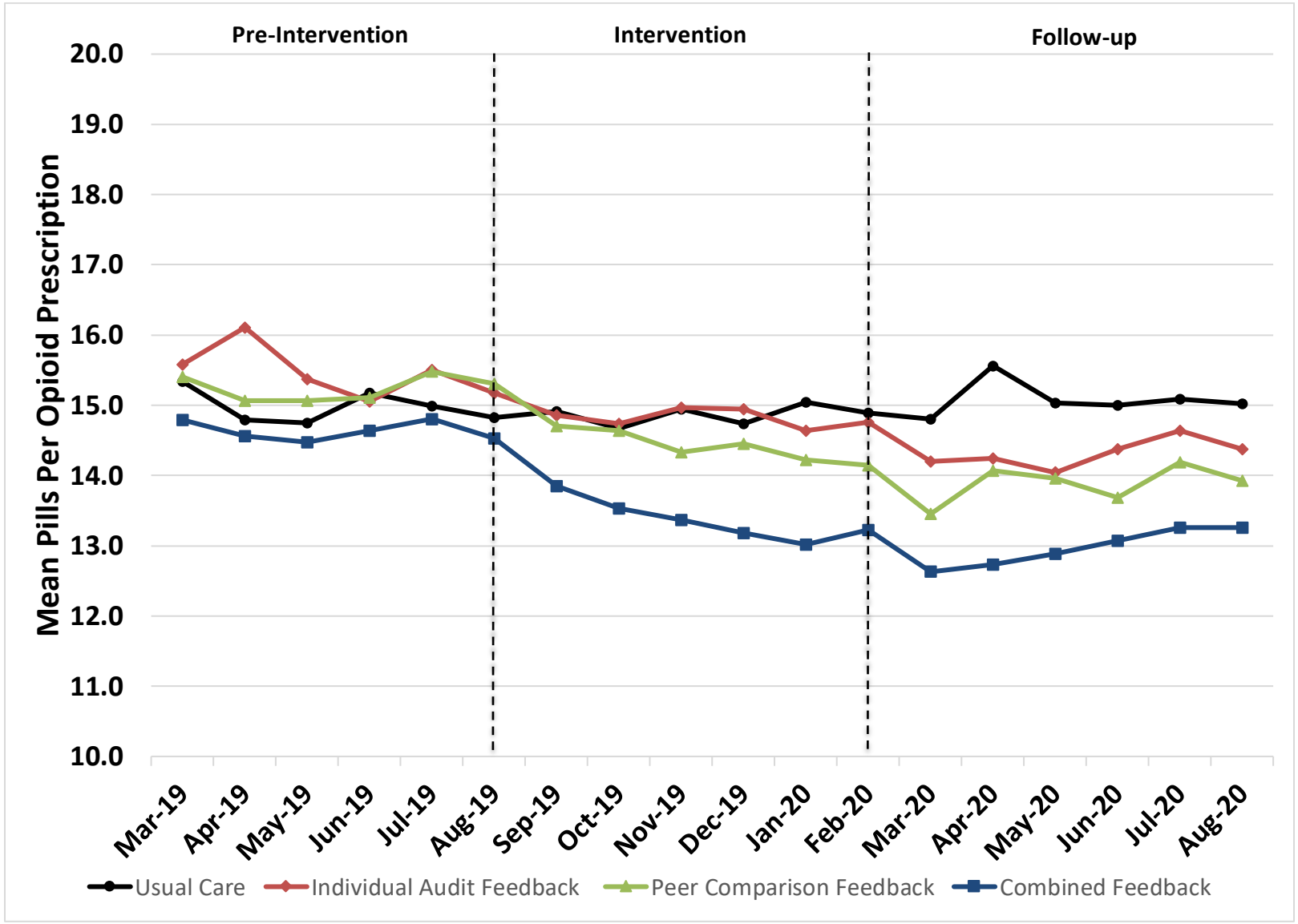
UNIVERSITY of WASHINGTON

Appendix Exhibit 4. CONSORT Diagram.

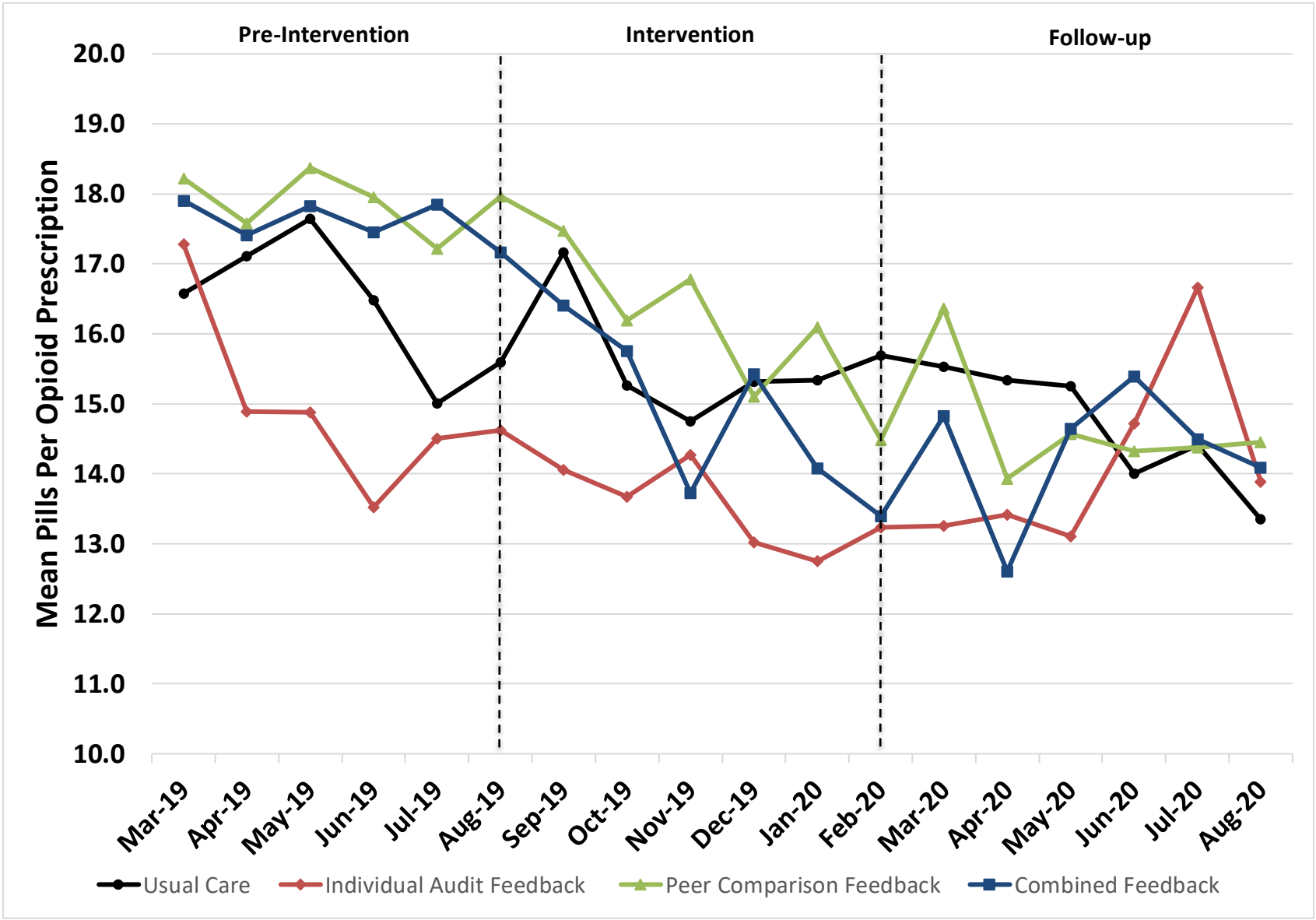


Appendix Exhibit 4. CONSORT Diagram. Emergency departments and urgent care clinics were cluster randomized, stratifying by site type, to usual care, a monthly email to clinicians with individual audit feedback on outlier opioid prescriptions, a monthly email to clinicians on peer comparison feedback on opioid prescriptions, or a monthly email to clinicians with both individual audit feedback and peer comparison feedback combined.

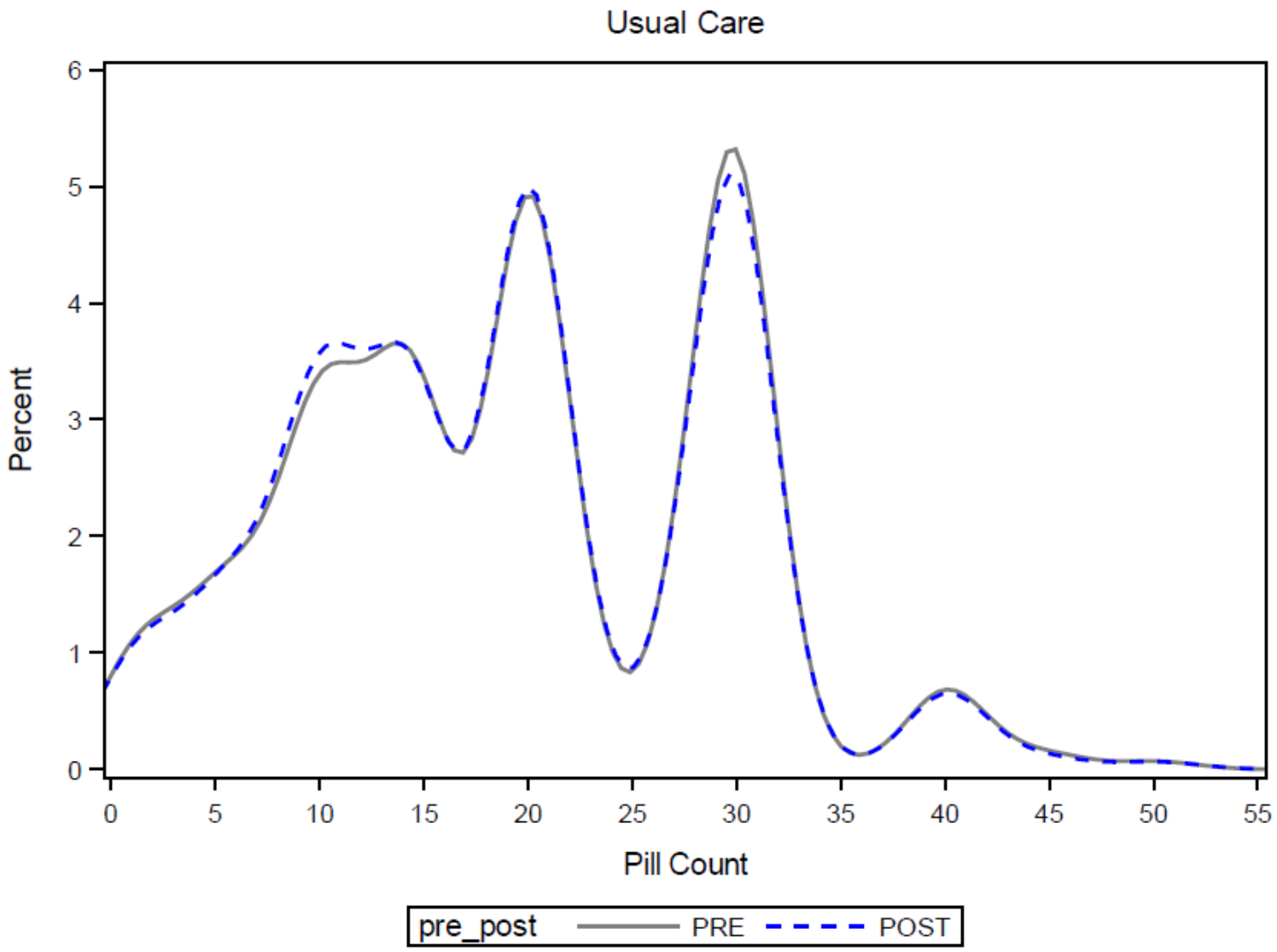
Appendix Exhibit 5. Trends in Mean Pills Per Opioid Prescription Among Emergency Department Sites



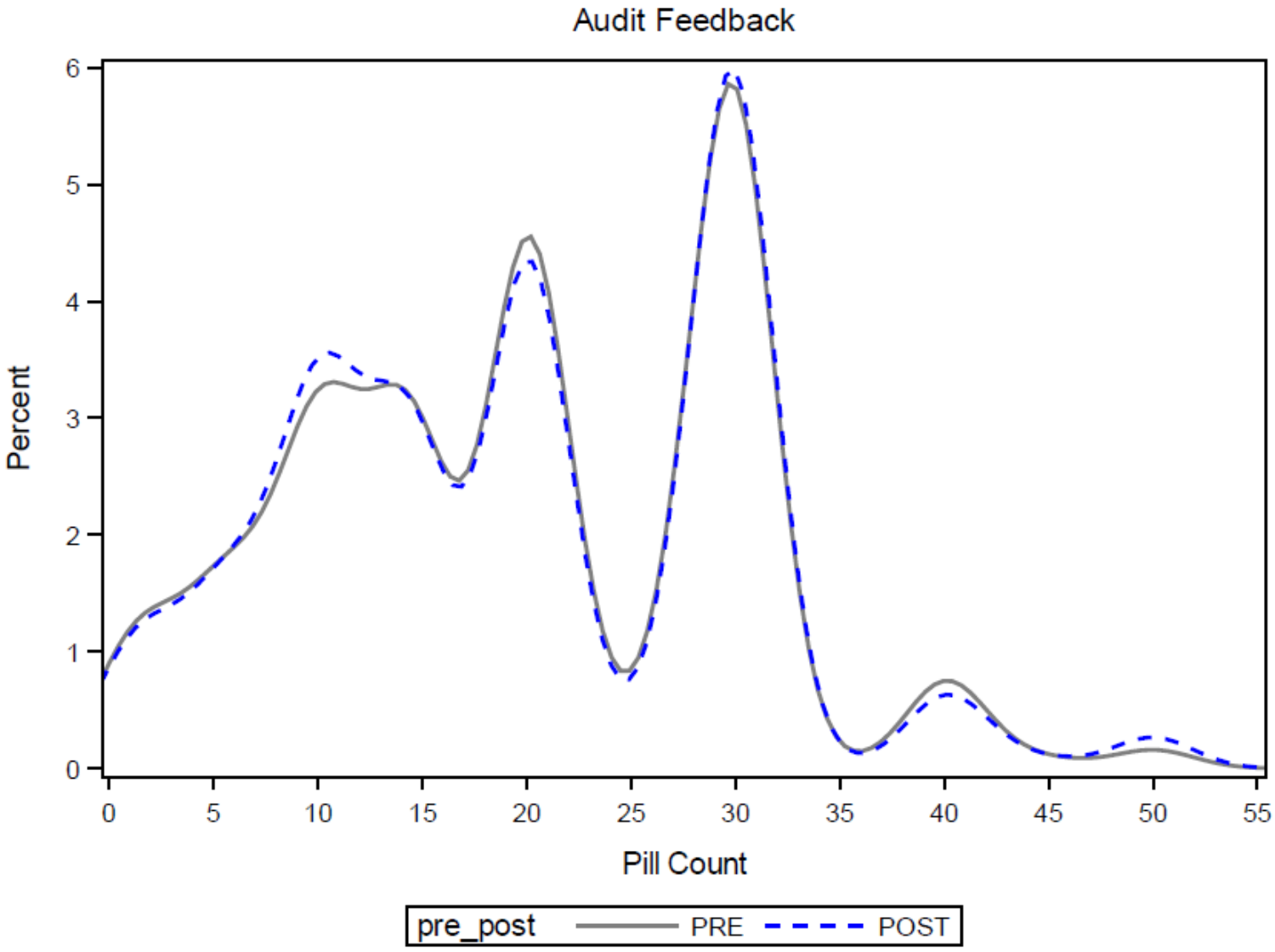
Appendix Exhibit 6. Trends in Mean Pills Per Opioid Prescription Among Urgent Care Sites



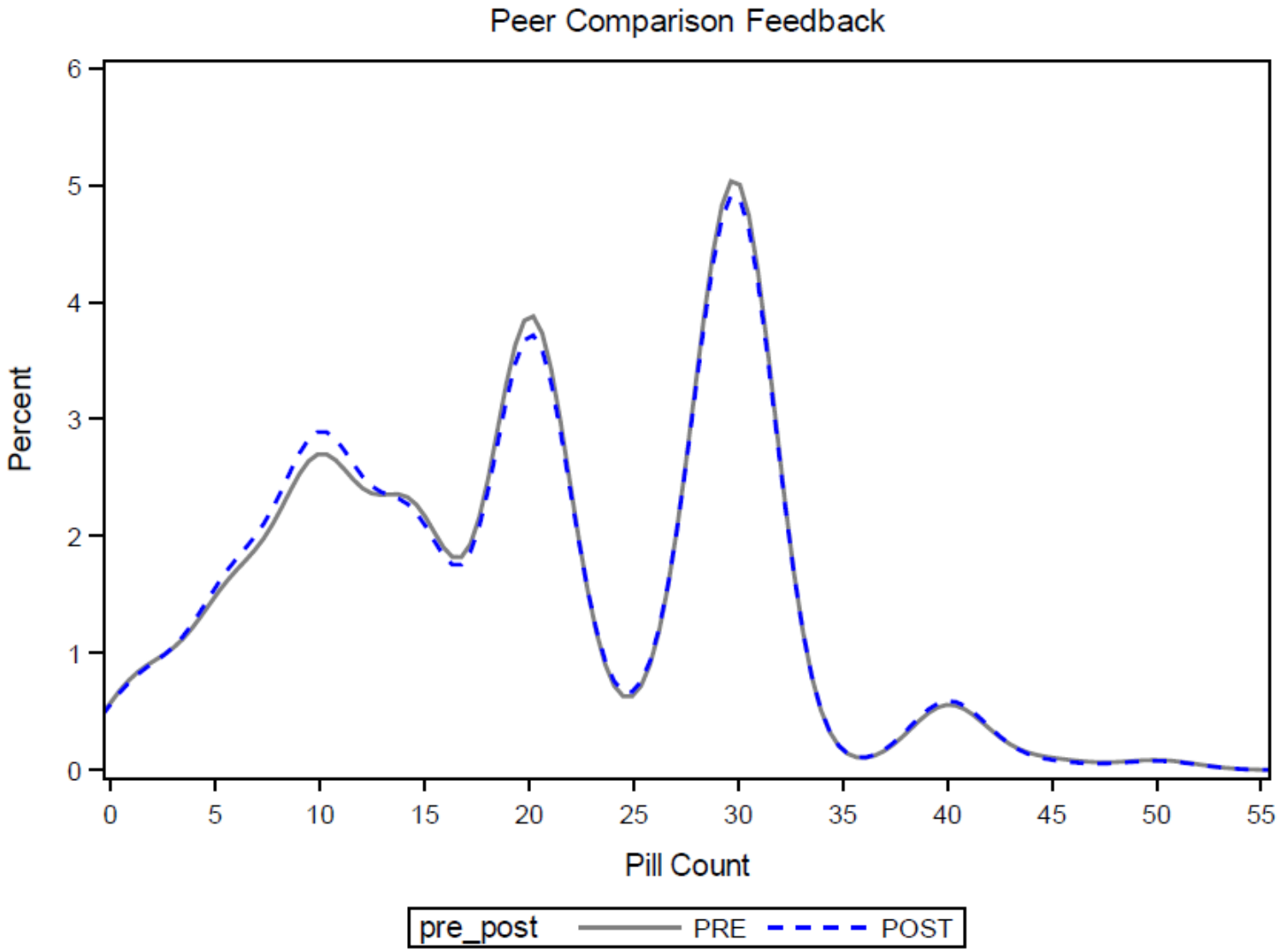
Appendix Exhibit 7. Distribution of Prescription Pill Size During the Pre-Intervention and Intervention Periods in the Usual Care Arm



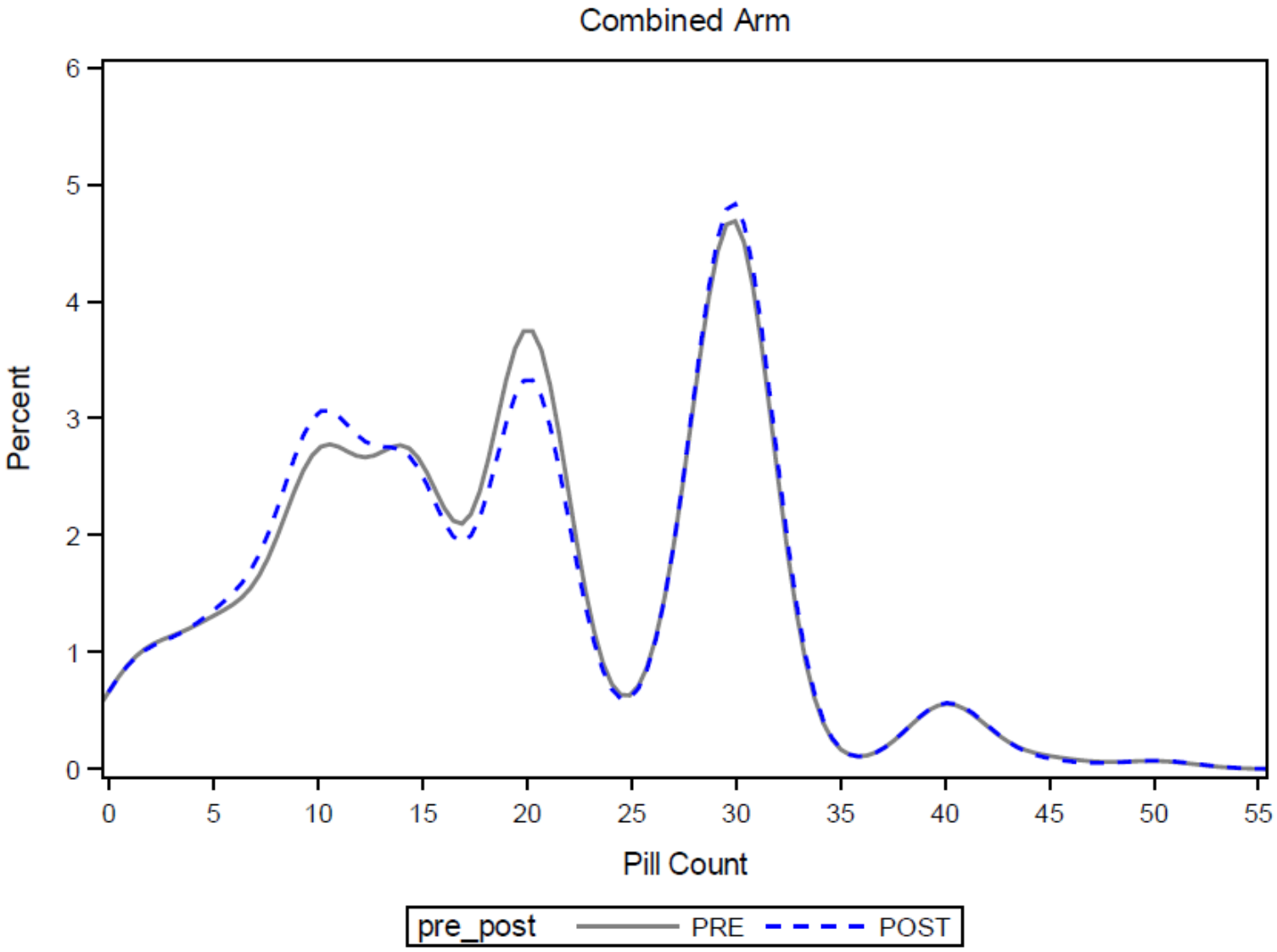
Appendix Exhibit 8. Distribution of Prescription Pill Size During the Pre-Intervention and Intervention Periods in the Individual Audit Feedback Arm



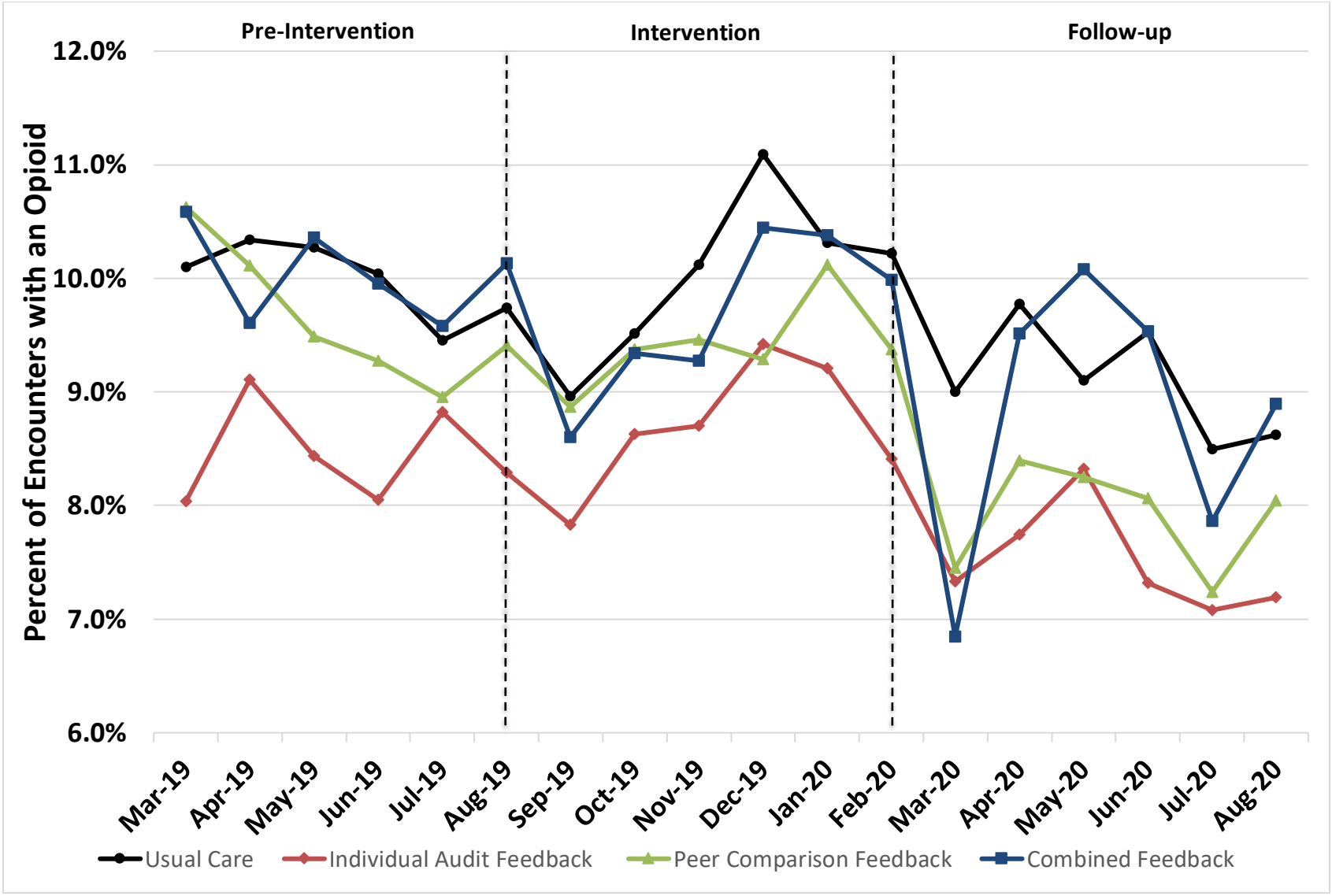
Appendix Exhibit 9. Distribution of Prescription Pill Size During the Pre-Intervention and Intervention Periods in the Peer Comparison Feedback Arm



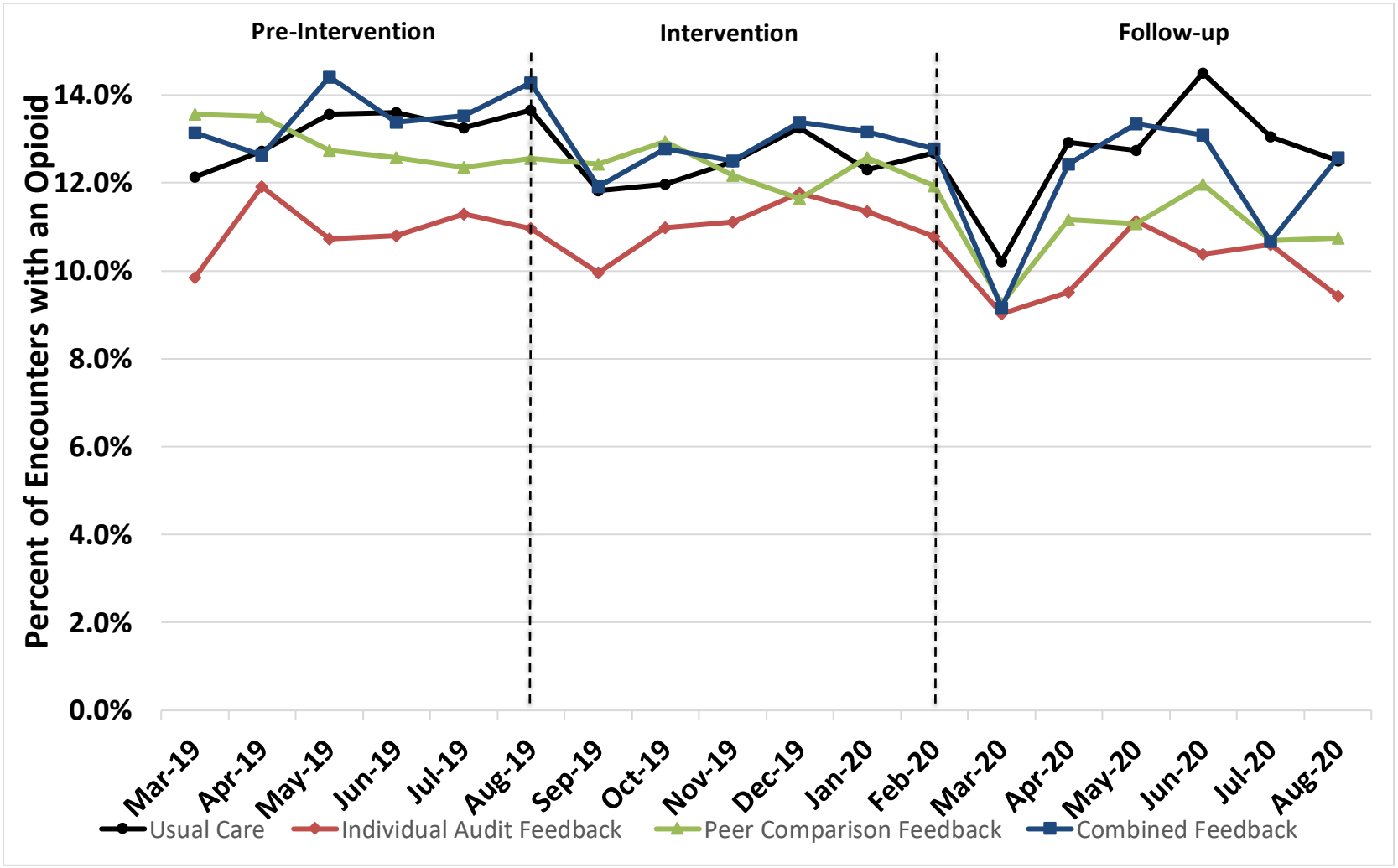
Appendix Exhibit 10. Distribution of Prescription Pill Size During the Pre-Intervention and Intervention Periods in the Combined Feedback Arm



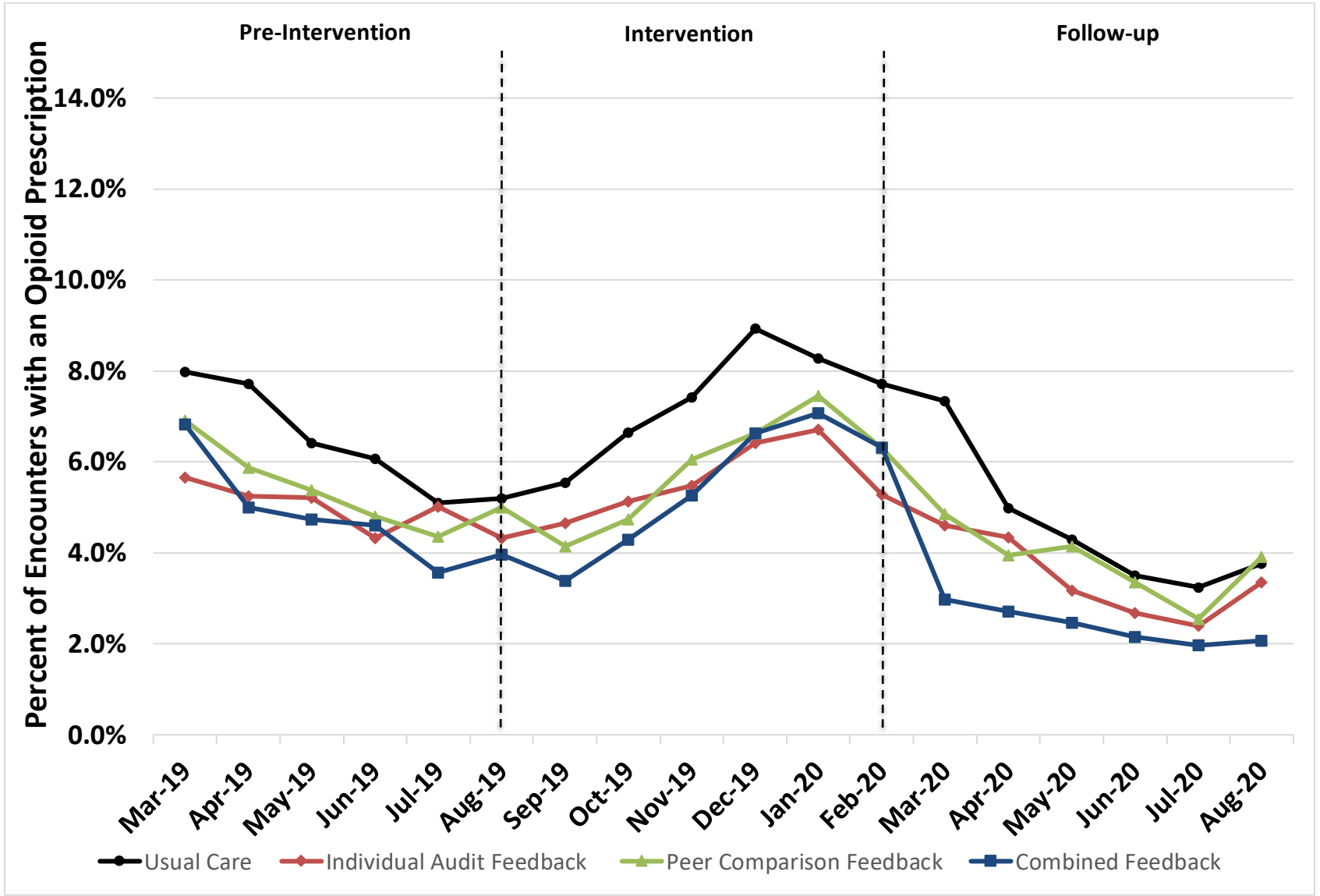
Appendix Exhibit 11. Trends in Percent of Encounters with an Opioid Prescription.



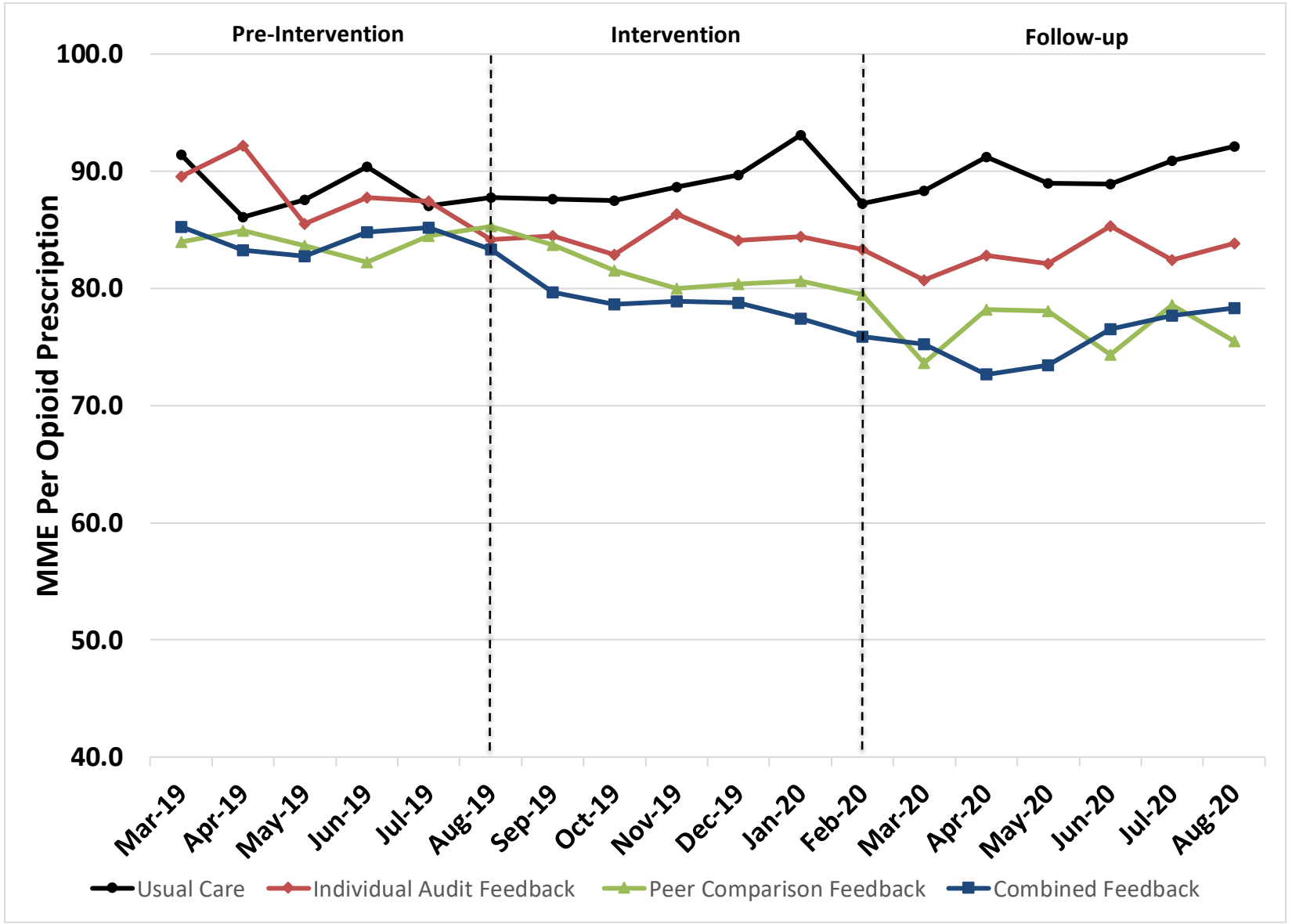
Appendix Exhibit 12. Trends in Percent of Encounters with an Opioid Prescription Among Emergency Department Sites



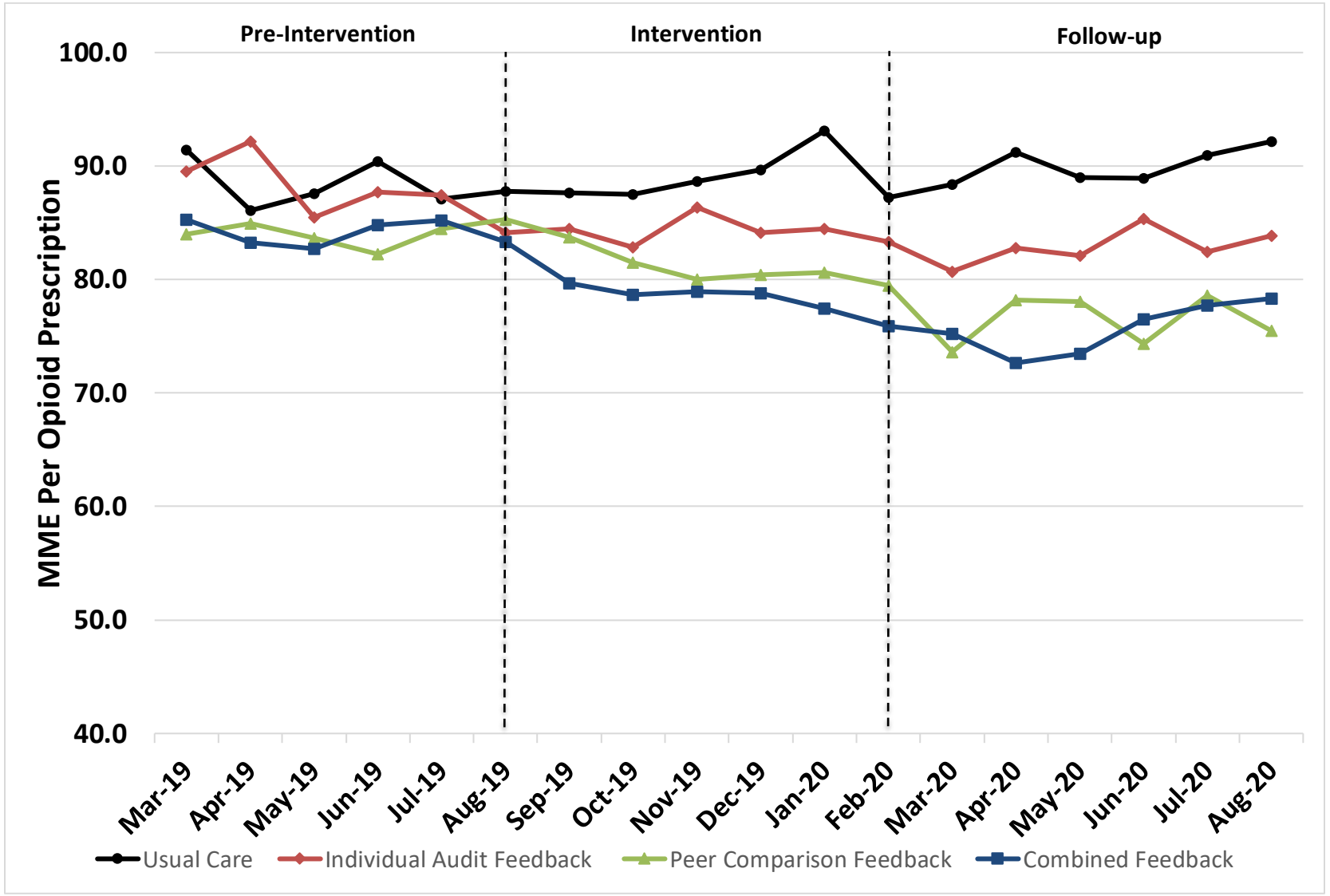
Appendix Exhibit 13. Trends in Percent of Encounters with an Opioid Prescription Urgent Care Sites



Appendix Exhibit 14. Trends in Milligram Morphine Equivalents Per Opioid Prescription.



Appendix Exhibit 15. Trends in MME Per Opioid Prescription Among Emergency Department Sites



Appendix Exhibit 16. Trends in MME Per Opioid Prescription Among Urgent Care Sites