# Disposal Interventions for Safe Prescription Opioid Surplus Elimination: The DISPOSE Trial

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This most recently approved protocol dated August 13, 2019 contains the following items:

- Summary of protocol changes (Approved August 13, 2019)
- Original IRB-approved protocol (approved May 6, 2019)
- Original statistical analysis plan

DISPOSE Protocol Supplement TOC

**Table: Summary of protocol changes**

| Date | Description of change |
|---|---|
| May 13, 2019 | Pre-enrollment refinement of randomization, allocation concealment, masking of outcome assessments, and inclusion/exclusion criteria<br>• Clarified that randomization occurs based on day of prescription drop off<br>• Added allocation concealment conducted by lead pharmacist using computer-generated random assignments prepared and communicated electronically by study statistician<br>• Changed masking for outcome assessors to be blinded to treatment group assignment<br>• Clarified enrollment criteria to include prescriptions written for individuals <18 years of age which were picked up by a designated family member ≥18 years of age |

DISPOSE Protocol Supplement: Summary of Protocol Changes **PROTOCOL: Disposal Interventions for Safe Prescription Opioid Surplus Elimination (DISPOSE)**

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## ABSTRACT:

Many people who receive a prescription for opioids report having leftover opioids once they are no longer needed to treat pain. These leftover opioids, which are rarely disposed of, can enable the opioid crisis by serving as a reservoir of drug available for misuse. For example, 90% of people who misuse prescription opioids report obtaining them from a family member or friend, or their own legitimate prescription. One way to reduce the amount of leftover opioids remaining in homes is to dispose of them once they are no longer needed. As a result, the Food and Drug Administration currently recommends that patients dispose of leftover prescription opioids by returning them to an authorized permanent collection site (e.g., medication drop boxes), or, when this is not feasible, flushing leftover opioid down the toilet. A newly available home disposal option involves use of a drug disposal kit. One such kit is DisposeRx. This product, which is available for purchase without a prescription, provides a safe and quick way to dispose of prescription medication. When a person mixes leftover drug with the DisposeRx powder and water, DisposeRx traps the medication in a gel which can then be safely disposed of in household trash. However, it is not known whether provision of drug disposal kits will increase the likelihood that leftover opioids will be disposed of by patients as compared to the currently accepted best practice, which is to provide instructions on how to safely dispose of leftover medications at home. This study will test the hypothesis that participants who receive a drug disposal kit such as DisposeRx will have the same rate of disposing of leftover prescription opioids as participants who are given standard instructions on how to dispose of leftover prescription opioids (i.e., currently accepted best practice). We will conduct a randomized controlled trial of individuals filling a new prescription for an opioid medication in the Johns Hopkins pharmacies to answer this question. Individuals will be called by telephone up to 6 weeks after they fill their prescription to determine whether or not they have disposed of their leftover prescription opioid medications, and if so by what means.

## OBJECTIVES:

The primary objective of this study is to determine the impact of provision of the DisposeRx drug disposal kit on the proportion of participants who dispose of leftover prescription opioids once they are no longer required to treat pain. This aligns with the overall goal of reducing the presence of leftover opioids after participants conclude therapy, because leftover opioids serve as a reservoir for the misuse and diversion of opioids which can then contribute to the opioid crisis.

The secondary objective of the study is to determine the impact of Disposal Interventions (i.e., DisposeRx or an informational handout that lists disposal methods recommended by the Food and Drug Administration) on the proportion of participants who dispose of leftover prescription opioids in any manner.

**BACKGROUND:**

The opioid crisis represents the most pressing public health epidemic at this time, with more than 47,000 deaths in 2017.[1] While deaths from illicit fentanyl have recently increased, given that over 40% of all opioid overdose deaths involve a prescription opioid, nonmedical use of prescription opioids remains a key contributor to the crisis.[1] Prescription opioids are the number one category of pharmaceutical products that Americans misuse, and 11.1 million Americans reported misusing opioids in 2017.[2] Ninety percent of those who misuse prescription opioids report obtaining them from a family member or friend, or from their own legitimate prescription. Also, a majority of people who are prescribed opioids fail to adequately store or dispose of them once they conclude therapy. When people dispose of prescription opioids, they often do so using methods that are not recommended by the Food and Drug Administration. For example, only 9% of individuals prescribed opioids after surgery reported disposing of leftover medication in a manner recommended by the Food and Drug Administration.[3] Thus, methods to enhance the safe disposal of leftover prescription opioids deserve investigation.

Different interventions are currently available to promote the safe disposal of leftover prescription opioids. One of the most basic methods is to provide patients with an educational pamphlet or written instructions describing recommended disposal methods. Past studies have examined the impact of these educational interventions and found either no change[4] or an increase[5] in the proportion of participants who dispose of leftover prescription opioids. For example, Rose and colleagues reported that the proportion of participants who disposed of leftover prescription opioids using a recommend method increased from 5% to 27% (difference 22%, 95% CI, 5% to 38%) when subjects were provided with an opioid disposal pamphlet.[5]

An alternative disposal intervention involves providing patients with a drug disposal kit. These kits typically contain a substance that the patient mixes with leftover prescription opioids once they are no longer required to treat pain. One such kit is DisposeRx, a product that is now available at many major retailers without a prescription. The DisposeRx formulation is manufactured of components that are generally recognized as safe (GRAS) by the Food and Drug Administration; these substances are often included in various foods and drugs, and are not toxic. The desiccant silica powder is also listed by the FDA as a GRAS ingredient (GRAS Notice (GRN) No. 298: http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/default.htm). Of note, while the kit can be purchased, Walmart currently offers DisposeRx free of charge to patients at all of its pharmacy locations. To use DisposeRx, a participant combines the DisposeRx powder with water in the original prescription bottle and then shakes the mixture together. When activated by water, DisposeRx traps the drugs (i.e. pills, capsules, caplets, liquids or tablets) in a semi-solid gel. The trapped drug cannot be retrieved from the resulting gel material for abuse or leach into landfills. The participant can then throw away the biodegradable solid material in the prescription bottle as it is safe for the environment. Importantly, the contents of DisposeRx are also safe if eaten. To date, no published studies have examined the impact of any opioid disposal kits on rates of safe disposal of leftover prescription opioids. Disposal interventions are the focus of two trials on ClinicalTrials.gov, NCT03179566 and NCT03285061. However, both trials examine other drug disposal kits than DisposeRx.

At Johns Hopkins Outpatient Pharmacies, the current standard of care is that individuals who fill prescriptions are not provided with instructions on how to safely dispose of prescription opioids. Despite this case, opioid prescriptions have been a central focus of the Opioid Stewardship Clinical Community, since its inception in early 2017. Drawing on clinician leaders across the institution, the Opioid Stewardship Clinical Community has focused on improving the judicious use of prescription opioids from the time the medications are considered to their prescribing, dispensing, use, and finally disposal. JHHS and the Opioid Stewardship Clinical Community have undertaken a number of initiatives to enhance the ability of patients to dispose of prescription medications, including opioid prescriptions. For example, the Johns Hopkins Department of Pharmacy has installed drug disposal units for patients to drop off leftover prescription medications at outpatient pharmacies located at the Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center in Baltimore. However, not all 11 Hopkins pharmacies support the drug disposal units. As a result, JHHS and Johns Hopkins Department of Pharmacy are considering alternate interventions to promote safe drug disposal. The goal of this randomized, controlled trial will help determine whether our health system should provide certain patients with individual drug disposal kits when an opioid prescription is filled at a Johns Hopkins pharmacy. This study is necessary because, as acknowledged above, no published studies have examined the impact of opioid disposal kits on rates of safe disposal of leftover prescription opioids.

Design: This study is a randomized controlled trial. This approach was selected to best achieve robust and unbiased results.

Setting: This study will take place in select Johns Hopkins Health System outpatient pharmacy locations.

Participant screening: As a part of routine care at Johns Hopkins pharmacies, a pharmacist currently examines and verifies every opioid prescription that is brought in to the pharmacy to be filled. The pharmacist who does this examination and verification is called the pre-verification pharmacist. This examination and verification is required by Johns Hopkins policy (available for review at Johns Hopkins Policy & Document Library at https://hpo.johnshopkins.edu/hopkins/policies/65/14154/policy_14154.pdf?_=0.854965807447). The pre-verification pharmacist currently examines various characteristics of the opioid prescription including, but not limited to the type of opioid (name, whether short-acting or longacting), dose, route, number of pills and days' supply. Characteristics of the individual for whom the prescription was written are also part of this state required examination and include demographics such as age and gender, the insurance company or payer, and the telephone number of the patient. The pre-verification pharmacist reviews this data using two computer systems, McKesson Enterprise Rx (an electronic management system specific to Johns Hopkins Pharmacy) and EPIC (the electronic health record for the Johns Hopkins Health System). All procedures performed by the pre-verification pharmacist that have been described up to this point take place as a part of routine care. This Johns Hopkins policy required review of the prescription and the patient which occurs during normal business hours in the Johns Hopkins Outpatient Pharmacies will serve as the review for eligible participants with qualifying prescriptions in this study.

Randomization and Disposal Intervention: Randomization will occur by day of the week using a computer generated schedule as determined by the study statistician. Randomization by day of the week was chosen due to pragmatic reasons, given logistical difficulties in the pharmacy of randomizing individual prescriptions. Randomization will occur to one of three possible conditions using an "add-on" design: (1) the 'control' group will receive standard of care, which is provision of no specific disposal information; (2) the 'fact sheet' group will receive an informational sheet with disposal instructions; or (3) the 'drug disposal kit' group will receive the same informational sheet with instructions, Dispose Rx, and instructions on how to use Dispose Rx. For example, on Monday all participants could receive an information sheet with Dispose Rx as the Disposal Intervention along with their opioid prescription. Then on Tuesday all participants could receive only an informational sheet with disposal instructions as the Disposal Intervention along with their opioid prescription. Then on Wednesday all participants could receive no intervention (current standard of care) when their pick up their opioid prescription. An IRB approved study team member will inform the pharmacist of the Disposal Intervention for that particular weekday. No change in any other aspect of the participant's pharmacy encounter will take place (i.e., the participant will fill the opioid prescription for the amount/dose as originally prescribed).

Baseline data collection: Baseline information about the individual for whom the prescription was written will be collected from Enterprise Rx and EPIC using a standardized chart data extraction form (e.g., demographics [i.e., age, gender, race/ethnicity], opioid prescription characteristics, telephone number) by an IRB-approved member of the study team.

Follow up telephone survey: Participants will be contacted by an IRB-approved member of the study team via telephone at 3 weeks after filling the opioid prescription and asked to complete a standardized survey. Up to three contacts via telephone will be attempted between 20 and 26 days after the prescription is filled. If the participant has not completed opioid therapy at that time or does not respond to any of the 3 phone calls, they will be contacted at 6 weeks to complete the survey. For these participants, up to three contacts via telephone will be attempted between 40 and 46 days after the prescription fill.

During data collection and with annual progress reports to the IRB, we will include counts of the number of subjects who decline to provide data at the week 3 and week 6 outcome assessments, and provide counts of the number of subjects, if any, who express displeasure with learning that they have been entered in a research study without their prior consent.

We are requesting a waiver for consent for the randomization to the disposal intervention portion of this study; however, when we call patients at 3 and/or 6 weeks later, we will ask them if they are willing to answer survey questions related to the disposal of their opioid medication/s. If they do not want to respond to any questions, we will not continue with the survey nor will we attempt to contact them again. If the patients indicate they are willing to answer the survey questions, then we will obtain oral consent for the survey portion of this study from participants at that time.

Study duration: Each participant will be asked to complete one 6-minute telephone survey at 3 weeks after the date of filling the opioid prescription. Participants who have not stopped using

opioids at 3 weeks or who did not respond to any of the 3 phone calls at 3 weeks will be asked to complete a follow-up telephone survey at 6 weeks after the date of filling the original opioid prescription. No additional study visits or interactions will be required. This study is expected to begin as soon as IRB approval is obtained and will last for approximately one year to include data analysis.

Blinding: Participants and researchers will be aware (i.e., not be blinded) to the Disposal Intervention. It is not feasible to blind either group to either Disposal Intervention.

## INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria

1. Adult participants (age ≥ 18 years) who pick up an opioid prescription for themselves or a family member at a Johns Hopkins pharmacy
2. English speaking
3. Residential address and phone number in the United States
4. Filling a new prescription consisting of an immediate release opioid medication (i.e., immediate release morphine, oxycodone, hydromorphone, hydrocodone, tramadol; alone or in combination with acetaminophen) with ≤ 7 days' supply

Exclusion Criteria

1. Age < 18 years
2. Non-English speaking
3. Residential address and/or phone number unavailable or outside the United States
4. Opioid medication listed in participant's active medication list prior to prescription fill
5. Filling any prescription consisting of any opioid with 8 or more days' supply
6. Filling any prescription consisting of any extended-release / long-acting opioid medication (i.e., extended-release morphine, oxymorphone, oxycodone, hydromorphone, fentanyl, methadone, buprenorphine)

## DISPOSAL INTERVENTIONS:

This study will evaluate two Disposal Interventions: 1) the DisposeRx drug disposal kit with instructions on how to use DisposeRx and 2) an informational handout listing opioid disposal methods recommended by the Food and Drug Administration, along with the current standard of care of no Disposal Intervention.

The DisposeRx drug disposal kit was selected as the potential drug disposal system of choice for the Johns Hopkins Health System after a review process conducted by the Johns Hopkins Department of Pharmacy and the Johns Hopkins Opioid Stewardship Clinical Community. First, seven drug disposal systems or kits were assessed on various criteria. Five of those seven were selected for use in focus groups by frontline staff (15 physicians, nurses, and pharmacists at Johns Hopkins, which included study co-investigators) and patients (13 members from the Johns Hopkins Home Care Group Patient and Family Advisory Council). The top two products were then brought to the Johns Hopkins Opioid Stewardship Clinical Community for consideration. DisposeRx was selected as the potential preferred product due to ease of use. The DisposeRx

formulation is manufactured of components that are generally recognized as safe (GRAS) by the Food and Drug Administration; these substances are often included in various foods and drugs, and are not toxic. The desiccant silica powder is also listed by the FDA as a GRAS ingredient (GRAS Notice (GRN) No. 298: http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/default.htm). In addition to providing the DisposeRx drug disposal kit, participants will be given an fact sheet or informational handout with instructions on how to use DisposeRx. This document was created in part by the Johns Hopkins Medicine Patient and Family Education and is a publicly available document at http://johnshopkinsibportal.staywellsolutionsonline.com/Search/22,655.

The fact sheet or informational handout lists information on the safe use of prescription opioids, including disposal methods recommended by the Food and Drug Administration. The paper document is a HealthSheet™, which is an evidence-based, peer-reviewed document written specifically for patients. These documents cover diseases and conditions, diagnoses and treatments, surgeries and procedures, and wellness and safety for people of all ages and walks of life. The main methods of drug disposal recommended on the handout and by the FDA include using medication take-back programs, which are available at select local and Hopkins pharmacies, or flushing leftover medication down the toilet. This document was created in part by the Johns Hopkins Medicine Patient and Family Education and has been hosted on the StayWell web portal at http://johnshopkinsibportal.staywellsolutionsonline.com/Search/22,279. This document incorporates recommendations from the Food and Drug Administration on how to dispose of leftover prescription opioid medications in a safe way.

Finally, the current standard of care in the Johns Hopkins Outpatient Pharmacies is for persons filling prescriptions to not receive written information from the pharmacy on the safe disposal of leftover prescription opioids upon filling a prescription for an immediate release opioid medication.


1. Centers for Disease Control and Prevention. *Multiple cause of death data on CDC WONDER*. Atlanta, GA: US Department of Health and Human Services, CDC, 2018.

2. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health*. *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, 2018.

3. Bicket MC, Long JJ, Pronovost PJ, Alexander GC, Wu CL. Prescription Opioid Analgesics Commonly Unused After Surgery: A Systematic Review. *JAMA Surg* 2017; 152: 1066–1071.

4. Maughan BC, Hersh E V, Shofer FS, Wanner KJ, Archer E, Carrasco LR, et al. Unused opioid analgesics and drug disposal following outpatient dental surgery: A randomized controlled trial. *Drug Alcohol Depend* 2016; 168: 328–334.

5. Rose P, Sakai J, Argue R, Froehlich K, Tang R. Opioid information pamphlet increases postoperative opioid disposal rates: a before versus after quality improvement study. *Can J Anaesth* 2016; 63: 31–7.

6. Bicket MC, White E, Pronovost PJ, Wu CL, Yaster M, Alexander GC. Opioid Oversupply After Joint and Spine Surgery: A Prospective Cohort Study. *Anesth Analg* 2019; 128: 358–364.

7. Monitto CL, Hsu A, Gao S, Vozzo PT, Park PS, Roter D, et al. Opioid Prescribing for the Treatment of Acute Pain in Children on Hospital Discharge. *Anesth Analg* 2017; 125: 2113–2122.

**Analysis Plan**

Sample size estimates: Sample size is calculated based on estimated effects on the primary outcome measure, the number of participants using a safe drug disposal method for leftover prescription opioids. This is defined as participants who report "yes" to disposing of leftover prescription opioid medication using a disposal intervention that aligns with recommendations from the Food and Drug Administration (i.e., using a take-back program, drug disposal kit, or flushing in the toilet) up to 6 weeks after prescription fill. At the time of writing this protocol, no published studies have examined the impact of disposal kits on rates of safe disposal of leftover prescription opioids. We estimate that the 'fact sheet' group will have a disposal rate of one in six patients (~17%), and that the 'drug disposal kit' group will have a disposal rate of one in three patients (~33%). To achieve 80% power with alpha = 0.05, each group will require 126 patients. We will allocate patients 1:1:1 among the 'drug disposal kit' group, 'fact sheet' group, and 'control' groups, and thus require a sample size totaling 378 patients. Based on prior studies, we anticipate a dropout rate of 10-15%; allowing for a conservative non-response rate of 2425%, we will need to enroll 499 participants.

We estimate that the 'no intervention' group (i.e., current standard of care) will have a disposal rate of 5%, based on previous studies of patients after surgery reporting disposal at 1 month.[3,6,7] When we compare the 'no intervention' group with 'fact sheet' group, this sample will provide 82% power to detect a difference . When we compare the 'no intervention' group with the 'drug disposal kit' group, this sample will provide >99% power to detect a difference.

Primary analyses: We will use an intent-to-treat analysis approach, including all eligible patients in the group to which they were originally assigned. We will compare baseline characteristics and potential confounders between the three groups. Any imbalance will lead to additional analyses, as described in the "potential confounding" section below. The amount of opioids will be described as total morphine-equivalent mg using standard conversion tables from the CDC Guideline for Prescribing Opioids for Chronic Pain.

Aim 1: To compare disposal interventions on safe drug disposal up to 6 weeks after filling an opioid prescription.

The primary outcome is the number of participants using a safe drug disposal method for leftover prescription opioids, as defined in the "sample size estimates." The primary comparison of interest is comparison of the 'drug disposal kit' group and the 'fact sheet' group. The secondary comparisons of interest are the comparisons of each of these two groups with the 'no intervention' group. Based on the study design and methods, we will examine outcomes for each individual at one point in time in follow up (i.e., 3 weeks or 6 weeks after filling at prescription). Thus, results from the 3-week follow up will be combined with results from the 6-week follow up for the purposes of statistical analyses. Additionally, the primary outcome of using a disposal intervention is only applicable for individuals who have completed their course of therapy. In other words, individuals who have not completed their course of opioid therapy would not be eligible to use a disposal intervention given they are still using their prescription opioid therapy. As a result, the primary outcome will be analyzed only in the subset of individuals who have reported that they have stopped taking prescription opioids at the time of follow up.

Preliminary analyses will use intent-to-treat analyses to compare the number of individuals reporting the use of a safe drug disposal method for leftover prescription opioids using chisquared tests to compare proportions. In an adjusted models for the primary analysis, we will use log-binomial regression to determine the risk ratio of safe drug disposal comparing two groups. We will conduct sensitivity analyses using Poisson models with robust error variance. We will present outcome measures with 95% confidence intervals and make no adjustment for multiple comparisons.

Missing data and potential confounding: We anticipate a low rate of missing data. Reasons for missing data will be recorded. We will compare observed outcomes at time points prior to dropout between the three groups. We do not plan on imputing missing data nor fitting complex models for missing data. We will examine groups to determine if potential confounding variables (e.g., amount of prescribed opioids in standardized morphine milligram equivalents, age, sex, etc.) are balanced. If they are not, we will conduct additional analyses to evaluate whether the findings are due, in part, to these imbalances. We will add potential confounders as covariates in models to adjust for them, and we will also examine for the potential effects of interactions between confounders and treatment groups by adding interaction terms to the models.

Secondary analyses:

Aim 2: To compare disposal interventions on secondary outcomes, including use of any disposal method, safe storage of prescription opioids, and completion of therapy up to 6 weeks after filling an opioid prescription.

The approach described above (log-binomial regression, with consideration of adjustment for potential confounders) will be used to analyze data for secondary outcomes. Using the same rationale as presented in Aim 1, the secondary outcome of use of any drug disposal method will be analyzed only in the subset of individuals who have reported that they have stopped taking prescription opioids at the time of follow up. The secondary outcome for safe storage and therapy completion will be analyzed in all individuals.

| Secondary outcome | Description |
|---|---|
| Number of participants using any drug disposal method for leftover prescription opioids | Participants who report "yes" to disposing of leftover prescription opioid medication using any method up to 6 weeks after prescription fill |
| Number of participants with safe storage of prescription opioids | Participants who report "yes" to safely storing prescription opioid medication (i.e., in a locked location) up to 6 weeks after prescription fill |
| Number of participants who completed prescription opioid therapy | Participants who report "yes" to completing therapy for prescription opioid medication up to 6 weeks after prescription fill |

Aim 3: To compare disposal interventions on safe drug disposal up to 6 weeks after filling an opioid prescription for pediatric vs. adult prescription recipients.

The approach described above (log-binomial regression, with consideration of adjustment for potential confounders) will be used to analyze data for safe drug disposal with model including an indicator variable based on the age of the individual for whom the prescription was written (0-<18 years of age vs. ≥18 years of age). Using the same rationale as presented in Aim 1, the outcome of safe drug disposal will be analyzed only in the subset of individuals who have reported that they have stopped taking prescription opioids at the time of follow up.

For this study, no interim analyses will be conducted and no stopping rules will be included.