A Preliminary Study of Sublingual Fentanyl for the Management of Breakthrough Pain Analgesia in Patients with Advanced Cancer

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A. Study Objectives

Primary objective: To determine the **effective dose** of fentanyl sublingual spray (FSS) in the management of breakthrough pain in hospitalized patients with advanced cancer receiving continuous opioid infusion and seen by the palliative care team (consultation service or palliative care unit).

Secondary objective #1: To estimate the differences in the **pain response between intravenous opioid** breakthrough and FSS at effective dose.

Secondary objective #2: To determine the safety, tolerability, pattern of use, and efficacy of FSS in patients with advanced cancer during the first month post-hospital discharge.

B. Background

More than 80% of patients develop cancer pain before they die [1]. The vast majority of these patients are receiving opioid analgesics until the time of their death [2]. Pain in cancer patients can be constant interspersed with breakthrough pain episodes. Breakthrough pain is defined as “a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.”[10] There are at least 4-5 episodes of BT pain in cancer patients per day [3, 4]. The treatment of cancer pain consists of providing opioid analgesia on a constant basis. However BT episodes are not typically covered by scheduled analgesics. Hence short acting opioids are useful for these settings. However, most available opioids do not peak in activity and match the onset and duration of BT episodes. Unfortunately, the great majority of patients develop difficulties with swallowing before death. This is due to a number of factors including delirium, dysphagia, bowel obstruction, and emesis.

These patients frequently receive sublingual medications with unreliable bioavailability, including sublingual administration of parentally available drugs, transdermal ointments, or subcutaneous or intramuscular administration of opioids. Intravenous administration of opioids at home is complex due to the need to maintain an intravenous line under the guidance of a home health service. Hence a class of rapidly acting opioid analgesics has been introduced to address this issue. The number of preparations includes oral transmucosal fentanyl, fentanyl buccal film, fentanyl buccal tablet, fentanyl nasal spray, and recently a sublingual spray of fentanyl (5, 6, 7, 8, and 9). For most preparations only 50% of the drug is absorbed. The absorption of sublingual spray is about 70-75 % (8).

Patients with inability to take oral medications can frequently be managed well with transdermal fentanyl patches administered once every 2-3 days or oral/rectal opioids administered once a day. However, when breakthrough pain occurs it might be very hard for some of these patients to swallow oral breakthrough tablets. While all the rapid onset fentanyl preparations have proved useful, fentanyl sublingual spray is preferred due to ease of administration and high bioavailability (8).

FSS has been approved for breakthrough cancer pain in opioid tolerant patients. However, all the studies have been conducted in the ambulatory setting, and no study has compared FSS to intravenous opioid for breakthrough pain. Furthermore, most studies used a multiple dose titration approach which is not always feasible in the inpatient setting. In this study, we will examine the effective dose of FSS in hospitalized cancer patients using an escalated titration approach, and compare the effect of FSS to intravenous opioid.

This study is novel because it examines the use of FSS for breakthrough pain in patients who are hospitalized, receiving continuous opioid infusion, and under the care of palliative care. Furthermore, this study will examine the use of a rapid titration approach (coupling proportional dosing with titration) which may allow us to identify the appropriate dose more efficiently. The preliminary data obtained from this study will allow us to design an adequately powered randomized controlled trial comparing FSS to intravenous opioids.

C. Experimental Approach

C.1. Overall Study design. This is an investigator-initiated, single arm, open-label study that utilizes a quasi-experimental design to examine the use of FSS in cancer patients with breakthrough pain (Figure 1). After study consent, eligible patients will be asked to complete a number of surveys. They will then receive one single dose of intravenous opioid rescue for their first episode of breakthrough pain, and then receive up to 4 doses of FSS for subsequent episodes of breakthrough pain using a rapid titration approach, in which the initial FSS starting dose will be proportional to the patient's MEDD. At the time of discharge, patients who identified an effective dose may be able to continue with FSS use for up to 1 month.

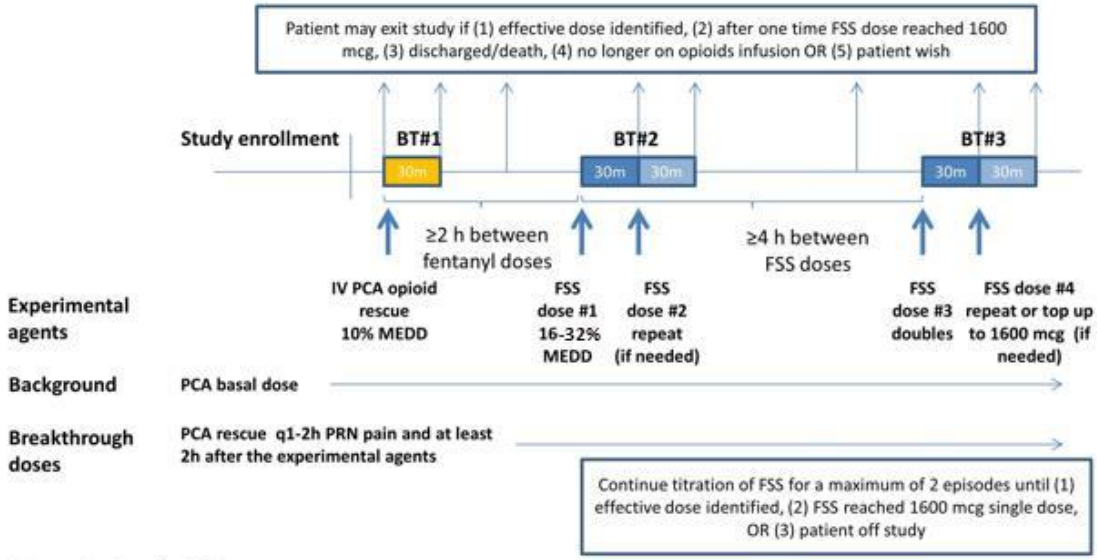

Figure 1. Study Scheme

C.2. Eligibility Criteria. The eligibility criteria are shown in Table 1.

Table 1. Study Eligibility Criteria

Inclusion criteria

1. Patients with advanced cancer (locally advanced, metastatic, recurrent and/or incurable cancer)
2. Opioid tolerant, taking daily doses of strong opioid pain medication in the past 1 week
3. On strong opioid intravenous continuous infusion MEDD >= 70 mg/day at the time of enrollment
4. Inpatient at MD Anderson seen by palliative care team
5. Background cancer pain that is <=3/10 in the last 24 hours
6. Breakthrough cancer pain that is >=4/10 in the last 24 hours
7. Stable pain control defined as rescue doses <=6 in last 24 hours
8. Age >=18
9. Ability to communicate in English

Exclusion criteria

1. Memorial Delirium Assessment Scale >13/30
2. History of opioid abuse
3. CAGE positivity (>=2/4)
4. Allergy to fentanyl
5. Grade 2 or higher oral mucositis
6. Unable/unwilling to sign consent

C.3. Study screening. A 2 step consent process will be used. First, a verbal consent will be obtained by the study staff to proceed with screening of potential participants for eligibility. Eligible patients will then be formally enrolled onto the study after they have signed the informed consent indicating a willingness to participate in the trial. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal for eligible patients will also be captured.

C.4. Study Interventions.

The commercial supply of study medication will be provided by Insys Therapeutics Ltd. FSS was FDA approved in 2012 for "For the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain." This study consists of two stages:

Stage 1. In-hospital pain management. Once patients are enrolled, our research nurse will be notified to provide careful instructions on medication use. Patients will be monitored for 3 episodes of breakthrough pain (Figure 1).

(1) First episode – patients will be given a single dose of breakthrough opioid from their existing PCA pump that is equivalent to 10% of their MEDD. The dose used in this study is consistent with our routine clinical practice. Immediately upon patient enrollment, the study physician will be notified and will determine the morphine equivalent daily dose (MEDD) in real time using standardized

equianalgesic ratios. We will then determine the doses of intravenous opioid needed (i.e. 10% of MEDD as per standard of care). For example, a patient had a MEDD of 200 mg/day at the time of enrollment. The IV opioid dose will be morphine 8mg IV x1 dose (or equivalent).

(2) Second episode
   a. The patient will be given a single dose of FSS that is equivalent to 16-32% of their MEDD (Table 2). Because FSS is available in fixed dosage forms, the actual % of MEDD will be determined. Pain intensity will be assessed at 30 minutes. A breakthrough pain intensity reduction of >=2/10, >=33% of baseline pain intensity, reduction of pain intensity to personal pain goal (PPG) score or below, OR absolute value below background pain level will be considered as an effective dose.
   b. If breakthrough pain not effective at 30 minutes, the patient will repeat the same dose one more time (with a cap of 1600 mcg total; i.e. dose given 30 minutes ago + dose now = 1600 mcg maximum), and their pain intensity will be reassessed over the next 30 minutes again.

(3) Third episode (at least 4 hours after second episode)
   a. If the patient required 2 breakthrough FSS doses for the last episode of breakthrough pain, or if the effective dose has not been identified, he/she will double the last administered dose, and pain intensity will be assessed at 30 minutes.
   b. If breakthrough pain not effective at 30 minutes, the patient will repeat the same dose one more time (with a cap of 1600 mcg total; i.e. dose given 30 minutes ago + dose now = 1600 mcg maximum), and their pain intensity will be reassessed over the next 30 minutes again.

(4) The study assessments will be conducted Monday to Friday between 8AM and 4PM in the institution while under the supervision of our research nurse. Outside of this window, patients will need to use regularly prescribed breakthrough medications.

(5) While we expect a majority of patients will be able to identify an effective dose within the first 2 episodes of breakthrough pain, some patients may be discharged or their opioid infusion may be discontinued before an effective dose is identified. If that is the case, then their data will be censored for the primary objective.

(6) Once the effective dose is found, the first stage of this study is complete and they will no longer be on FSS. Patients who have identified an effective FSS dose may proceed to the next stage of this study upon discharge.

(7) We are limiting the total number of episodes to minimize attrition, minimize variability in basal opioid doses, and also because we are using an accelerated titration process so many patients will be starting already at higher doses than in the outpatient setting.

Table 2. FSS Dose for Breakthrough Pain Episode Based on Morphine Equivalent Daily Dose

Morphine equivalent daily dose (mg)	FSS (mcg) starting dose	FSS starting dose % equivalent of MEDD	Titration schedule while in hospital (if effective dose already identified, there will be no need to titrate upwards)
70-109	100	16.1-25.0%	100/100 – 200/200
110-219	200	16.0-31.8%	200/200 – 400/400
220-289	300	18. 2-23.9%	300/300 – 600/600
290-379	400	18.5-24.1%	400/400 – 800/800
380-469	500	18.7-23.0%	500/500 – 1000/600
470-579	600	18.1-22.3%	600/600 – 1200/400
580-669	700	18.3-21.1%	700/700 – 1400/200
670-750	800	18.7-20.9%	800/800 – 1600/NA

For intravenous opioid, the medication will be given by the research nurse or bedside nurse via the infusion pump. FSS will be provided by Dispensing Pharmacy. After providing careful instructions, the research nurse will keep the spray with the patient for ease of administration.
The following instructions will be given to the patient:

1. Swallow any saliva in your mouth.
2. Hold the medication spray unit upright using your index and middle fingers and thumb.
3. Point the nozzle into your mouth and under your tongue.
4. Squeeze your fingers and thumb together to spray the medication under your tongue.
5. Hold the medicine under your tongue for 30-60 seconds. Do not spit out any medicine. Do not rinse your mouth.
6. The spray unit will remain locked after use.

If a patient did not complete stage 1 on day 1, he/she will resume standard of care outside of study hours, and continue on where he/she left off with the next episode of breakthrough pain when the study resumes (i.e. Monday to Friday 8AM and 4PM).

Stage II. Out-of-hospital pain management. Upon completion of stage I, patients will revert back to their intravenous opioid regimen as prescribed by the Supportive Care team. Patients will be monitored and treated as per routine clinical practice. At the time of discharge, patients will be able to proceed to Stage II if they meet the following criteria:

- Must be willing to return to the Supportive Care Center within one to four weeks of discharge
- Discharged on a standard regimen of long acting and short acting opioid (non-FSS), with MEDD of at least 60 mg/day
- Effective FSS dose identified in Stage I

- The MEDD at time of discharge should be within 2 fold (i.e. 50% - 200%) of the MEDD at the time of effective dose.
- Willing to use FSS at home as their first choice for breakthrough pain for 4 weeks

During stage II, patients will be asked to use FSS (at effective dose) as their first choice of their rescue pain medication instead of oral opioid for breakthrough pain. FSS will be prescribed as q4h PRN for pain use to a maximum of 4x/day for up to 4 weeks. Patients will always have their regular short acting oral opioid as a backup every 2 hours PRN for breakthrough pain (but not given at the same time as FSS). For example, after FSS use if a patient still has pain, he will wait for at least 2 hours before using the short acting opioid. After at least another 2 hours if another episode of breakthrough pain occurred, he may use another dose of FSS for pain relief.

We will document the pattern of FSS use, its safety, and adverse effects in the outpatient setting. During this time, patients will have access to Supportive Care Service by telephone or in person 24/7. Furthermore, they will be able to discuss FSS use with our research team, with physicians available to discuss titration if needed.

C.5. Medication use during the study.
Stage I. The use of opioids will be recorded during the study, and may be adjusted by the clinical team as per standard of care. If patients required an opioid rotation, they will not be able to continue with stage I of the study. If patients had breakthrough pain but were not able to use FSS (e.g. between 4 hour wait period or outside of study period in which research nurses are not available), they may continue with standard of care with intravenous opioids for breakthrough pain.

Stage II. Patients will be discharged on long and short acting oral opioids. They will be asked to use FSS as first choice for breakthrough pain (up to q4h PRN, maximum 4x/day). If they had significant pain not controlled by FSS, they will be asked to use their oral medication with at least 2 h since the last FSS dose. The use of long/short acting opioids will be titrated by the clinical supportive care team.

C.6. Research staff. An orientation will be held with research staff involved in this study to introduce them with the study design and to standardize the provision of each intervention.

C.7. Stopping rules. Patient may drop out of stage I if (1) after one time FSS dose reached 1600 mcg and effective dose not yet identified, (2) discharge, (3) death, (4) no longer on opioid infusion, (5) opioid rotation required, or (6) patient wish. Treatment will be stopped or adjusted based on the patient's vital signs. If the respiratory rate is 8 or less or if oxygen saturation is less than 90% for 2 minutes, the patient will be placed on oxygen (2 liters per minute) and our service will be notified.
Patients will drop out of stage II if (1) death, (2) no longer on opioid, or (3) patient wish.

C.8. Study assessments (Tables 3 and 4).

Table 3. Summary of Study Assessments during Stage 1

	Baseline	BTP1 (IV opioid)	BTP2 (FSS)	BTP3 (FSS if needed)[10]
Demographics and baseline symptoms[1]	✓	-	-	-
Alberta Breakthrough Pain Assessment tool[2]	✓			
Pain assessment[3]	✓	0, 15m, 30m	0, 15 m, 30 m, 45 m[9], 60 m[9]	0, 15 m, 30 m, 45 m[9], 60 m[9]
Neurocognitive testing and vital signs[4]	✓	30m	30 m, 60 m[9]	30m, 60 m[9]
Opioid use[5]	-	-	✓	✓
Use of other pain medications[6]	✓	✓	✓	✓
Acute adverse effects[7]	✓	✓	✓	✓
Overall preference and global impression[8]				End of stage I

[1] patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, co-morbidities, ECSCP, CAGE questionnaire, Edmonton Symptom Assessment Scale (ESAS), personalized pain score. The study staff will retrieve the information from clinic station, and ask the patient for clarification if needed. ESAS is a validated questionnaire that measures 10 common symptoms in the past 4 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well being) using numeric rating scales.[38]

[2] ABPAT is a validated assessment tool for breakthrough pain in cancer. The initial validation study used a Delphi process. It consists of 15 questions with three having 2 items, resulting in a total of 18 questions. The questions include the following: relationship to baseline pain, last time experienced, frequency, peak intensity of the BTP (0=no pain, 10=worst possible pain) and on an ordinal scale from (1=mild, 2=moderate, 3=severe), location (body map), pain quality with specified descriptors, time from onset to peak intensity, time from onset to end of episode, cause of BTP (triggers), predictability, general relief, relief from BTP medication, satisfaction with BTP medication, onset of pain relief, and satisfaction with onset of pain relief.

[3] a 0-10 numeric rating scale that assesses pain intensity now, where 0= no pain at all, and 10=worst possible.

[4] neurocognitive testing will be conducted using finger tapping, arithmetic, reverse memory of digits, and visual memory. We will also be monitoring vitals including heart rate, respiratory rate and blood pressure and O2 saturation.

[5] all opioid use (name, dose, frequency, and use of breakthroughs) during the study, including the need for any dose escalation/reduction, will be recorded. The effective FSS dose be will recorded

[6] use of other pain medications such as acetaminophen, NSAIDs, steroids will also be documented

[7] acute adverse effects related to the use of opioids, such as dizziness, drowsiness, nausea, vomiting, anxiety itching/sneezing, and taste disturbance will be assessed using a numeric rating scale from 0-10 to assess the intensity “now”.

[8] Patient global impression will be documented by the question “after starting your new treatment, how are your symptoms (i.e. pain)?” This has been used in multiple previous studies to assess patient perceived change.[11, 12] We will also ask patients which treatment (intravenous/spray/don’t know) they prefer.

[9] if a repeat FSS dose is needed

[10] Breakthrough pain episode #3 will only be assessed if the patient did not achieve an effective dose after the first FSS dose

Table 4. Summary of Study Assessments during Stage 2

	Days 1-28 post discharge
Average pain intensity over last 24 hours[1]	Daily
Use of FSS[2]	Daily
Pain medication and doses[3]	Daily
Adverse effects[4]	Daily
Complications[5]	As they occur
Karnofsky Performance status[6]	Weekly
Ease of use and perceived effectiveness[7]	Weekly
Satisfaction with breakthrough opioid use[8]	Weekly
Study satisfaction[9]	End of study once

[1] a 0-10 numeric rating scale that assesses average pain intensity over the past 24 hours, where 0= no pain at all, and 10=worst possible.
[2] The number of BTP episodes and doses of FSS used per day will be documented. The duration of BTP episodes will also be recorded.
[3] all opioid use (name, dose, frequency, and use of breakthroughs) during this stage, including the need for any dose escalation/reduction, will be recorded. Use of other pain medications such as acetaminophen, NSAIDs, steroids will also be documented.
[4] adverse effects related to the use of opioids, such as dizziness, drowsiness, nausea, vomiting, anxiety, itching/sneezing, taste disturbance and constipation will be assessed using a numeric rating scale from 0-10 to assess the average intensity of last 24 hours.
[5] the dates and reasons for acute complications such as re-admission, emergency room visits and falls will be recorded as they occur
[6] an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity [37]. A patient self-rated version will be used.
[7] Ease of use and perceived effectiveness will be assessed using a 0-10 numeric rating scale
[8] Satisfaction with breakthrough opioid use will be assessed by asking "How satisfied were you with the sublingual spray medication, taking the side effects, logistics and pain control into account? 0-10".
[9] Study satisfaction will be assessed with the following questions, "Was it worthwhile for you to participate in this research study?", "If you had to do it over, would you participate in this research study again?", "Would you recommend participating in this research study to others?", "Did you quality of life get better by participating in this research study?", "Did you quality of life get worse by participating in this research study?"

Patients will be provided with a diary, and will be contacted by phone at least 2x per week by the research nurse to ensure data is collected properly and record the dispensed FSS based on the usage. If patients developed significant concerns, the research coordinator will notify the study PI. Patients will be asked to bring the leftover doses of FSS and return to Supportive Care center in 2-4 weeks for followup as per clinical team. Patients' diary will be checked at the time of clinic visit which is every 2 weeks during the study period.

C. 9 Disposal of unused FSS. We will follow the MDACC institutional policy used in the Supportive Care Clinic (SCC) for disposing transmucosal opioids (Appendix Q). All unused FSS will be collected from the patients and will be disposed of in the sharps container by a research nurse, with either a clinic nurse or pharmacist to witness the disposal.

C.10. Feasibility data. In addition to clinical outcomes, we will also collect feasibility data in this study, including the following:

- Rates of recruitment and retention (% of subjects able to complete stage I and II of the study)
- Reasons for refusal and dropout
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall

C.11. Patient Safety, Monitoring, and Confidentiality. During the study, trained research staff will be performing study assessments and monitoring the patients carefully throughout the study period. They will have access to study investigators and the Supportive Care Center can see these patients on the same day upon request. Patients with severe pain crisis may need to present to the emergency room. With the planned doses of fentanyl in opioid-tolerant patients, we do not expect any significant side effects.

Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board (IRB), and the Data Safety and Monitoring Board (DSMB). Patient confidentiality will be ensured by use of study numbers, secure storage of clinical data, and anonymous reporting.

D. Statistical Analysis

D.1. Power Calculation. This investigator-initiated, single arm, open-label study will enroll a total of 30 hospitalized patients. Considering an attrition rate of 25% for the reasons of but not limited to consent withdrawal, early drop-out or primary endpoint not achieved, etc, 22 patients are expected to be treated with FSS and reach the effective dose measured as % MEDD dose. We expect to enroll approximately 2-3 patients per month for this study. Thus, we expect to complete the study in approximately 10-12 months.

The primary objective is to determine the effective dose of FSS for powering future studies. After being enrolled, each patient will be treated with intravenous opioid for the first episode of breakthrough pain and up to two more episodes treated with FSS for the purpose of the primary objective. If the effective dose is not found after a total of three episodes, patients will be considered inevaluable for the primary objective. With 22 evaluable patients, a two-sided 95% confidence interval for %MEDD of effective dose will extend 2.1%, 4.2%, 6.3% or 8.4% from the observed mean, if the standard deviation

is 5%. 10%, 15% or 20% and the confidence interval is based on the large sample z statistic.

Table 5. Sample Size Justification

Standard Deviation	5%	10%	15%	20%
Confidence Interval	2.1%	4.2%	6.3%	8.4%

At the end of the study we will summarize the effective dose of FSS measured by % MEDD dose using descriptive statistics such as mean, standard deviation, and 95% confidence interval. The pattern of FSS effective dose such as episodes and number of doses will be summarized by tabulation. It is also important to estimate percentage of patients who have been treated with FSS however did not reach the effective dose. We will provide detailed description of reasons of drop-out.

Secondary endpoints include the differences in the pain response between intravenous opioid breakthrough and FSS at effective dose, safety, tolerability and pattern of FSS use, and efficacy of FSS during the first month post-hospital discharge.

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, concurrent opioids, various physiological parameters, and other collected variables such as the changes of pain score after each episode, neurocognitive testing and digital substitution, overall preference and global impression, ease of use and perceived effectiveness, satisfaction with breakthrough opioid use and study satisfaction by using proportions, medians, means, 95% confidence intervals, and other statistics as appropriate for the measure. Each endpoint may be evaluated repeatedly at each episode and during the first month post-hospital discharge. Repeated measures analysis may be employed to evaluate the change of these measures over time. The effect of treatment on the changes of these measures will also be estimated in the same model when possible. Other statistical analysis may be employed when appropriate.

E. Data Confidentiality Procedures

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart.

Collection of identifiers: We will collect and securely store patients' identifiers (including name, medical record number, and demographic specifications). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be guaranteed. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principle investigators and co-investigators, will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities. The data will be kept by the principle investigator in a locked file cabinet.

Final disposition of study records: These data will be used only for this research study data files will be destroyed 5 years after publication of the findings.

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