Title:

STOMP – Scenario-Tailored Opioid Messaging Program: An interactive educational intervention to prevent opioid-related adverse drug events in children and adolescents

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STOMP – Scenario-Tailored Opioid Messaging Program: An interactive educational intervention to prevent opioid-related adverse drug events in children and adolescents

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BACKGROUND

Pain *and* the opioid epidemic are intertwined and largely inseparable public health concerns, each affecting millions of lives and costing billions of dollars.[27,28] Many pain experts now recognize the unintentional but widespread and often devastating adverse outcomes from the recent emphasis on pain and concurrent quadrupling of opioid prescriptions.[29,30] This realization has led to policy changes and, by some accounts, a plateau in prescribing rates and opioid analgesic use.[31,32] Yet, pain remains a leading symptom for those seeking healthcare, and millions of opioids will continue to be prescribed annually as a part of multi-modal strategies to manage acute and chronic pain. This leaves an ongoing and real potential for opioid-related adverse outcomes, including accidental overdose, diversion, misuse and addiction.

Children and adolescents are particularly vulnerable to poor outcomes with high rates of pain, adverse drug events (ADEs) and opioid misuse. Up to 90% of healthy youth report recent pain for which most had taken analgesics.[33-35] Nearly 3 million opioid prescriptions are dispensed annually to manage pain in this population.[1-3] These early pain and opioid exposures not only pose immediate threats to the well-being of children but formulate analgesic perceptions that contribute to future use, misuse and abuse. We and others have found that legitimate use of opioids is highly associated with later misuse.[23,36,37] Adolescents who are prescribed opioids by 12th grade are 33% more likely to misuse opioids by 23 years of age – even if they have no history of illicit substance use.[23] Higher over-the-counter analgesic use during youth also doubles the risk of later opioid misuse, underscoring the relationship between pain and the potential for opioid misuse.[36]

An important challenge is to test and implement new strategies that will enhance parents' understanding of critical and life-threatening risks while ensuring appropriate pain management. This will require transforming the way providers give information at the time of prescribing. The rates of serious analgesic-related ADEs in children and adolescents run parallel to prescribing rates.[38-41] More than 21,000 emergency room admissions[4] and hundreds of accidental overdose deaths occur among our youth annually.[40] Every day, 237 adolescents visit an emergency department for an opioid-related event[42] and teens are at particular risk for serious opioid-related medical outcomes.[41] Of note, children's personal prescriptions have been found to be responsible for the vast majority of *unintentional* opioid-related toxicity events in this group.[43] These data underscore the risk that prescription opioids pose to children and adolescents.

Poor Analgesic Knowledge is associated with Risky Opioid Use

Widespread parental uncertainty and lack of knowledge about analgesics pose serious risks for children and adolescents. Poor understanding leads some parents to withhold analgesics altogether in order to reduce the known or uncertain risks to their children. Conversely, 1 in 10 parents has admitted to giving more than the prescribed doses[44,45] and some continue giving opioids even when excessive sedation (i.e., the earliest sign of toxicity) is present.[7] We have found that risky opioid behaviors reflect in large part, parents' strong preference to relieve their children's pain.[46] However, findings that parents often failed to recognize and respond to signs of toxicity prior to their children's accidental opioid-related deaths and neurologic injury[9,11,47] emphasizes the need for improved understanding to prevent opioid-related morbidity and mortality in children.

Another critical challenge is to enhance parental understanding of the critical risk that is posed by keeping left-over opioids unsecured in the home setting. Easy access to personal, family or friends' prescriptions provide the most common source for adolescents who misuse opioids.[17] One third of adolescents misuse their own past prescription and 56% that of a friend or family member who, in 80% of cases had the drug prescribed to them.[12,13,36,48-51] Thus, healthcare providers are the most common original source for prescribed opioids that are misused by adolescents. Importantly, 54 to 90% of prescribed opioid doses have been found to be left-over after acute pain treatment in children[18,19,52] and 3 out of 4 middle-schoolers have unsupervised access to risky medications.[17] More than half of parents admit to keeping their children's left-over opioids in their homes, and nearly 1 in 10 use them for other family members.[21] Nearly 3 of 4 adults endorse saving their own left-over pain relievers after initial use.[53] Of concern, only one third of parents with opioids in the home report their safe storage.[54] These unsafe practices are alarming since retention of left-over opioids and their unsupervised access are top risk factors for adolescent opioid misuse.

Analgesic Self-Efficacy, Competency and Pain Outcomes

The need for pain relief is the most common motivation for parents who give opioids to their children as well as for opioid misuse among adolescents and young adults.[12,15] Up to one third of youth report long-lasting aches and pains[33,35,55,56] and pain remains a leading cause for unplanned pediatric healthcare visits.[34,57-60] Parental motivation to relieve their child's pain and their worry about unrelieved pain are highly associated with the number of prescribed opioid analgesic doses they give their children.[46,61] Our Co-I, Dr. Boyd and colleagues have reported that opioid misuse among our youth is largely motivated by a need for pain relief and is influenced, in part by the perception that opioids are safe when prescribed by a doctor.[15] Even when under the care of a physician for pain, 1 in 4 adolescents are non-adherent to their opioid prescriptions, sometimes doubling their doses to relieve pain.[62] The gap between how drugs are meant to be used and their actual use is concerning given the amounts of opioids that remain unused after treatment of acute pain.[18,19]

Evidence suggests that parents lack competence in managing pain and that this contributes to poor pain outcomes in children. For instance, suboptimal relief is common among children who are treated for acute pain with up to 22% reporting persistent pain for weeks or months after surgery.[57,58] Parents' analgesic administration correlates only poorly to moderately with the child's pain level[63-66] and some parents discontinue analgesics despite ongoing pain symptoms, leaving their children with untreated pain.[44,59] Parents who are uncertain about analgesic effects often ignore pain signals and undertreat their child's pain.[67] Lack of competency is concerning given that most opioid prescriptions are written to be given as needed (i.e., PRN) which can contribute to increased opioid-related mortality risk and early discontinuation.[68-70]

Parental competency is particularly crucial since children's self-pain management and opioid misuse reflects learned behavior. Adolescent's self-appraisal of pain and their analgesic use mimics maternal behaviors.[71] Self-treatment of pain starts in early adolescence and analgesic attitudes and knowledge are influenced primarily by parents who are role-models for both use and misuse.[72] Children whose mothers used analgesics are 3 times more likely than others to self-treat their own pain even when adjusted for degree of pain.[73-75] Since mothers often share their own prescription medications with their teens[71] it is not surprising that more than two thirds of teens also share their prescriptions with a friend.[37,76] A majority of children who self-treat their pain with analgesics exhibit poor knowledge about these drugs and most obtain their information from a parent.[77] Given that most adolescents who admit to misusing opioids do so before they enter college and while still under the supervision of a parent, preventive efforts must begin with parents.

OBJECTIVES AND AIMS

The goal of our research is to improve opioid analgesic safety *and* efficacy by optimizing opioid risk understanding, informed decision-making, and disposal behaviors among parents of youth who are prescribed these agents for home use. We recently pilot tested an interactive, multi-media intervention (Scenario-Tailored Opioid Messaging Program - **STOMP)** that presents clinically relevant scenarios together with analgesic decision-exercises and immediate feedback to enhance risk perceptions and analgesic decisions.[25] Parents randomized to the intervention gained immediate and sustained improvements in opioid risk knowledge and perceptions and made better decisions about *both* when to give *and* when to withhold opioids. The current proposal builds on this preliminary work by enhancing the intervention with tailored storage and disposal risk messages and testing the enhanced STOMP with regard to the following aims:

Aim 1: To assess the efficacy of the STOMP intervention to improve opioid risk understanding and decision-making among 840 parents whose children aged 5-18 years are prescribed opioids for acute pain after surgery. We hypothesize that parents randomized to the intervention will exhibit; **(H1)** Greater and sustained understanding of opioid risks (e.g., perceived seriousness of signs of toxicity, potential for poisoning, misuse); and **(H2)** Improved decisions regarding when it's safe to give opioids (i.e., pain present *and* ADEs are absent), when to withhold opioids (i.e., symptoms of excessive sedation are present), and when to stop and dispose of left-overs (i.e., functional recovery evident).

Approach Aim 1: We will use a randomized controlled trial (RCT) to test the ability of our interactive, scenario-tailored opioid risk messaging program (STOMP) to enhance parental risk perceptions and improve the safety of situational-based opioid use, storage and disposal decision-making.

Aim 2: To demonstrate that the interactive STOMP intervention will enhance parents' safe and effective use of opioid and adjuvant analgesics to manage their child's pain and facilitate functional recovery. We will collect analgesic administration and pain outcome data for up to 30 days postoperatively to measure the clinical effect of the STOMP intervention. Opioid and non-opioid use and child pain outcomes will be compared to test the hypotheses that, compared to controls, the intervention will; **(H3)** enhance parents' **a**) analgesic self-efficacy and **b**) adjuvant analgesic administration, and **c**) opioid storage behaviors, and will **(H4)** improve the child's pain outcomes (reduced pain interference, earlier opioid discontinuation and return to function, and decreased opioid adverse effects).

Approach Aim 2: We will use longitudinal postoperative data to assess the sustained ability of the STOMP to build parents' self-efficacy and competency in using opioids and non-opioids to manage pain and achieve better pain outcomes (both pain relief and lower adverse effects) for their children. Our tailored messages are designed to exploit the synergy between heightened risk appraisal and self-efficacy and to provide the level of opioid risk and benefit knowledge needed to promote decisions that will reduce both risk and pain.

Aim 3: To demonstrate that providing parents with a cost-efficient, yet environmentally appropriate, disposal receptacle for leftover opioids (a zip-lock baggy of used coffee grounds with instructions)[26] will increase disposal rates among parents randomized to this intervention. We will conduct a four-group factorial analysis to test the hypothesis that **H5)** "nudging" parents by way of a salient disposal means will increase the rate of opioid disposal either in isolation or in conjunction with the STOMP (i.e., risk knowledge) intervention.

Approach Aim 3: We will embody the "nudging" approach by providing parents with a how-to-dispose kit that a) eliminates uncertainty about whether action is needed, b) makes the required steps concrete, and c) creates an injunctive norm that use of the kit is expected behavior. Behavioral economic theorists have emphasized the importance of shaping the choice architecture to make preferred actions more salient, easier to perform, and/or the implied default or expected behavior.[112,113] Nudges such as making healthy food choices readily accessible have been shown to increase their consumption.[114,115] Providing a simple, handy means to properly dispose of left-overs could, therefore, motivate disposal rates over and above what other, less convenient methods have achieved thus far. This "nudge" would not only minimize the steps needed but would also serve to enhance the perception that disposal is the expected behavior (subjective norm). Although commercially available drug disposal pouches have recently become available on the market (e.g., Deterra®), their impact on disposal rates has not been tested and the required purchase could impose a new barrier to action.Our nudge will in effect boost parents' response efficacy by putting the risk reduction behavior within their immediate control. We will use a four group factorial design and randomize half of parents in *both* the control and STOMP intervention groups to receive our nudge intervention to motivate disposal of left-over opioids after the child recovers from the acute pain event.

Aim 4: We will examine the potential effect of the "Start Talking Opioid Consent Document" (mandated by law on June 1, 2018) on parental opioid risk knowledge and perceptions, and disposal intentions.
Approach Aim 4: We will modify our data collection to include an item indicating whether or not the parent received and signed the new "Start Talking Consent". We will account for receipt of this consent document in our models for Aim 1 & 3, and will examine (in univariate analyses) whether parents who received the consent differed with regard to risk perceptions, disposal intentions and behaviors.

Aim 5: We will examine the potential effect of the Michigan opioid prescribing law (limits opioid prescription to 7 days beginning July 1, 2018) on postoperative opioid consumption, opioid left-overs and pain outcomes in children.
Approach Aim 5: As we are already collecting data regarding prescribed amount of opioid and opioid consumption, the approach here will involve only an addendum to analysis. We will account for the effect of the law by adding prescribed amount of opioid in our model for Aim 2; we will conduct a univariate analysis to test the hypotheses that (adjusted for surgical procedure), 1) opioid **consumption will decrease after the law**

is in effect 2) left-over opioid volume will decrease after the law is in effect; and 3) there will be no difference in pain interference at day 14 after the law is in effect.

POTENTIAL RISKS AND BENEFITS

Potential benefits of the proposed research to the subjects and others: Our opioid messages were developed with the guidance of pediatric pain and risk communications experts. Our preliminary data showed that the intervention enhanced parents' opioid risk awareness and perception while preserving and enhancing their ability to make effective decisions to manage pain. Participation in our studies thus offers parents the potential benefit to gain knowledge and awareness of opioid risks as well as to develop effective pain management and risk reduction competency. The knowledge gained from our studies is directly translatable into practice with the potential to reduce the risks of opioids to children and communities.

Potential risks and protections: As such, the intervention poses only minor over minimal risk to parents and children with regard to potential breach of confidentiality.

To reduce potential risk to children, their routine management will not be altered and we will exclude those who cannot, by nature of their underlying condition be safely prescribed the usual combination of opioids and non-opioids for postoperative pain. We will record all adverse events and will review non-serious AEs quarterly and serious AEs as they are learned to determine the relationship to study participation and actions needed, if any.

We will minimize the risk for breach of confidentiality of the parent and child by training of study team members, use of electronic and physical security measures for data capture and storage, and by obtaining a Certificate of Confidentiality. Unique study identifiers (ID) for each subject will permit linkage between surveys and follow-up data while maintaining the privacy of parents and children. ID links between subjects and their data will be kept separately in an encrypted file with access limited to only trained research personnel. Data will only be stored on fire-walled databases which will limit access only to those assigned appropriate permissions.

Data and safety monitoring plan (DSMP): Our study specific DSMP provides details of how we will collect, review, evaluate and manage adverse events that may happen as part of routine care or study participation. Of particular note, we will review the child's outcome data (up to 30 days postoperatively) for any adverse events. These will be reviewed, compiled and reported to the IRB and the NIH as outlined in the DSMP.

SUBJECT ELIGIBILITY

Sample inclusion: We will include 840 English speaking parents of all races and their cognitively intact children (boys and girls aged 5 to 17 years) who are undergoing painful procedures and who are expected to be prescribed opioids for acute, short-term postoperative pain following elective ambulatory or short stay (<48 hours) surgical procedures. We previously found that children who undergo general and orthopedic surgery are at high risk for moderate to severe pain, typically require opioid analgesics, and have higher opioid consumption compared to other surgical procedures.[7] Dr. Veliz, our Co-I also found that children who play sports have high opioid prescribing rates and higher rates of misuse.[117] Given many prescribing changes in the perioperative setting, some children who are expected to experience moderate to severe pain may not end up going home with an opioid prescription. We will not withdraw these children as their parental pain management knowledge and actions remain of great interest for this study. Retaining these children in the study may reveal important differences about parental analgesic risk perceptions, changes in pain outcomes over time, and will enable us to better address the new Aim 4 (which will also assess the impact of the new MI opioid prescribing law).

Sample exclusions: We will exclude children (and their parents) who are undergoing emergency procedures, cannot self-report their pain, have a hematologic-oncologic, kidney or liver condition (precluding the usual analgesic prescription patterns), or who have been treated with chronic opioids.

Recruitment, informed consent/assent: Comprehensive written consent will be obtained only by our trained research personnel from all parent participants and assent from children who are developmentally able to

understand the nature of the study. Eligible parents and children will be consecutively recruited and consented before or during the child's surgical visit and prior to all procedures. To best assess the impact of the intervention on follow-up decisions while controlling for parent characteristics, we will recruit the parent (mother or father) who self-identifies as making the majority of pain management decisions after discharge. Recruitment will take place in the preoperative surgery or anesthesia clinic rooms where patient privacy is fully protected.

STUDY DESIGN AND PROCEDURES

Design and Hypotheses: We will use a prospective, randomized, controlled, longitudinal, factorial design to test the following hypotheses:

Hypothesis (H)1: Parents who receive the STOMP intervention will exhibit a greater and sustained understanding of prescription opioid risks (e.g., seriousness of toxicity, potential for poisoning, misuse).

H2) Parents who receive the STOMP intervention will demonstrate improved decisions regarding when it's safe to give opioids (i.e., pain remains present *and* ADEs are absent), when to withhold opioids (i.e., symptoms of excessive sedation are present), AND when to stop administration and dispose of left-over opioids (i.e., functional recovery evident).

H3) Parents who receive the STOMP intervention will demonstrate higher **a**) analgesic self-efficacy, **b**) higher use of adjuvant non-opioids and **c**) safer opioid storage behaviors (family and child prescriptions).

H4) Children in the intervention group will have improved pain outcomes (reduced pain interference, earlier opioid weaning, early return to normal function and fewer opioid-related adverse effects).

H5) Provision of a simple, tangible means to dispose of unused drug will increase the rate of opioid disposal independently of and in conjunction with the STOMP (i.e., knowledge) intervention.

Outcomes

Aims 1 & 4) Parental opioid risk knowledge and perceptions and safe and effective opioid decisions (i.e., situational decisions to give, withhold, stop and dispose of opioids to manage symptoms and risks)

Aims 2 & 5) Parent analgesic self-efficacy, analgesic adherence (total doses of opioids and non-opioids), storage behaviors, and child's pain outcomes (pain interference and adverse events)

Aims 3, 4) Disposal intention and behaviors

Main Measurements

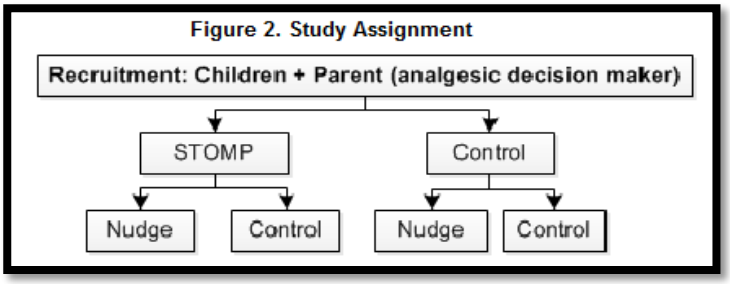
- **Opioid risk knowledge:** Parents' awareness of common and critical opioid risks will be assessed using the ADE knowledge instrument, where parents use nominal responses to record which are possible when a child is taking opioids or when opioids are in the home.[7,8,124] These items were developed with established content and face validity and, together with risk perceptions, were found to have predictive validity.[7,8]
- **Opioid risk perceptions:** Perceived seriousness of opioid risks (e.g., excessive sedation, misuse, addiction) will be assessed using a 6 point Likert scale where 0=Not serious to 5=Extremely serious.[7,8,46] We have previously demonstrated predictive validity of these items toward situational and analgesic decisions.[7,8,46] Perceived risk severity has been shown to predict intention and health behavior.[82]
- **Opioid decisions:** Situational decisional exercises will be used to assess parents' safe and effective opioid use. We previously demonstrated that parent decisions are strongly associated with risk knowledge, perceptions and preferences, and with postoperative analgesic use supporting their construct and predictive validity.[7,8,46] The first scenario depicts the child with high pain (7 out of 10 on the FACES Pain Scale - the commonest threshold parents use to treat pain)[46,125] and no signs of ADEs. This exercise will be used to measure parents' willingness to give the prescribed opioid to a child with no evident risk (i.e., safe and effective use). A second scenario depicts a child with the same degree of pain but also with the earliest warning of toxicity, excessive sedation. This exercise will be used to assess the parent's decision to withhold the prescribed opioid in an unsafe situation. A third scenario will present a child with low pain (FPS=3) and returning to usual function. This will assess the decision to discontinue the opioid and dispose of the remaining drugs. A final scenario will present a child at risk for poisoning or misuse due to easy

access to opioids. This will assess parents' opioid storage and disposal decision-making (their own and the child's). Opioid decisions will be coded as binary data (give/withhold, keep/dispose, safe/unsafe).

- **Analgesic self-efficacy:** Parents' analgesic self-efficacy will be measured using a six item scale where parents will score their confidence to safely and effectively give and stop analgesics when managing their child's pain and other symptoms.[126-128] Self-efficacy is the perceived confidence to perform specific behaviors to attain effective health outcomes.[129] Measures of medication self-efficacy mediate symptom management and health behavior and predict medication behavior and therapeutic change.[130]
- **Opioid storage and disposal behaviors:** We will use a modified Opioid Storage self-report survey[54] to assess parents' opioid storage and retention intentions and behaviors. The survey assesses the frequency (i.e., never to always) with which parents use secure locations to store their own and their children's active and past prescribed pain medicines. The survey also assesses parents' perceptions of benefits and barriers to safe storage. We will modify the survey to ask about parents' opioid storage practice (current and planned), their risk perceptions of opioid access in their home. and how they plan on disposing of the child's current left-over opioids. Meta-analyses show that health intentions are moderately correlated with actual behavior and that this association increases when the risk behavior is within the control of the subject *and* when expected behavior change and follow-up is <5 weeks post-intervention.[106] Further, self-report has been universally used to ascertain storage and disposal behavior[54,131,132] and will therefore be used as our primary outcome measure given the obvious challenges in obtaining an independent confirmation of disposal. However, to validate and support our self-report measure, we will ask all parents who indicate disposal intention to submit a photo of the disposal "*as a means to help us better understand whether and how parents get rid of left-overs*". This innovative, feasible, albeit exploratory approach will avoid the potential confounding that other instruction or methods might impose (e.g., bring back opioids for disposal). Disposal outcome will be reported as Retained/Disposed.
- **Pain interference:** The Parents' Postoperative Pain Measure-Short Form (PPPM-SF)[133] will be used to measure the degree to which pain interferes with the child's functioning (scored 0-10 with 10=most pain interference) each post-op day. This survey has excellent internal consistency (α 0.85)[133] and agreement with self-reported pain intensity in children 4 to 17 years.[134] The 8-item PROMIS pain interference proxy measure will also be used to measure overall pain interference at the end of 1 week.[135-137]
- **Child's self-reported pain intensity:** Parents will record the child's self-reported pain intensity prior to analgesia using the r-FPS (0=no pain to 10=worst possible pain) which reliably assesses the degree of pain in children as young as 4 years of age.[138] Average 3 and 7 day pain scores will be calculated.
- **Adverse side effects:** Parents will document all analgesic-related side effects and their calls or return to the hospital (reasons, changes in care).[7] We will also review the clinic notes (30 days) for surgical and analgesic-related calls or return visits to the clinic or hospital.
- **Analgesic adherence:** All parents will use a semi-structured diary to record postoperative analgesics administered (date, time, dose), the child's self-reported pain score prior to each analgesic, adverse effects (as they occur) and the PPPM-SF (daily recording only). The diary method is recommended by the PedIMMPACT clinical trials outcome measures for children,[139] and has been widely used in postoperative, longitudinal pain studies.[8,46,63,67,140] We have previously found excellent associations between documented doses, invasiveness of surgery, and child's pain scores, supporting the construct validity of parents' analgesic recordings.[8] Additionally, as we have done previously, parents will be instructed that their recordings may help them track the child's medications and recovery. Parents will also be informed that we will use their information to help us better understand the children's unique experiences after surgery since individual children vary in how much pain they have and how much medicine they need. In this non-biased manner we expect greater reliability of recordings, similar to studies and recommendations from medication adherence studies.[141] Opioids will be converted to oral morphine equivalents, and opioid and non-opioid consumption will be reported as total mg/kg given (in the hospital and at home). Adherence will be reported as the percentage used of the total opioid and non-opioid doses prescribed.[8,46] Duration of opioid use will be calculated as number of days (including fractions). The number of left-over doses of opioids will be calculated at discontinuation (amount dispensed minus amount used).[19]

Measurements of Contributing Factors

- **Key biologic and other characteristics of the child and parents:** The sex and race of the parent and child will be recorded. We previously found a moderating effect of female sex and parent role on analgesic decision-making and will account for these and other parent and child factors in our models.[46]
- **Parent health literacy:** We will assess the parents' health literacy using the REALM-brief which has established reliability and validity in adults[142] to control for this factor in our models.
- **Pain history and opioid familiarity:** History of parent and child pain, their opioid and non-opioid use as well as preoperative opioid presence in the home will be assessed with simple categorical items. Opioid familiarity will be dichotomized to include opioids used and/or present in the home versus not used or present.[8,46] **Familiarity with opioid use disorder** (others and those in household) will be assessed using selected items derived from the Drug Abuse Screening Test (DAST-10).[143,144] There is a conceptual difference between knowing someone who has struggled with OUD and having someone with OUD who is in the household or visits the household. Each of these items may or may not contribute to the parent's opioid management and retention of opioids. Two items will therefore be included to assess familiarity. Additionally, we will assess parental perceptions of the appropriateness of opioid misuse (i.e., sharing or later use) with items in the pain history and opioid familiarity survey.



- **Pain relief preference (PR-Pref):** This instrument assesses the parents' desire to provide pain relief relative to their desire to minimize ADE risks for their children. The instrument includes 6 risk–benefit items[7,8,46] similar to those used to assess the importance patients place on chronic medication benefits versus their concern for adverse effects.[145-147] Agreement with each statement is ranked on a 5 point Likert scale from strongly disagree (-2) to strongly agree (+2), to yield a total score ranging from -12 to +12, where lower numbers indicate a preference for risk avoidance, higher numbers pain relief, and the middle range, indifference or ambivalence.[145,147] We previously have demonstrated the instrument's internal consistency, construct and predictive validity (higher scores predict parental opioid administration).[46]
- **Surgical factors:** The child's procedure, prior injury, duration of surgery, all perioperative analgesics given and details of the child's prescription and analgesic instructions will be recorded from the medical record. We will also document whether or not the parent signed and received the Opioid Start Talking Consent document, and the date/time it was given.

Study Procedures

Group assignment: Parents will be randomly assigned a priori by computer generated randomization to either the Control Group (i.e., Routine provider written/verbal analgesic instruction) versus the Intervention Group: (i.e., Routine provider information plus the STOMP feedback). Parents in these groups will be further randomized so that 50% of STOMP and 50% Controls will receive the "nudge" intervention after completion of all baseline and Time 1 assessments (see Figure 2). We will stratify the randomization by surgical service to account for potential differences in clinic instruction.

Table 1 depicts the sequence of study assessments.

Table 1. Sequence of study assessments

Measures	Test	Time 0 Baseline	Time 1 (Immediately Post-Session)	Time 2 (3 days)	Time 3 (7 days)	Time 4 (14-21 days)
Demographics		x				
Pain & Opioid History		x				
Familiarity re opioid abuse items		x				
Health literacy		x				

Pain relief Preference		**x**		**x**		**x**
Opioid knowledge/ risk perceptions	H1	**x**		**x**		**x**
Opioid storage, misuse risk perceptions		**x**	**x**	**x**		**x**
Scenario (situational) decision-making	H2	**x**		**x**		**x**
Analgesic self-efficacy	H3a	**x**	**x**	**x**		**x**
Pain interference	H4			**x**	**x**	**x**
Opioid storage behavior	H3c	**x**			**x**	**x**
Opioid left-over disposal	H5				**x**	**x**
Analgesic use and ADEs	**H3b**			**X (diary data)**		
Perioperative data		**x**				

Time 0 (Baseline): Baseline assessments and interventions will take place in our surgery/anesthesia settings after routine instructions have been given with the dispensing of prescribed opioids (routine practice in our setting is that the parent picks up the prescription when the child is taken to surgery). In this way, provision of STOMP will occur in proximity to opioid prescribing when education should ideally take place clinically. Privacy of all patients/parents will be fully protected in these areas. All parents will complete the baseline surveys and assessments using a Qualtrics survey link via dedicated iPADs to ensure consistency, completeness and privacy. Parents will enter only an assigned, unique ID number with no other identifying information. Parents will record their own demographics and pain history, opioid familiarity, past use and storage practices, opioid risk knowledge, perceptions, the DAST-10 items, PR Pref, and self-efficacy. STOMP vs. Control info/feedback will be provided together with each decision exercise. Health literacy will be assessed by trained research assistants. Our pilot showed that completion of similar surveys and decision exercises took parents 20-25 minutes without difficulty or interruption during this timeframe. The electronic survey will include appropriate logic and prompts to minimize the potential for missing items.

Time 1: Immediately after the decision exercises and Intervention session, all parents will repeat the analgesic self-efficacy assessment.

Discharge through end of prescription opioid use: Parents will be instructed on the use of the diary prior to discharge. Parents will be instructed to document the child's pain score prior to each analgesic, and to record every analgesic dose administered as well as adverse events as they occur. To improve the reliability of recordings and minimize loss to follow-up (LTF), we will send regular text reminders to encourage parents' real-time pain assessments and medication tracking.[148] To enhance accuracy in recordings, parents will be reminded that all children are different and that their diary data will not only help them track the child's medicines, but will help us to better understand children's needs and experiences after surgery.

Time 2: On day 3 all parents will repeat the study assessments (PR pref, self-efficacy, opioid knowledge and risk perceptions, and decision-making) and will document pain interference via emailed web-link survey.

Time 3: On day 7 parents will document pain interference and will complete the storage and left-over intention assessments. Parents who indicate an intention to keep left-overs will use semi-structured and open-ended responses to provide their reasons for retention. Those who indicate a positive disposal intention will be asked how they plan on disposing and to email or text a picture of the disposal process (including their unique study ID). So as not to confound parents' motives, we will inform all parents that this picture will help us better understand how parents dispose of unused pain medicines when they do so. To determine the feasibility of this additional measure, we will ask whether parents have the means to send a picture (e.g., smartphone or email). Lack of access should present a barrier for only few parents in our setting since 92% recently reported having a smartphone which is higher than the national average (64% overall and 85% of young adults in 2015).[149]

To determine the accessibility of the nudge at the 7 (or 14) day survey (i.e., that they did not throw the baggy out), we will also ask parents assigned to this intervention to report a unique identifier included with the baggy instructions[150] and parents will record their qualitative perceptions about this intervention.

Parents will be asked to return the diary at 7 days or at the end of opioid use (whichever is later) either by bringing to the return visit or by using a stamped return envelope (a phone call or text reminder will be sent to improve return rates, and an incentive will be given upon diary receipt).

Time 4: Parents will be re-contacted 14 to 21 days after hospital discharge for a final assessment of PR pref, opioid risk knowledge and perceptions, perceived risk of misuse and diversion, as well as a final assessment of storage and disposal behaviors.

DATA COLLECTION, MANAGEMENT AND QUALITY

The following data will be retrieved from review of the child's electronic medical records: opioids and non-opioids given during the brief hospital stay (total oral morphine mEq mg/kg), surgical procedure and duration, nature of the child's condition or injury, and 30 day adverse events.

Each subject will be assigned a unique study ID number. All surveys, the parent diary and data collection sheets will be labeled with this unique study ID only. No information that could identify subjects will be recorded on any survey or datasheet. The list connecting the unique ID numbers to subject identifiable information will will be maintained in a separate data file on a password protected departmental (maintained by UM) computer with secure login only accessible to study team members. Signed consent forms will be kept separately from all data collection sheets.

Data entry and management: All baseline and follow-up survey data will be entered by parent participants directly into the University of Michigan Qualtrics Survey Data Account which incorporates Level 3 Security, that is, information that is restricted only to University parties who are given permission directly by the University of Michigan survey owner (i.e., the Principal Investigator). Parents will not record any identifying information in these surveys, but will instead enter their own unique study ID. In this manner, parents' survey responses will be known only to them.

Survey data will be downloaded to our protected servers on a weekly basis and later merged (via unique IDs) with the parents' diary data and the child's perioperative data. In this manner, not even the researchers will know the private answers of individual parents and their personal confidentiality maintained.

Health literacy assessments, hospital data collection, and data management (entry of data from diaries and hospital) will be conducted only by trained research team members. These data will be identified with the unique ID (linked separately to patient identifiers).

Data Quality Assurance Plan: All data collected and hand entered by trained personnel will be double checked for accuracy and reliability. Training and oversight of data management processes will be provided by our highly experienced pediatric project manager, Monica Weber, BSN, CCRP. Merging of data (baseline, follow-up surveys, diary data, hospital data) will be managed by the project manager with oversight from the PI (Voepel-Lewis) and quality checks from independent and trained team members. The study manager will ensure adherence to the randomization assignments and a non-investigator team member will enter the randomization code (I vs. C) into the database after merging of data. However, analysts will be blinded to study group assignment.

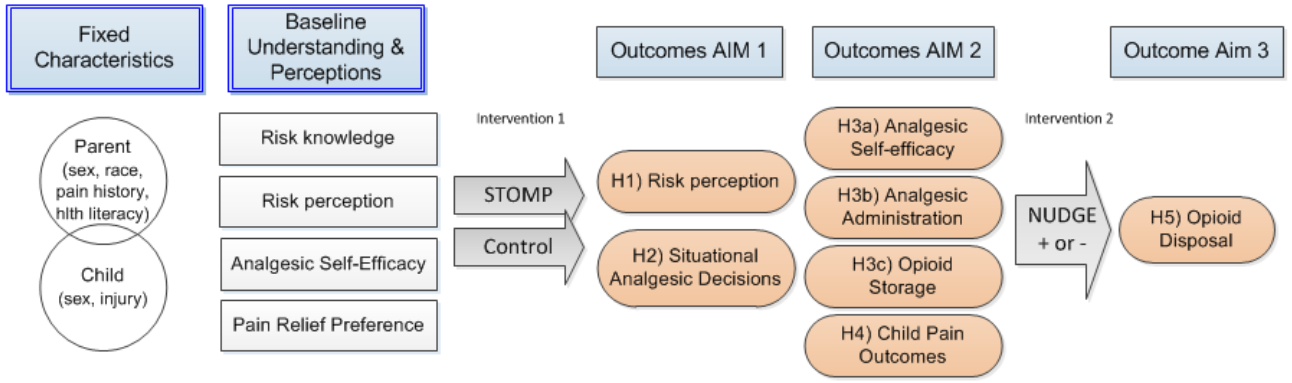
DATA ANALYSES

Generalized estimating equations (GEE) will be used to model both continuous (i.e., negative binomial and Gaussian) and binary outcomes (i.e., binomial) for each aim.[151,152] All models will include both time-varying measures (e.g., opioid risk perceptions) and time-invariant covariates (e.g., sex, race, etc.) and will use either an independent or exchangeable correlation structure to correct for within subject correlations. Analyses will use Stata's (STATA/SE v.13; STATA Corp., College Station, TX) 'xtgee' option as appropriate. All hypotheses per our conceptual model (Figure 3) will be tested at the 0.05 alpha level. Standardized coefficients and adjusted odds ratios will be computed to determine the relative effect size for each of the key independent variables.

Missing data: The use of electronic surveys with built-in prompts for incomplete items will reduce the potential for missing responses. In-person collection of critical data such as sex, race, and health literacy will minimize missing covariates. Parents will be contacted by phone, text or email (per their preference) to promote ongoing recording of postoperative data and to reduce the potential for missing data and LTF. We have used similar procedures to successfully ensure complete data and minimize loss to follow-up.[8,25,94,153]

Any remaining missing data on surveys (e.g., DAST or PR-Pref) will be examined for randomness and we will impute only partial non-response (e.g., missing 1 to 2 items of PR-Pref or DAST-10) using a horizontal (i.e., per individual) approach. Largely incomplete or total survey non-response will be examined for non-randomness and potential bias (e.g., missing DAST-10). These missing data will not be imputed, however, outcomes will be compared for persons with missing vs. complete data to determine selection bias. We have adjusted our sample size to account for the potential for missing data. We will use pairwise deletion to use the available, complete cases to test our hypotheses.

Figure 3. Conceptual Model of our Research and Hypothesis Tests



Aim 1: Using GEE, we will examine the association between the STOMP intervention and the outcomes (risk seriousness perception, and situational opioid decisions). It is hypothesized that, compared to controls, parents who receive the STOMP intervention will have 1) enhanced risk perceptions (continuous measure) and 2) improved opioid decisions (scenario-based). Hypotheses 1 and 2 will be tested using both main and interaction effect models. In the main effects models, STOMP group assignment is our binary independent variable of interest. Time by intervention interaction effect models will be used to examine whether the STOMP group has improved opioid risk perceptions and decisions at the follow-up assessments compared to the control group. It is expected that there will be no difference between the intervention group and control group at baseline. However, significant interaction effect terms should emerge for the intervention group at the follow-up assessments.

Aim 2: We hypothesize that the STOMP intervention will **Ha**) improve parents' analgesic self-efficacy, **Hb**) increase their use of non-opioid adjuvants, **Hc**) improve safe storage of opioids, and **H4)** will lead to better pain outcomes in children (lower pain interference, earlier opioid weaning, earlier functional return, and fewer ADEs). Main effects models that control for relevant covariates (i.e., child and parent characteristics [see Aim 1], procedure, in-hospital analgesic use) will examine whether STOMP assignment significantly effects each outcome of interest. Moreover, to examine how the STOMP intervention influences each of the pain-related outcomes, multivariate multiple regression (i.e., Stata's mvreg command) will be used to determine if there are unique differences in how the intervention influences each of these related pain outcomes, and whether self-efficacy moderates pain management and outcomes.

Aim 3: As with AIM 1 and 2, GEE will be used to test our hypothesis (**H5**) that the "nudge" intervention group will be more likely to dispose of left over opioid analgesics compared to the control group, adjusted for multiple confounding factors (e.g., sex, pain history, PR-Pref, Risk Perception, etc.). Both a main effect and interaction effect model (STOMP by "Nudge") will be estimated to examine the effects of both the STOMP and Nudge interventions and their combined effect on the outcome, disposal.

Sample Size Determination

We based our sample size on the most conservative estimate needed to detect a small effect of the STOMP intervention on parents' opioid administration and the child's pain interference reduction (Aim 2). Previously we found a small to medium effect (based on Cohen's criteria) of parental preferences and other main constructs on opioid use after surgery.[46] In order to obtain a similar effect size (eta squared = 0.033) of our intervention on opioid use in a model of up to 15 covariates ($\alpha = 0.05$; $\beta = 0.20$) we would require a sample size of 581 participants. Allowing for a potential LTF of approximately 30%, similar to our recent pain studies[8,153] we plan to approach 840 parents for this study. This sample size will also be more than sufficient, in a factorial design, to

test for the expected larger effects (estimated eta squared = 0.14) of our interventions on parents' decisions to safely withhold and to dispose of opioids (i.e., sample needed = 147).

Timeline

<table>
<tr><th colspan="2">Year 1</th><th>Year 2</th><th>Year 3</th></tr>
<tr><td>Intervention revisions, pilot testing</td><td colspan="2">Recruitment and longitudinal follow-up (approximately 24 months)</td><td></td></tr>
<tr><td colspan="3"></td><td>Analyze data; Manuscript preparation</td></tr>
</table>

Anticipated Problems and Solutions:

The main potential limitation to achieving our aims is the efficient recruitment of eligible parents/children and the potential LTF. Modest monetary incentives will be given for baseline and follow-up surveys which we've found to enhance recruitment rates and minimize LTF in high enrollment studies (Up to $50 for completion of all parts of the study: $20 for completion of 3-day follow-up; $30 for return of diary and follow-up surveys).[95,153] Incentive will be mailed to subject as one lump sum at the end of subject participation. Parents will receive reminders by text, phone or email (per preference) which we have used to successfully reduce LTF and boost return of diaries in our previous longitudinal pain studies.[8,46,153] We will evaluate our recruitment and retention rates quarterly to determine whether we are on target or whether we need to enhance our recruitment plan.

Dissemination Plan:

A major strength of our proposal is that the knowledge gained will not simply have academic importance but also the potential to be readily translated into settings with high opioid prescribing rates for children and adolescents (e.g., orthopedic surgery, emergency room settings, dental, and sports medicine). Our multi-disciplinary team is well positioned to disseminate findings at important national meetings such as the American Academy of Pediatrics and Society of Pediatric Nurses (Voepel-Lewis), Societies of Pediatric Pain Medicine and Pediatric Anesthesiology (Voepel-Lewis, Tait), Pediatric Orthopedic Society of North America (Farley), American College of Sports Medicine (Grant and Veliz), and the American Society of Addiction Medicine (Boyd, McCabe), College on Problems of Drug Dependence and the Society for Prevention Research (Boyd, McCabe and Voepel-Lewis). We expect this research to yield multiple publications in major medical and pain management journals. Our intent is to influence the way opioid risk information and advice is provided to parents and ultimately patients, themselves, such that opioid-related morbidity and mortality is minimized.