COMIRB Protocol

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Protocol #:	**16-2538**
Project Title:	**Parent-Reported Symptom Assessments in Children Taking Multiple Medications**
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I. **Hypotheses and Specific Aims**:

An increasing number of children with complex chronic conditions (CCCs) who have intractable illnesses or multi-organ dysfunction are exposed to daily polypharmacy.[1-3] Parents of children with polypharmacy often administer 5 or more medications each day, sometimes for months[1], including high-risk medications prescribed by many different specialists in multiple settings of care.[4,5] While medications can be life-saving, polypharmacy increases the risk of additive adverse effects[6], drug-drug interactions[2,3], and can lead to serious adverse drug events (ADEs). Pediatric ADEs result in over 4.3 million estimated ambulatory visits annually[7], including >150,000 pediatric emergency room visits.[8] Despite the risks associated with polypharmacy, we do not understand how polypharmacy escalates and how polypharmacy should be managed. To enable children to thrive at home using medications while minimizing unwanted symptoms, this proposal aims to implement a prospective, parent-reported symptom assessment system to guide and monitor pharmaceutical care for high-risk children. Strategies to improve recognition of problematic symptoms will have a substantial impact on the health of children. Thus, we propose the following specific aims, specifically focusing on the high-risk population of children with NI and polypharmacy:

Aim 1: <u>Conduct cross-sectional parent-reported symptom assessments (PRSA)</u>: In a clinic population of 300 children, we will administer an electronic validated symptom inventory to parents to advance our understanding of signal-to-noise and signal detection challenges in this population.

Hypothesis 1a: Patients with higher level of polypharmacy have greater symptom diversity and intensity.

Hypothesis 1b: Parent reports will identify more symptoms than concurrent medical record notes.

Aim 2: <u>Conduct a prospective cohort study to quantify the detection of known ADEs using PRSA</u>: We will follow 50 children expected to have medication changes (empaneled in Aim 1) and assess whether using PRSA prior to and after specific medication changes detects known and expected side effects.

Hypothesis 2: Known anti-epileptic side effects will be detected as within-person symptom changes following an anti-epileptic medication change of either a new drug start or a substantial dosage increase.

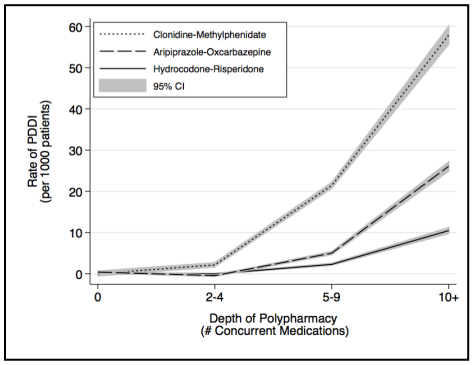
II. **Background and Significance**:

In 2010, more than 263 million outpatient prescriptions were dispensed to pediatric patients in the United States.[9] According to the Institute of Medicine report “Preventing Medication Errors,” the outpatient “environment in particular should be a high priority [for medication safety] given the growing reliance on home care for increasingly complex [pediatric] medical conditions.”[10] Children with complex chronic conditions (CCCs), such as intractable epilepsy or degenerative neurologic disease, rely on multiple medications to sustain their lives.[11] Children with CCCs, who comprise

<5% of the pediatric population but are responsible for 40% of costs associated with hospitalizations[12] are frequently exposed to daily polypharmacy.[1-3,11] Children with polypharmacy may take >5 medications simultaneously, and these regimens frequently include complex mixtures of high-risk medications including psychotherapeutics, anticonvulsants, cardiovascular agents, and opioids.[1,2,13,14] We know that the highest-risk children are exposed for many months to high levels of polypharmacy.[1] These same children have multiple CCCs and technology-dependence, often with neurological impairment (NI), that makes self-report of adverse symptoms unreliable.[1] The Best Pharmaceuticals for Children Act has prioritized the need for further study of outcome measures of drug safety and efficacy in children with intellectual and developmental disabilities.[15]

Our scientific premise, that the successful use of medications in children is not without risk, is rooted in our prior research. Polypharmacy poses significant problems. Our prior work has demonstrated that polypharmacy increases the risk of additive side effects[2,6] and significant potential drug-drug interactions (Figure 1),[1-3,13] and can lead to serious adverse drug events (ADEs),[7,8] defined as any adverse effect resulting from the use of a drug. Medication use has measureable risks: Pediatric medication errors and ADEs are frequent and costly,[6,16-19] with an increased incidence among children with CCCs.[8,20] Reports of pediatric ADEs submitted to the United States Food and Drug Administration have tripled over the past decade. Pediatric ADEs result in 4.3 million estimated ambulatory visits annually.[7] Our work has demonstrated that 150,000 ADE-related emergency room visits occur each year[8] with an increased risk of subsequent prolonged hospitalizations.[17] Strategies to improve safe medication practices, particularly through early recognition of problematic symptoms, will have a substantial impact on the health of children.

Figure 1: Exposure to 3 serious potential drug-drug interactions increases by level of polypharmacy



Despite the risks associated with polypharmacy, we do not clearly understand precisely how polypharmacy escalates. Furthermore, we lack a system to detect developing problematic symptoms in children with medical complexity. The epidemiology of pediatric polypharmacy has largely been researched in the inpatient setting,[11,21] and the management strategies do not easily translate to the ambulatory setting. Practices such as real-time assessment of patient data to assess for ADEs are not currently feasible in the ambulatory setting, where children are cared for by many providers across multiple settings of care.[22] Thus, the use of a variety of uncoordinated and unproven management strategies is common.[16,23] Part of the problem is that we do not thoroughly understand the sequence of events leading to increases in polypharmacy, hampering our ability to identify important periods of increased risk during which to intervene. Another part of the problem concerns the identification and management of problematic symptoms, which is complicated by the limited availability of objective patient data in the ambulatory setting. Furthermore, children with NI may experience multiple ongoing symptoms and this background symptom noise limits the conduct of clinical trials and of post-marketing surveillance studies to detect signals of ADEs. Our overarching hypothesis is that repeated parent-reported symptom assessments (PRSA) before and after medication changes will provide clinically pertinent information, improve signal detection, and enhance medication safety.[24,25]

Fortunately, new research opportunities exist to address both issues. First, we can improve our understanding of the sequence of events leading to the escalation of polypharmacy, and thereby identify possible targets to control polypharmacy. Longitudinal Medicaid data contain the variables necessary to study daily medication use in children. Second, we can improve our recognition of potential ADEs by utilizing comprehensive symptom assessment techniques initially tested and validated in the field of palliative care.[24] By prospectively assessing changes in parent-reported patient symptoms before and after medication changes, we aim to detect problematic symptoms

earlier, in order to more efficiently alert prescribers of potential problems. If this proposal confirms that prospective parent-reported symptoms assessments in children with polypharmacy is feasible and improves our ability to identify medication-related issues, then the next step is to disseminate this approach and to standardize ambulatory medication monitoring practices.

This proposal is significant because pediatric polypharmacy is associated with major morbidity and cost, but our ability to recognize, monitor, and manage problems associated with polypharmacy is underdeveloped. Therefore, the best way to elucidate factors involved in the escalation of polypharmacy is to use a large comprehensive database containing detailed medication data, and the best method to attempt to measure problematic symptoms in children with polypharmacy before and after medication changes is through prospective parent-reported symptom assessments.

We believe that there are 3 ways in which the proposed research is innovative both conceptually and methodologically. First, we will apply a validated parent-reported symptom assessment tool tested in palliative care research in a novel manner to assess the prevalence of symptoms among children with polypharmacy. Second, our proposal potentially could demonstrate the utility of assessing changes in symptoms to identify ADEs in the ambulatory setting. Third, our proposal could provide evidence to support the use of parent-reported symptom assessments more broadly to evaluate other therapies and interventions in children with CCCs.

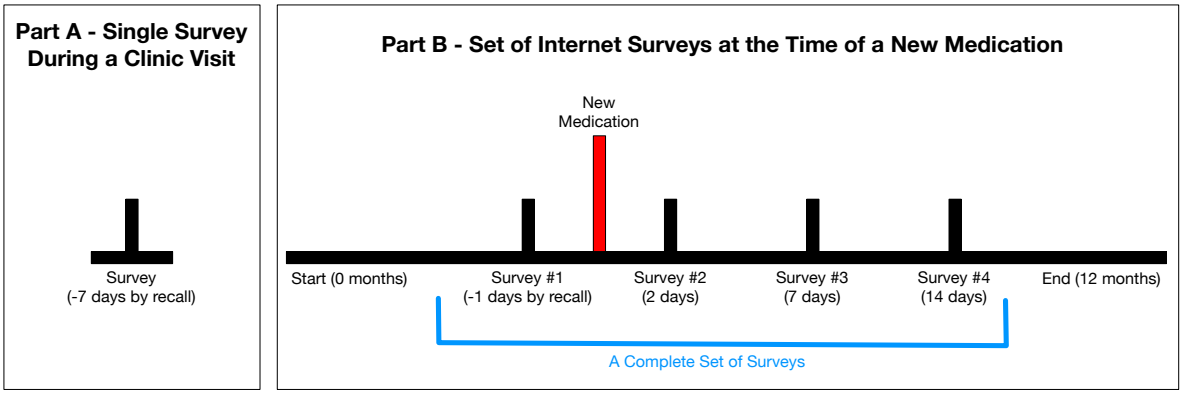
III. Preliminary Studies/Progress Report:

Preliminary Data Relevant to Specific Aim 1: Our study population will be drawn from the Special Care Clinic (SCC) for special needs patients at Children's Hospital of Colorado (CHCO). Of 3,600 active patients annually (and growing rapidly), 50% of children have ≥5 active total medications, and 25% have ≥10 total medications (Table 2). In 2015, there were at least 450 patients prescribed an anti-epileptic medication.

Preliminary Data Relevant to Specific Aim 2: We conducted a review of the children cared for in the Special Care Clinic during 2015 and at least 450 children were prescribed an anti-epileptic medication. The majority of these children received at least 5 anti-epileptic prescriptions during the year.

IV. Research Methods (We present the requested information in order by each aim).

Overview: To accomplish our aims, we will focus on the population of children with neurological impairment (NI) because of their prototypical exposure to polypharmacy. However, the following approach will provide generalizable learning and is expected to translate to other high-risk populations. We will strictly apply the scientific method to ensure robust and unbiased experimental design, methodology, and analyses.



Identification of Neurologically Impaired (NI) Children: For aims 1 and 2, we will identify children with NI using ICD-9-CM and ICD-10-CM diagnostic codes that have been previously published and validated.[26] Within the diagnostic classification scheme, sub-categories of types of NI (e.g. cerebral palsy, epilepsy) are available to facilitate comparisons and analyses between different types of NI, as necessary.

Definition of Polypharmacy: No standard definition of pediatric polypharmacy exists. Conservatively, polypharmacy involves using ≥2 distinct drugs concurrently, although the adult definition is typically ≥5 medications. We are interested in the latter, because these are the children who are expected to have the greatest pharmacovigilance needs. We will use National Drug Codes (NDC) and the Anatomical Therapeutic Chemical (ATC) classification system[27] to ensure that polypharmacy counts are based on distinct medications (i.e., two dosage forms of the same medication are counted as a single medication). We will exclude vaccinations and topical medications from our analyses.

Table 2: Potential Subjects

	2012	2013	2014	2015
# of Meds	**SCC Patients (n=3600/year)**			
0-4	2,736	2,628	2,376	1,800
5-9	540	576	756	900
≥10	324	396	468	900

Aim 1: Conduct cross-sectional parent-reported symptom assessments (PRSA): In a clinic population of 300 children, we will administer an electronic validated symptom inventory to parents to advance our understanding of signal-to-noise and signal detection challenges in this population.

Hypothesis 1a: Patients with higher levels of polypharmacy have greater symptom diversity and intensity.

Hypothesis 1b: Parent reports will identify more symptoms than concurrent medical record notes.

A. Outcome Measure(s):

Aim 1a
Outcome Measures: For general symptom burden, the global symptom score (continuous, from 0-100).

Exposure Variable: Medication count variable (continuous variable).

Additional clinical covariates: We will collect additional clinical information, including biologically relevant variables, at the time of the visit (Table 3, below).

Aim 1b
Outcome Measures: Counts of distinct symptoms.

Exposure Variable: PRSA versus clinic visit notes.

B. Description of Population to be Enrolled:
We will include all patients with NI and ≥5 scheduled medications aged 0-17 years-old and their parents. Because Aim 1 only requires a 1-day study period, the maximum age limit will be 17 years and 364 days. We will include patients with English or Spanish speaking parents (which represents 96% of potential SCC patients), as the study instrument has been validated for both languages.[28] All eligible subjects and their primary parent caregiver will be screened and enrolled, without bias. We anticipate a gender distribution representative of the children cared for in the Special Care Clinic, and a 2:1 female-to-male ratio for their parent caregiver.

C. Study Design and Research Methods:
This will be a cross-sectional analysis of parent-reported symptoms among a cohort of 300 children with NI and polypharmacy recruited from the SCC.

D. Description, Risks, and Justification of Procedures and Data Collection Tools:
Study instrument: As the basis for PRSA, we will use the PediQuest Memorial Symptom Assessment Scale (PQ-MSAS), which is an adapted pediatric-specific version of the validated adult MSAS that assesses 24 physical and psychological symptoms over the past week (the forms are provided in the Appendix).[24,29,30] The study instrument is designed to be completed by a full-proxy parent, and 2 versions tailored for specific age groups are available (0-3, 3-18 years-old). Spanish versions are available for both instruments. The study instrument has been previously tested and administered in electronic format to children with cancer and their parents. The PQ-MSAS contains 24 symptom items, each with 4-point scores for domains of frequency, severity, and extent of bother.[24] Based on these components, a global symptom score and individual symptom scores can be calculated (0-100 scale, with 100 being the worst).[24] Both Drs. Feudtner[24,29,30] and Fairclough[31-34] have extensive experience with the conduct and analysis of MSAS-related research..

Study Procedure: COMIRB will approve all recruitment materials and activities. Children and their primary parental caregivers will be recruited from the Special Care Clinic at the Children's Hospital Colorado. For the studies, an investigator or research coordinator will review the SCC appointments daily. For all patients identified as potential subjects, we will review the medical record to ensure that the patient is eligible. Prior to study enrollment, the study team will obtain and document informed consent from the parent caregiver, as well as assent from the child depending on the level of NI. For eligible patients, data will be recorded prospectively through administration of the PRSA system. Children enrolled in the prospective cohort study will also have clinical information extracted from their EPIC electronic medical record at Children's Hospital Colorado. For patients deemed ineligible at the time of first screening, we will record only patient age and the reason for ineligibility.

Dr. Feinstein or a trained research assistant will obtain paper-based informed consent prior to the start of the clinic appointment. Before the visit, the parent or parent will then complete the electronic tablet-based study instrument. To minimize the burden of completing this symptom assessment, we will use an electronic delivery system employing Research Electronic Data Capture (REDCap), a secure, HIPAA-compliant web-based application designed for data collection for research studies, which is supported free of charge to University researchers. PQ-MSAS information will be transmitted directly to REDCap servers from the electronic capture device for subsequent scoring and analysis. Parents will receive a $25 reloadable debit card upon completion of the study instrument. Relevant clinical data (Table 3) will be electronically exported into REDCap from the electronic medical record (EMR) by the Research Informatics Team at Children's Hospital Colorado. A member of the study team blinded to the results of the PRSA will review each subject's electronic medical record (EMR) 48 hours after completion of the visit (to ensure complete chart data is reviewed) and extract symptoms from the progress note and/or coded visit diagnoses.

Potential Risks and Justification: This is an observational study with minimal psychological, social, and/or legal risks to the subjects. The study design will not alter the natural course of medical care provided to the subject. The main potential risks are related to data privacy. Privacy concerns will be managed through appropriate data collection and storage. Confidentiality will be protected by limiting access to the research data and by maintaining coded databases. Each child and their primary parental caregiver will be assigned the same unique study number. PRSA data will be transmitted directly to REDCap servers from the electronic capture device for subsequent scoring and analysis, so that no private information is stored locally. Clinical EMR data will be exported by the Children's Hospital Colorado Research Informatics group directly into a RedCap™ database compliant with regulatory requirements, again so that no intermediary repositories of data are created. PRSA and clinical data will be linked by the study number. Paper-based consent forms and a key that links study numbers to patient medical record numbers will be kept in the primary investigator's locked office within a badge-accessed research office suite (ACCORDS) within a badge-accessed research building with 24-hour on-site security. Medical record numbers will be required for the clinical EMR data extractions. Once data extraction has been completed, the key

will be destroyed in a confidential manner. All analyses will be completed on Dr. Feinstein's whole disk-encrypted personal computer stored in a locked office within the badge-accessed ACCORDS research office suite. Additional detailed information about institutional safeguards for data safety are included in the Facilities & Other Resources attachment.

Data Safety and Monitoring: The proposed studies do not meet the definition of clinical trials defined by Public Law as a drug or device trial, and a Data Safety and Monitoring Board will not be required. However, the PI will be responsible for ongoing oversight, review, and reporting of any unforeseen events related to the study. The consent form and study instruments will reinforce that the study information collected is not a communication with the participant's provider. In the unlikely event that worsening symptoms are observed out-of-proportion to what is expected, the PI will review the case within 24 hours and potentially contact the patient's provider.

E. Potential Scientific Problems and Alternative Approaches:
Given the cross-sectional design of this study, we fully acknowledge that we will not be able to investigate causality between medications and symptoms; that is the goal of Aim 3.

F. Data Analysis Plan:
To analyze Aim 1**,** we will generate descriptive statistics of individual symptoms present among eligible patients. We will stratify findings by level of polypharmacy, such that we can report, for example, "Among children with NI taking ≥10 medications, in the past week 70% experienced constipation, 50% somnolence, and 20% pain." We will further stratify by the most common medication classes.

To test hypothesis 1a, that increasing levels of polypharmacy will be associated with a greater symptom burden, we will employ multiple linear regression techniques. We will model the number of medications as a continuous predictor variable with the symptom composite score as the continuous outcome variable. We will perform transformations of the outcome variable as necessary depending on its distribution. We will adjust for age, number of acute diagnoses, and number of CCCs.

Power and Sample Size Calculation: To detect a minimum 4-point difference in global symptom scores (which has previously been reported as a clinically relevant difference[24]) between those children taking 5 medications and those children taking 10 medications, with a power of 80% and a significance of 0.05, we would require 168 subjects (112 in the 5 medication group and 56 in the 10 medication group).

To test hypothesis 1b, we will test differences in means of PRSA and clinic visit counts of symptoms using a two-sided paired t-test.

Power and Sample Size Calculation: With a sample size of 300, significance of 0.05, standard deviation of 5, and correlation of 0.5, we will have 90% power to detect a minimum 1-point difference in mean counts.

G: Summarize Knowledge to be Gained:
Almost no drug trial or post-marketing surveillance data exist to guide medication safety in this complex population. Two major problems impede the identification of ADEs in children with NI and polypharmacy: 1) No system exists to assess multiple symptoms among children who cannot self-report and 2) we lack prevalence information about the background symptoms commonly experienced in this population against which to look for problematic signals. Systematic parent-based symptom inventories have been used to measure symptom burden in complex patient populations, such as children with terminal cancers.[24,29,30] Like children with NI, these complex oncology patients often experience a multitude of symptoms[24] with limited ability to report them. Thus, validated parent-based assessments have been developed to measure symptom burden at

the end of life, in order to tailor symptom management. Such tools have been successfully administered to children with cancer as frequently as monthly even during their terminal decline.[24]

Deliverable: We will provide estimates of the most prevalent symptoms among children with NI and polypharmacy, stratified by both level of polypharmacy and certain drug classes. These data will help providers understand the symptoms typically encountered by their patients, in order to optimize their prescribing and monitoring decisions. This will also allow us to target classes of medications potentially associated with commonly experienced symptoms, which when prescribed, may benefit from proactive, increased monitoring.

Aim 2: Conduct a prospective cohort study to quantify the detection of known ADEs using PRSA: We will follow 50 children expected to have medication changes (empaneled in Aim 2) and assess whether using PRSA prior to and after specific medication changes detects known side effects.

Hypothesis 2: Known anti-epileptic side effects will be detected as within-person symptom changes following an anti-epileptic medication change of either a new drug start or a substantial dosage increase.

A. Outcome Measure(s):

Exposure Variable of Interest: New start prescription of an antiepileptic medication (or subsequent dose increase).

Primary Longitudinal Outcome of Interest: Reported symptom levels during peri-exposure monitoring. Symptoms will be assessed using the age-appropriate PQ-MSAS proxy form as described above in Aim 2. *A priori*, we will focus on the known ADE of somnolence[6], and expand the analysis to other common and significant symptoms as identified in Aim 2.

Covariates: We will collect additional clinical information, including biologically relevant variables (**Table 3**).

B. Description of Population to be Enrolled:
We will include all patients with NI and ≥5 scheduled medications aged 0-17 years-old and their parents. Because Aim 2 requires a 12-month study period, the maximum age limit at study enrollment will be 17 years and 0 days. We will include patients with English or Spanish speaking parents (which represents 96% of potential SCC patients), as the study instrument has been validated for both languages.[28] All eligible subjects and their primary parent caregiver will be screened and enrolled, without bias. We anticipate a gender distribution representative of the children cared for in the Special Care Clinic, and a 2:1 female-to-male ratio for their parent caregiver.

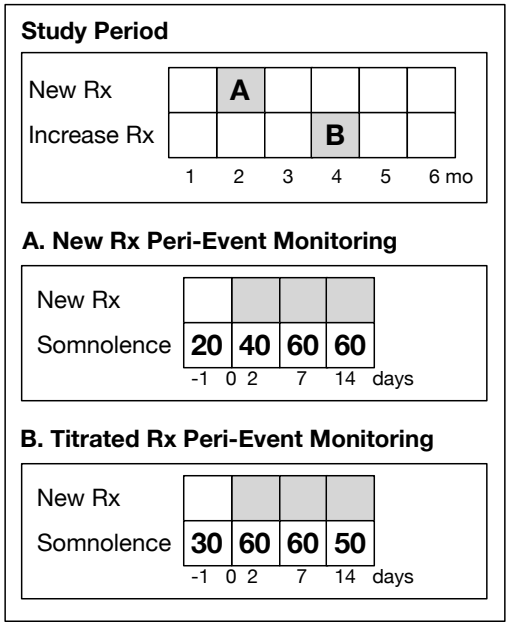
C. Study Design and Research Methods:
This will be a 12-month prospective cohort study of 50 children with NI and polypharmacy, aged 2-17 years-old who receive primary care in the SCC. To increase the likelihood of exposure to a new anti-epileptic, we will identify children with evidence of poor seizure control who are most likely to receive new anti-epileptic prescriptions, including an encounter in the past month for seizure control or current use of multiple anti-epileptics.

D. Description, Risks, and Justification of Procedures and Data Collection Tools:
Study Procedure: COMIRB will approve all recruitment materials and activities. Children and their primary parental caregivers will be recruited from the Special Care Clinic at the Children's Hospital Colorado. For the studies, an investigator or research coordinator will review the SCC appointments daily. For all patients identified as potential subjects, we will review the medical record to ensure that the patient is eligible. Prior to study enrollment, the study team will obtain and document

informed consent from the parent caregiver, as well as assent from the child depending on the level of NI. For eligible patients, data will be recorded prospectively through administration of the PRSA system. Children enrolled in the prospective cohort study will also have clinical information extracted from their EPIC electronic medical record at Children's Hospital Colorado. For patients deemed ineligible at the time of first screening, we will record only patient age and the reason for ineligibility.

Dr. Feinstein or a professional research assistant will obtain paper-based informed consent upon identification of a potential subject. After enrollment, we will identify exposure events by generating daily EHR-based medication reports on enrolled subjects that will flag new AED prescriptions. When an event occurs, we will email the parent within 24 hours with a link to a REDCap survey containing the age-appropriate PQ-MSAS proxy form. If the parent has hasn't yet administered the new prescription, we will ask about current symptoms; if they have, we will ask about the 24 hours prior to starting the medication. The parent will receive the survey at additional times (**Figure 3**) chosen to capture potential immediate, acute, and longer term symptoms. To minimize recall bias, all surveys will ask parents to report symptoms in the past 24 hours. We will also generate monthly EHR-based reports of subjects' medication lists; office, ED, and hospital visits; and, any acute diagnoses. All data will be stored in a HIPAA-compliant REDCap database. Parents will also be compensated with a $25 reloadable debit card for up to 2 instances of peri-event monitoring and a $50 reloadable debit card upon study completion (the total possible reimbursement is $100).

Figure 3: Design of Data Collection



Potential Risks and Justification: This is an observational study with minimal psychological, social, and/or legal risks to the subjects. The study design will not alter the natural course of medical care provided to the subject. The main potential risks are related to data privacy. Privacy concerns will be managed through appropriate data collection and storage. Confidentiality will be protected by limiting access to the research data and by maintaining coded databases. Each child and their primary parental caregiver will be assigned the same unique study number. PRSA data will be transmitted directly to REDCap servers from the electronic capture device for subsequent scoring and analysis, so that no private information is stored locally. Clinical EMR data will be exported by the Children's Hospital Colorado Research Informatics group directly into a RedCap™ database compliant with regulatory requirements, again so that no intermediary repositories of data are created. PRSA and clinical data will be linked by the study number. Paper-based consent forms and a key that links study numbers to patient medical record numbers will be kept in the primary investigator's locked office within a badge-accessed research office suite (ACCORDS) within a badge-accessed research building with 24-hour on-site security. Medical record numbers will be required for the clinical EMR data extractions. Once data extraction has been completed, the key will be destroyed in a confidential manner. All analyses will be completed on Dr. Feinstein's whole disk-encrypted personal computer stored in a locked office within the badge-accessed ACCORDS research office suite. Additional detailed information about institutional safeguards for data safety are included in the Facilities & Other Resources attachment.

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required. However, the PI will be responsible for ongoing oversight, review, and reporting of any unforeseen events related to the study. The consent form and study instruments will reinforce that the study information collected is not a communication with the participant's provider; the RedCap-based internet PRSAs will reinforce that if a participant feels that their child is having a problem, the participant will need to call their child's provider immediately. In the unlikely event that worsening symptoms are observed out-of-proportion to what is expected, the PI will review the case within 24 hours and potentially contact the patient's provider.

E. Potential Scientific Problems:
There is a risk of reporting fatigue that may result in missing or incomplete data. However, prior studies utilizing this instrument in a different capacity demonstrated that the majority of respondents completed the inventory on at least a monthly basis.[30] We will encourage reporting through the use of electronic reminders.[35] Should reporting fatigue occur, this will help us to elucidate the optimal frequency of reporting, and to complete our analyses, we will employ robust methods to handle missing longitudinal data. Additionally, there exists a small likelihood that children may receive specialty or emergency care outside the Children's Hospital Colorado network, which may limit our ability to detect new medication starts. We have attempted to mitigate this by enrolling those who receive primary care in SCC.

F. Data Analysis Plan:
To test hypothesis 2, we will analyze the ability to detect changes in somnolence following the exposure of interest. To summarize the data, we will graphically depict individual trajectories over time, group trajectories over time, and report group means of key variables over time. During peri-event monitoring, to test if exposure to a new (or subsequently increased) AED was associated with changes in somnolence, we will employ repeated measures mixed models to estimate the effects of a new-start AED on the level of somnolence over time. This type of analysis will enable us to study intra-individual changes in symptoms, while also providing flexibility in case missing data is present. We will model as fixed effects the time from start of AED and the starting level of polypharmacy; and, random effects to account for correlation among observations from the same patient. We will test using higher-order terms to model changes over time as necessary.

Implementation Analysis: We will report measures of implementation including the ability of participants to carry out the intervention activities, positive/negative effects on the target population, cohort retention, and the amount and type of resources needed to implement the intervention.

Power and Sample Size Calculation: The main objective is to determine whether we can detect changes in expected adverse symptoms (e.g. somnolence) within subjects using the study instrument. The prevalence and severity of symptoms is unknown among children exposed to polypharmacy. We based our conservative power calculation on studies using PQ-MSAS in children with cancer (the composite symptom score was 12.7 on a scale of 0-100, with a standard deviation of 8.6).[30] We expect that in a population of NI children, the somnolence symptom score will be much higher and more variable with medication changes than the composite score we used for this power calculation.[6] Because of the powerful within-subjects design, using a sample size of 50 subjects, a power of 80%, an alpha of 0.05, a conservative within-subject correlation between symptom measurements of 0.5, and accounting for 10% missing data, we will have the power to detect a clinically meaningful average 4-point change in a 100-point symptom score, such as somnolence.[24]

G. Summarize Knowledge to be Gained:
Amidst a complicated background of symptom noise, we will capitalize on parent-reported outcomes to improve the quantity and quality of data to detect significant symptom changes that could signal ADEs. Healthcare systems primarily rely on passive surveillance of ADEs, i.e. an adverse event is identified when a patient worsens enough to present for evaluation of a medication-related problem. The use of patient reported outcomes, particularly in patients with oncologic processes, has been shown to provide significantly more toxicity and symptom data than

clinician-based assessments[36,37], facilitate improved communication between patients and providers, and to improve clinical outcomes.[38] In both pediatric and adult cancer populations, electronic completion of symptom inventories is feasible and acceptable to patients.[24,39]

Deliverable: Aim 2 will assess the ability of a PRSA system to detect changes in symptoms consistent with known ADEs, which will be ready for definitive evaluation of its impact on improving patient safety and for implementation in additional high-risk populations.

H. References:

1. Feinstein JA, Feudtner C, Valuck RJ, Kempe A. The depth, duration, and degree of outpatient pediatric polypharmacy in Colorado fee-for-service Medicaid patients. *Pharmacoepidemiology and drug safety.* 2015.
2. Feinstein J, Dai D, Zhong W, Freedman J, Feudtner C. Potential Drug-Drug Interactions in Infant, Child, and Adolescent Patients in Children's Hospitals. *Pediatrics.* 2015;135(1):e99-e108.
3. Dai D, Feinstein JA, Morrison W, Zuppa AF, Feudtner C. Epidemiology of Polypharmacy and Potential Drug-Drug Interactions Among Pediatric Patients in ICUs of U.S. Children's Hospitals. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2016.
4. Antonelli R, Stille, C., and Freeman, L. *Enhancing Collaboration Between Primary and Subspecialty Care Providers for Children and Youth With Special Health Care Needs.* Washington, DC2005.
5. McPhillips H, Stille C, Smith D, et al. Methodological Challenges in Describing Medication Dosing Errors in Children. In: Henriksen K, Battles JB, Marks ES, Lewin DI, eds. *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology)*. Rockville (MD)2005.
6. Anderson M, Egunsola O, Cherrill J, Millward C, Fakis A, Choonara I. A prospective study of adverse drug reactions to antiepileptic drugs in children. *BMJ Open.* 2015;5(6):e008298.
7. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiology and drug safety.* 2010;19(9):901-910.
8. Feinstein JA, Feudtner C, Kempe A. Adverse drug event-related emergency department visits associated with complex chronic conditions. *Pediatrics.* 2014;133(6):e1575-1585.
9. Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D. Trends of outpatient prescription drug utilization in US children, 2002-2010. *Pediatrics.* 2012;130(1):23-31.
10. Aspden P, Institute of Medicine (U.S.). Committee on Identifying and Preventing Medication Errors. *Preventing medication errors.* Washington, DC: National Academies Press; 2007.
11. Feudtner C, Dai D, Hexem KR, Luan X, Metjian TA. Prevalence of polypharmacy exposure among hospitalized children in the United States. *Arch Pediatr Adolesc Med.* 2012;166(1):9-16.
12. Simon TD, Berry J, Feudtner C, et al. Children with complex chronic conditions in inpatient hospital settings in the United States. *Pediatrics.* 2010;126(4):647-655.
13. Lebowitz MB, Olson KL, Burns M, Harper MB, Bourgeois F. Drug-Drug Interactions Among Hospitalized Children Receiving Chronic Antiepileptic Drug Therapy. *Hosp Pediatr.* 2016;6(5):282-289.
14. Blackmer AB, Feinstein JA. Management of Sleep Disorders in Children With Neurodevelopmental Disorders: A Review. *Pharmacotherapy.* 2016;36(1):84-98.
15. National Institues of Health. Best Pharmaceuticals for Children Act (BPCA) Priority List of Needs in Pediatric Therapeutics. 2015.
16. Rinke ML, Bundy DG, Velasquez CA, et al. Interventions to reduce pediatric medication errors: a systematic review. *Pediatrics.* 2014;134(2):338-360.
17. Zed PJ, Black KJ, Fitzpatrick EA, et al. Medication-related emergency department visits in pediatrics: a prospective observational study. *Pediatrics.* 2015;135(3):435-443.

18. Ferranti J, Horvath MM, Cozart H, Whitehurst J, Eckstrand J. Reevaluating the safety profile of pediatrics: a comparison of computerized adverse drug event surveillance and voluntary reporting in the pediatric environment. *Pediatrics.* 2008;121(5):e1201-1207.
19. Bourgeois FT, Mandl KD, Valim C, Shannon MW. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. *Pediatrics.* 2009;124(4):e744-750.
20. Walsh KE, Roblin DW, Weingart SN, et al. Medication errors in the home: a multisite study of children with cancer. *Pediatrics.* 2013;131(5):e1405-1414.
21. Sharek PJ, McClead RE, Jr., Taketomo C, et al. An intervention to decrease narcotic-related adverse drug events in children's hospitals. *Pediatrics.* 2008;122(4):e861-866.
22. Walsh KE, Kaushal R, Chessare JB. How to avoid paediatric medication errors: a user's guide to the literature. *Arch Dis Child.* 2005;90(7):698-702.
23. Zhong W, Feinstein JA, Patel NS, Dai D, Feudtner C. Tall Man lettering and potential prescription errors: a time series analysis of 42 children's hospitals in the USA over 9 years. *BMJ Qual Saf.* 2016;25(4):233-240.
24. Wolfe J, Orellana L, Ullrich C, et al. Symptoms and Distress in Children With Advanced Cancer: Prospective Patient-Reported Outcomes From the PediQUEST Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33(17):1928-1935.
25. Joyce BT, Lau DT. Hospice experiences and approaches to support and assess family caregivers in managing medications for home hospice patients: a providers survey. *Palliat Med.* 2013;27(4):329-338.
26. Berry JG, Poduri A, Bonkowsky JL, et al. Trends in resource utilization by children with neurological impairment in the United States inpatient health care system: a repeat cross-sectional study. *PLoS Med.* 2012;9(1):e1001158.
27. Methodology WCCfDS. *Guidelines for ATC classification and DDD assignment 2016.* 19 ed. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2015.
28. Zhukovsky DS, Rozmus CL, Robert RS, et al. Symptom profiles in children with advanced cancer: Patient, family caregiver, and oncologist ratings. *Cancer.* 2015;121(22):4080-4087.
29. Dussel V, Orellana L, Soto N, et al. Feasibility of Conducting a Palliative Care Randomized Controlled Trial in Children With Advanced Cancer: Assessment of the PediQUEST Study. *J Pain Symptom Manage.* 2015;49(6):1059-1069.
30. Wolfe J, Orellana L, Cook EF, et al. Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: results from the PediQUEST randomized controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(11):1119-1126.
31. Bekelman DB, Havranek EP, Becker DM, et al. Symptoms, depression, and quality of life in patients with heart failure. *J Card Fail.* 2007;13(8):643-648.
32. Kessler ER, Moss A, Eckhardt SG, et al. Distress among caregivers of phase I trial participants: a cross-sectional study. *Support Care Cancer.* 2014;22(12):3331-3340.
33. Kutner JS, Bryant LL, Beaty BL, Fairclough DL. Symptom distress and quality-of-life assessment at the end of life: the role of proxy response. *J Pain Symptom Manage.* 2006;32(4):300-310.
34. Kutner JS, Bryant LL, Beaty BL, Fairclough DL. Time course and characteristics of symptom distress and quality of life at the end of life. *J Pain Symptom Manage.* 2007;34(3):227-236.
35. Basch E, Iasonos A, Barz A, et al. Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(34):5374-5380.
36. Bruner DW. Should patient-reported outcomes be mandatory for toxicity reporting in cancer clinical trials? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(34):5345-5347.
37. Trotti A, Colevas AD, Setser A, Basch E. Patient-reported outcomes and the evolution of adverse event reporting in oncology. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(32):5121-5127.

38. Basch E, Deal AM, Kris MG, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015.
39. Judson TJ, Bennett AV, Rogak LJ, et al. Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(20):2580-2585.