


# Quantifying the intensity of adverse events with ibuprofen and oxycodone: an observational cohort study

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## ABSTRACT

**Objective** To quantify the frequency and intensity of adverse events (AEs), commonly known as side effects, experienced by children receiving either ibuprofen or oxycodone for pain management following an acute fracture. Secondary objectives were to quantify functional outcome impairment and describe demographic and clinical characteristics associated with AEs.

**Design** Observational cohort study.

**Setting** Paediatric emergency department.

**Patients** Patients (n=240) aged 4–16 years diagnosed with an acute fracture.

**Intervention** Prescribed either ibuprofen (n=179) or oxycodone (n=61) for pain.

**Main outcome measures** Families were called for the first 3 days after discharge to report the presence and intensity of AEs and their child's functional outcomes (ability to eat, sleep, play or attend school).

**Results** On day 1, children using oxycodone were more likely to report any AE ( $\chi^2_1=13.5$ ,  $p<0.001$ ), nausea ( $\chi^2_1=17.0$ ,  $p<0.001$ ), vomiting ( $\chi^2_1=11.2$ ,  $p<0.001$ ), drowsiness ( $\chi^2_1=13.7$ ,  $p<0.001$ ), constipation ( $\chi^2_1=8.9$ ,  $p=0.003$ ) and dizziness ( $\chi^2_1=19.1$ ,  $p<0.001$ ), compared with those using ibuprofen. Children receiving oxycodone reported greater severity of abdominal pain (oxycodone: mean 5.4 SD 3.1; ibuprofen mean 2.5 SD 1.4,  $F^1_{13}=6.5$ ,  $p=0.02$ ) on day 1 and worse intensity of constipation (oxycodone: mean 4.9 SD 2.1; ibuprofen mean 3.2 SD 2.2,  $F^1_{33}=4.5$ ,  $p=0.04$ ) over all 3 days. Use of oxycodone was associated with an increased odds of experiencing an AE on day 1 (OR=1.31 (95% CI 1.13 to 1.52)). Higher pain scores (OR=1.50 (95% CI 1.12 to 2.01)), lower extremity fracture (OR=1.25 (95% CI 1.07 to 1.47)) and undergoing ED sedation (OR=1.16 (95% CI 1.01 to 1.34)) were associated with missing school. Higher pain scores (OR=1.50 (95% CI 1.14 to 1.97)) and lower extremity fractures (OR=1.23 (95% CI 1.07 to 1.43)) were also associated with less play.

**Conclusions** Oxycodone is associated with more frequent AEs overall, higher intensity gastrointestinal AEs and greater functional limitations compared with ibuprofen. Lower extremity fractures cause more functional limitations than upper extremity fractures. Clinicians should consider these differences when providing fracture pain care for children.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ibuprofen and oxycodone have been previously shown to have similar analgesic efficacy when treating childhood fracture pain. While oxycodone is associated with more frequent adverse events than ibuprofen, the comparative intensity of these adverse events is not known.

## WHAT THIS STUDY ADDS

⇒ In children with fracture-related pain, oxycodone is associated with more frequent adverse events overall and higher intensity gastrointestinal adverse events compared with ibuprofen. Children with upper limb fractures experience more functional impairment when prescribed oxycodone, as compared with ibuprofen.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Researchers should consider measuring differences in adverse event intensity when conducting clinical trials with analgesic agents. Clinicians may consider the higher intensity of gastrointestinal symptoms associated with oxycodone prescribing, when making prescribing decisions.

## INTRODUCTION

Childhood pain is a common complaint across numerous healthcare settings and affects both short-term and long-term quality of life.<sup>1 2</sup> National societies have advocated for the use of ibuprofen and opioids in the treatment of moderate-to-severe pain in children.<sup>13 4</sup> In fact, the American Academy of Pediatrics advocates for the use of ibuprofen, acetaminophen and oxycodone at triage, in order to treat pain early and effectively.<sup>3</sup> Despite this, paediatric pain remains undertreated in the acute care setting, with only 35% of children receiving any analgesia after acute musculoskeletal injury.<sup>5</sup> Further,

pain management practices vary widely between practitioners<sup>5 6</sup>; this variability is at least partially influenced by a lack of clear evidence regarding optimal analgesic agent choice.<sup>1</sup>

Adverse events (AEs) associated with analgesic use are common and can decrease medication adherence. A more comprehensive understanding of analgesic profiles is needed to optimise pharmacological approaches to pain. As oral formulations of common analgesic medications have been shown to be similarly effective in pain reduction,<sup>6-9</sup> their safety profiles impact decision-making for clinicians and families. While oxycodone is associated with an increased incidence of AEs compared with ibuprofen,<sup>10</sup> quantification of the intensity of these AEs has not been well described and could influence both clinician medication choice and family compliance with therapy. Our primary objective was to quantify the frequency and intensity of AEs (commonly known as side effects) experienced by children receiving either ibuprofen or oxycodone for pain management following an acute fracture. Our secondary objectives were (1) to quantify the frequency of functional outcome impairment and (2) to describe the demographic and clinical characteristics that were associated with AE reporting on day 1.

## METHODS

### Study design and setting

This study is a secondary analysis of a prospective observational cohort study performed at the Stollery Children's Hospital (Edmonton, Alberta) emergency department (ED), which had an annual ED census of 27 000 at the time of study.

### Participants

Patients were recruited from June 2010 to July 2014. Eligibility criteria included all children aged 4–16 years who incurred a limb fracture within 24 hours of presentation and were prescribed either ibuprofen or oxycodone for at-home pain management. These, along with acetaminophen, were the three most frequently used outpatient analgesic medications in our institution at the time. We excluded children who were prescribed both oxycodone and ibuprofen at discharge, used daily medications for chronic pain, could not speak English, could not self-report pain due to cognitive impairment and/or could not be reached by telephone for follow-up. For inclusion in this substudy, participants must have used their prescribed medication on day 1 after ED discharge. Both the decision to prescribe ibuprofen or oxycodone and the recommended dosing were at the discretion of the treating physician. Recommended dosing was 10 mg/kg/dose (maximum 600 mg) for ibuprofen and 0.1–0.2 mg/kg/dose (maximum 10 mg) for oxycodone.

### Recruitment

Both consent and assent were obtained from caregivers and children, respectively. A research assistant interviewed each family daily for the first 3 days after discharge (with day 1 being the end of the first 24 hours after ED discharge); pain scores (using the Faces Pain Scale-Revised),<sup>11</sup> medication use, dosage, AEs and functional outcome impairment were collected.

### Data collection and management

Demographic (ie, age, sex) and clinical (ie, fracture type, procedural sedation) characteristics were collected from participants using structured medical record review. A trained data specialist was responsible for data entry and validation using OpenClinica.<sup>12</sup> MedDRA was used to code AEs, as per Health Canada recommendations for AE reporting.<sup>13</sup>

### Outcomes

Our primary outcome was the frequency and mean intensity of each AE. In the first 3 days following ED presentation, caregivers were asked to report whether their child experienced an AE (yes/no) and their child's self-reported severity of eight commonly occurring AEs (abdominal pain, appetite loss, constipation, dizziness, drowsiness, nausea, systemic rash, vomiting, other AEs). As no current validated tool exists for the short-term measurement of intensity of AEs, we adapted the validated 11-point numerical rating scale for pain to use a similar scale for AEs (where 0=none and 10=worst extent ever).<sup>14</sup> Overall AEs, or cumulative AEs, were calculated by counting any child with a minimum of one AE (of any intensity) as having experienced an AE. The secondary outcome was the frequency of functional outcome impairments and the differences in impairment experienced between cohorts taking ibuprofen and oxycodone as well as upper and lower extremity injuries. Functional outcomes were chosen based on prior literature and included eating, sleeping, playing and attending school.<sup>15</sup> For the purposes of logistic regression analyses, functional outcomes and AEs were treated as a binary variable (ie, presence or absence). Demographic and clinical predictors of AE reporting on day 1 post-ED visit included age, sex, medication taken, fracture type (upper vs lower), procedural sedation in the ED, whether any non-pharmacological agent was used, and maximum pain score on day 1.

### Sample size and power

This paper is a secondary analysis of data collected for a larger observational cohort study that measured pain reduction.<sup>16</sup> With the sample size available for this secondary analysis, an effect size of at least 0.48 was detectable for a two-sided, two-sample t-test ( $\alpha=0.05$ , power=90%) comparing medication group mean intensities.

### Statistical methods

Summary statistics (eg, mean, SD) were calculated for each day, separately and cumulatively, with missing data

omitted. Medication group differences were assessed with two-sided, two-sample t-tests for continuous variables and with  $\chi^2$  tests of association for categorical variables. Functional outcome impairment was stratified by fracture location (upper/lower). Multivariable logistic regressions were performed for each of the day 1 outcomes of presence of AE and each functional impairment separately. Age, sex, medication group, fracture type (upper vs lower), presence of sedation in the ED, whether any non-pharmacological agent was used, and maximum pain score on day 1 were predictors in the regression models, as they represent clinically plausible factors that might influence the experience of AEs. ORs and associated 95% CIs were provided. All analyses were conducted in R (V.4.04, R Foundation for Statistical Computing, Vienna, Austria) and a  $p < 0.05$  was considered statistically significant.

### Patient and public involvement

Patients and the public were not involved in the original design and implementation of the study. However, we have since engaged a knowledge broker, and will consult two patient and family partners to help design and disseminate the results of this study.

## RESULTS

### Demographic characteristics

This study included 240 children (ibuprofen  $n=179$ , oxycodone  $n=61$ ) who used their recommended medication on day 1. For children who were prescribed ibuprofen as needed, 83.4% (141/169) continued its use on day 2, and 55.9% (100/179) on day 3. For children who were prescribed oxycodone as needed, 63.9% (39/61) used in on day 2, and 39.3% (24/61) on day 3. Study participants were 66.2% male with a mean age of 11.0 years; 79.1% of participants had an upper extremity fracture, and 34.6% required fracture reduction in the ED. Location of fracture, fracture reduction, procedural sedation, use of casting and pain experience were comparable between groups (table 1).

### Frequency of AEs

The frequency of patients reporting any AE on day 1 after ED discharge associated with oxycodone was 81.7%, while the overall frequency of AEs associated with ibuprofen was 55.1% ( $\chi^2_1=13.5$ ,  $p < 0.001$ ). Specifically, on day 1, children prescribed oxycodone were more likely to report nausea ( $\chi^2_1=17.0$ ,  $p < 0.001$ ), vomiting ( $\chi^2_1=11.2$ ,  $p < 0.001$ ), drowsiness ( $\chi^2_1=13.7$ ,  $p < 0.001$ ), constipation ( $\chi^2_1=8.9$ ,  $p=0.003$ ) and dizziness ( $\chi^2_1=19.1$ ,  $p < 0.001$ ), compared with ibuprofen (table 2, online supplemental table 1).

### Intensity of AEs

Table 3 presents the mean intensity of reported AEs. Children using oxycodone on day 1 reported more severe abdominal pain than children taking ibuprofen (mean

intensity 5.4 SD 3.1 vs 2.5 SD 1.4,  $F^1_{144}=0.6$ ,  $p=0.02$ ). Children taking oxycodone reported worse constipation overall (cumulatively) than the ibuprofen cohort (mean intensity 4.9 SD 2.1 vs 3.3 SD 2.2,  $F^1_{33}=4.5$ ,  $p=0.04$ ). All other AEs had similar reported severity between groups. Notably, vomiting was reported as higher in intensity than all other AEs, regardless of medication taken (ibuprofen mean intensity 8.7 on day 1, oxycodone 7.3 on day 1). Mean intensity of AEs, by day, are presented in online supplemental table 2.

### Functional outcomes

Functional outcome impairments are described in table 4, stratified by fracture location and medication type. Children with lower limb fractures had similar incidence of functional outcome impairment between medication groups. Children with upper limb fractures prescribed oxycodone were more likely to experience impairment in play on day 1 ( $\chi^2_1=7.5$ ,  $p=0.006$ ). Cumulatively, children in the oxycodone cohort with upper limb fractures were more likely to experience impairment in play and attending school ( $\chi^2_1=14.2$ ,  $p < 0.001$  and  $\chi^2_1=8.1$ ,  $p=0.004$ , respectively).

Multivariable logistic regressions between demographic and clinical variables and AE occurrence on day 1 after fracture demonstrated that only use of oxycodone (OR=1.31, 95% CI (1.13 to 1.52) and higher maximum pain score (OR=1.04 per one unit increase, 95% CI (1.01 to 1.07)) were significantly associated with the patient experiencing an AE. Age, gender, fracture type, sedation in the ED and non-pharmacological agents did not provide evidence of a statistically significant effect (online supplemental table 3).

Logistic regression analysis was completed to identify demographic and clinical variables associated with a functional outcome impairment on day 1 after fracture. Higher pain score was associated with significantly increased odds of impairment in eating (OR=1.49 (95% CI 1.14 to 1.95)), playing (OR=1.50 (95% CI 1.14 to 1.97)) and attending school (OR=1.50 (95% CI 1.12 to 2.01)). Children with a lower extremity fracture also had increased odds of impairment in playing (OR=1.23, (95% CI 1.07 to 1.43)) and attending school (OR=1.25 (95% CI 1.07 to 1.47)). Children undergoing an ED sedation also had increased odds of impairment in attending school (OR=1.16 (95% CI 1.01 to 1.34)) (online supplemental table 4).

## DISCUSSION

We found that the proportion of children taking oxycodone for fracture-related pain who experienced an AE was almost 1.5 times higher than for ibuprofen on day 1. The proportion of children with specific AEs was higher for children in the oxycodone group for most AEs, including vomiting, drowsiness, constipation and dizziness. For children who were treated with oxycodone, AE intensity was greater on day 1 for abdominal pain and cumulatively for

**Table 1** Demographic characteristics

	Ibuprofen group (n=179)	Oxycodone group (n=61)	All participants (n=240)
Age, mean (SD), years	10.4 (3.6)	12.8 (2.5)	11.0 (3.5)
Weight, mean (SD), kg	41.5 (17.5)	50.4 (15.0)	43.7 (17.3)
Sex (Boys) n (%)	110 (61.5)	49 (80.3)	159 (66.2)
Fracture location* n (%)			
Upper body	139 (77.7)	50 (83.3)	189 (79.1)
Lower body	40 (22.3)	10 (16.7)	50 (20.9)
Procedural sedation n (%)	54 (30.2)	23 (37.7)	77 (32.1)
Fracture reduction n (%)	59 (33.0)	24 (39.3)	83 (34.6)
Buckle fracture* n (%)	20 (11.2)	2 (3.3)	22 (9.2)
Post-ED discharge follow-up n (%)			
Return to ED, PRN	4 (2.2)	1 (1.6)	5 (2.1)
Return to ED, scheduled	3 (1.7)	0 (0.0)	3 (1.2)
Referral to orthopaedic surgeon	125 (69.8)	51 (83.6)	176 (73.3)
F/U with family doctor	22 (12.3)	6 (9.8)	28 (11.7)
Other F/U	5 (2.8)	1 (1.6)	6 (2.5)
Not charted	20 (11.2)	2 (3.3)	22 (9.2)
Therapeutic interventions (non-pharmacological) (n, %)			
Cast	112 (62.6)	34 (55.7)	146 (60.8)
Splint	38 (21.2)	2 (3.3)	40 (16.7)
Comfort interventions (non-pharmacological) (n, %)			
Sling	55 (30.7)	31 (50.8)	86 (35.8)
Elevation	62 (34.6)	9 (14.8)	71 (29.6)
Tensor	3 (1.7)	2 (3.3)	5 (2.1)
Crutches	3 (1.7)	2 (3.3)	5 (2.1)
Ice	33 (18.4)	14 (23.0)	47 (19.6)
Other†	8 (4.5)	4 (6.6)	12 (5.0)
Maximum pain at day 1, mean (SD)	6.1 (2.2)	6.6 (2.1)	6.2 (2.2)
Delta pain at day 1, mean (SD)	3.6 (1.9)	3.9 (2.3)	3.7 (2.0)

\*n=239 for these results, where n=179 for ibuprofen group and n=60 for oxycodone group.  
†Other includes wheelchair, brace, tape, finger exercises.  
ED, emergency department; F/U, follow-up.

constipation. Interestingly, the occurrence of vomiting was universally ranked highest in intensity by children, regardless of medication taken, suggesting that vomiting might be one of the most distressing common AEs. Activities requiring movement, including playing and attending school, were affected in almost half of children with lower limb injuries, regardless of medication group. Differences in functional impairment between medication groups were significant only for children with upper limb injuries, where the proportion of children with disruption in playing and school attendance was significantly higher if oxycodone was prescribed.

Currently recommended first-line therapy for moderate pain in children is to combine acetaminophen with ibuprofen; if this is inadequate, oral opioids,

including oxycodone, can be added.<sup>16</sup> Still, up to 41% of trainees and 25% of practitioners indicate that they consider opioids a top choice for moderate pain treatment.<sup>17 18</sup> Considering both this and the fact that ibuprofen and opioids are reported as similarly efficacious for childhood fracture pain management,<sup>19 20</sup> AE profiles are an important consideration when making clinical prescribing decisions.

We stratified common AEs by intensity, which may help clinicians and families make more informed decisions regarding medication choice, as AEs are a critical consideration in early stopping of use of analgesics. For example, while often dismissed as a 'trivial side effect', constipation can result in significant morbidity, with an adverse effect on patient quality of life, and association

**Table 2** Adverse event frequency, day 1

Adverse event n (%)	Ibuprofen group (n=179)	Oxycodone group (n=61)	Total (n=240)	P value*
Any adverse event†	98 (55.1)	49 (81.7)	147 (61.2)	<b>&lt;0.001</b>
Drowsiness†	70 (39.1)	40 (66.7)	110 (46.0)	<b>&lt;0.001</b>
Lack of appetite†	48 (26.8)	22 (36.7)	70 (29.3)	0.15
Nausea	19 (10.6)	20 (33.3)	39 (16.3)	<b>&lt;0.001</b>
Dizziness	14 (7.8)	18 (30.0)	32 (13.4)	<b>&lt;0.001</b>
Constipation‡	10 (5.6)	11 (18.3)	21 (8.9)	<b>0.003</b>
Abdominal pain	10 (5.6)	5 (8.3)	15 (6.3)	0.45
Vomiting	3 (1.7)	7 (11.7)	10 (4.2)	<b>&lt;0.001</b>
Rash	3 (1.7)	1 (1.7)	4 (1.7)	1.00
Other	17 (9.5)	5 (8.2)	22 (9.2)	0.76

Bold type represents statistically significant results.  
 \*Pearson's  $\chi^2$  test.  
 †n=238.  
 ‡n=237.

with self-directed decrease in dose, leading to under-treatment of pain.<sup>21</sup> Intensity comparisons of AEs may help clinicians better understand the recovery experience in children with pain. Importantly, abdominal pain and constipation were experienced at higher intensity in children taking oxycodone, even though the proportion of children experiencing abdominal pain was not different between groups. Further, constipation is a well-described side effect of oxycodone in children<sup>22, 23</sup>; our data support previously published studies that promote coprescription of stool softeners or laxatives to prevent

this common and distressing AE.<sup>24</sup> Notably, vomiting was ranked higher in intensity than all other AEs regardless of medication used; clinicians may consider this when making prescribing decisions, especially for those with a propensity towards gastrointestinal upset.

While a higher proportion of children prescribed oxycodone with upper limb injuries struggled more to play and attend school (vs ibuprofen), lower limb fractures were universally debilitating for almost half of children, regardless of medication used. Consistent with our results, a recent study showed decreased quality of life in

**Table 3** Mean intensity of adverse events

Adverse event		Ibuprofen, mean (SD)	Oxycodone, mean (SD)	P value*
Drowsiness	Day 1 (n=110)	4.5 (2.1)	5.1 (1.9)	0.19
	Cumulative (n=125)	4.0 (2.0)	4.4 (1.6)	0.17
Lack of appetite	Day 1 (n=70)	5.1 (2.1)	4.4 (2.2)	0.17
	Cumulative (n=91)	4.4 (2.0)	3.8 (1.6)	0.19
Nausea	Day 1 (n=39)	4.6 (2.7)	5.9 (2.6)	0.15
	Cumulative (n=53)	4.5 (2.6)	5.2 (2.8)	0.37
Dizziness	Day 1 (n=32)	4.8 (2.2)	4.2 (1.8)	0.43
	Cumulative (n=42)	4.2 (1.9)	4.2 (1.7)	0.94
Constipation	Day 1 (n=21)	3.8 (1.9)	4.5 (2.2)	0.42
	Cumulative (n=35)	3.3 (2.2)	4.9 (2.1)	<b>0.04</b>
Abdominal pain	Day 1 (n=15)	2.5 (1.4)	5.4 (3.1)	<b>0.02</b>
	Cumulative (n=29)	3.3 (2.3)	3.6 (2.0)	0.70
Vomiting	Day 1 (n=10)	8.7 (1.2)	7.3 (3.1)	0.49
	Cumulative (n=17)	7.5 (3.3)	5.7 (3.6)	0.33
Rash	Day 1 (n=4)	4.7 (2.1)	4 (NA)†	0.81
	Cumulative (n=10)	3.8 (2.3)	4.3 (0.5)	0.74

Bold type represents statistically significant results.  
 \*Two-sample t-test.  
 †SD is not applicable, as sample size is 1.

**Table 4** Functional outcome impairment on day 1

	Functional outcomes N (%)	Upper limb			Lower limb		
		Ibuprofen group	Oxycodone group	P value*	Ibuprofen group	Oxycodone group	P value*
Day 1	Eat	31 (22.3)	16 (32.7)	0.15	15 (37.5)	4 (40.0)	0.88
	Sleep	60 (43.5)	25 (51.0)	0.36	20 (50.0)	3 (30.0)	0.26
	School	65 (48.1)	26 (55.3)	0.40	29 (74.4)	5 (50.0)	0.14
	Play	77 (55.4)	38 (77.6)	<b>0.006</b>	34 (85.0)	7 (70.0)	0.27
Cumulative	Eat	37 (27.8)	19 (41.3)	0.09	18 (45.0)	4 (40.0)	0.78
	Sleep	80 (59.7)	34 (69.4)	0.23	26 (65.0)	4 (40.0)	0.15
	School	76 (57.6)	38 (80.9)	<b>0.004</b>	32 (82.1)	9 (90.0)	0.54
	Play	88 (65.7)	45 (93.8)	<b>&lt;0.001</b>	35 (87.5)	9 (90.0)	0.83

Bold type represents statistically significant results.

\*Pearson's  $\chi^2$  test.

the domains of physical limitations and social aspects after lower limb fracture.<sup>25</sup> In contrast, paediatric upper limb fractures have been shown to be less debilitating; studies assessing quality of life report high physical and psychosocial function in both the short term and long term.<sup>26 27</sup> We have reaffirmed that clinicians should caution families that lower limb fractures will affect important activities in the acute recovery phase regardless of medication prescribed.

Higher pain score and oxycodone use were associated with experiencing any AE on day 1. While it is well known that oxycodone has a high frequency of AEs, pain itself may cause these same symptoms. Indeed, pain was associated with impairment in all four functional outcomes and was the lone predictor of impairment in eating and sleep. This demonstrates the importance of treating pain for improving quality of life in the acute recovery phase after childhood fracture.

There are several limitations to this study. Given the nature of observational cohort studies, we cannot assume direct causality between medication type and AEs experienced. While we showed similarity in our study groups through a comparison of demographic characteristics, including pain scores, we cannot definitively say that pain scores or other clinical factors did not influence our results. As we could not control sample sizes between groups, the oxycodone cohort was relatively smaller than the ibuprofen cohort. As this study was not a randomised trial, selection bias of patients may have occurred due to unidentified factors in clinician decision-making surrounding drug choice and may have led to underestimation of AEs. Additionally, patients were included in our study if medication was taken on day 1 after fracture, however, this same medication was not always taken on days 2 and 3. As such, the AEs and functional outcomes reported for these days reflect the pragmatic, lived experiences of patients that were prescribed a particular medication, rather than only the direct effects of the medications.

## CONCLUSION

We reaffirmed that oxycodone is associated with a higher proportion of children reporting AEs compared with ibuprofen for acute fracture pain. We discovered that the intensity of gastrointestinal side effects, including abdominal pain and constipation, was greater in children prescribed oxycodone, compared with ibuprofen. Lower limb fractures were associated with a higher proportion of children reporting functional impairment than upper limb fractures, regardless of pain medication prescribed. Children with upper limb fractures who were prescribed ibuprofen for pain management were less likely to report functional outcome impairment. Future research may benefit from incorporating comparative AE intensity data into clinical trials.

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**Contributors** SA conceptualised and designed the study protocol, secured funding for the study, coled data interpretation and analysis, codrafted the manuscript, and is the responsible for the overall content as a guarantor. KG conducted the literature review, coled data interpretation and analysis plan, and drafted the initial manuscript. RJR contributed to the study protocol design, secured funding for the study, coled the analysis plan, oversaw data analyses and reviewed and revised the manuscript. SO performed the analysis plan and reviewed and revised the manuscript. DWJ and ALD assisted in study protocol design, secured funding for the study, contributed to results interpretation, and critically reviewed and revised the manuscript. RW contributed to the study protocol design, oversaw digital data collection, and reviewed and revised the manuscript. AY and SLM assisted in study protocol design, results interpretation and critically reviewed and revised the manuscript. BC contributed to analysis plan and study protocol design, secured funding for the study, and critically reviewed and revised the manuscript. All

authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by the Research Ethics Board at the University of Alberta (Pro00005942).

**Provenance and peer review** Commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Data cannot be shared publicly because of consent and confidentiality reasons. Data are available from the Research Informatics Lead, Women and Children's Health Research Institute Mr. Rick Watts (rick.watts@ualberta.ca) or the corresponding author SA (sali@ualberta.ca) for researchers who meet the criteria for access to confidential data.

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