Supplemental Online Content

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**e Appendix 1.** Overview, Data Cleaning, and Data Definitions for the Health Facts Database

**e Appendix 2.** Creation of the Medication Database

**e Figure.** Forest Plots of Patients in the Control (IV Opioids Only) and Intervention (IV Acetaminophen Followed by IV Opioids) Groups Pre- and Postpropensity Score Matching

This supplemental material has been provided by the authors to give readers additional information about their work.
Health Facts® Data warehouse: The analytic dataset used for this analysis ranged from January 2009 to June 2016. The initial date corresponded to the point when the Health Facts® Data warehouse expanded to include, in general, the current set of data elements. Data cleansing included: a) eliminating duplicate and null values; and b) eliminating data inconsistent with valid entries (e.g. admission times of zero, data inconsistent with life, or negative values). Data cleansing relevant to each data type is detailed in the section for each data type.

**Pediatric Patients:** < 22 years of age

**Inpatient:** Inpatients were defined as those having a Health Facts® inpatient classification code or with evidence of care from an Intensive Care Unit (ICU) location including discharge from an ICU care setting, medication requested or dispensed to an ICU care setting, or a laboratory order from an ICU care setting.

**Pediatric Intensive Care Unit (ICU) Patients:** Patients were identified as the encounters that satisfy all the following characteristics:

- Pediatric patient (above).

- Age in hours not equal to 0.

- ICU patients were identified by the care setting associated with laboratory orders, cares setting to which the medication was requested or dispensed and/or the discharge care setting. The care setting required an ICU designation of at least one of the following: intensive care unit, intensive care unit – cardiac, intensive care unit – medical, intensive...
care unit – neurology, intensive care unit – surgical. Neonatal Intensive Care Unit (NICU) patients were excluded.

- The hospital outcome was known based on the hospital discharge disposition.

**Intensive Care Unit Entry and Exit Times:** The ICU entry and exit times were determined as follows. The ICU entry time was recorded as the earliest hour based on the laboratory order, medication request or medication dispensed associated with an ICU location (above). Following ICU entry, if there were no laboratory orders, medication requests or medication dispersals, the location was assumed to be the ICU.

We identified the ICU exit time using the following two conditions: First, the medication request, medication dispensed, or laboratory order came from a non-ICU location following ICU care. If the care setting was null or not mapped, the previous care setting was assumed. If multiple care settings including an ICU were observed during the same hour, the care setting was assumed to be an ICU care setting. Second, if the patient was discharged from the hospital from the ICU, the hospital discharge time was used as the ICU discharge time.

Since we recognized that there is imprecision in the assignment of entry and exit times, we assigned a minimum of 10 hours to each ICU stay for survivors (deaths could have a time period < 10 hours). For patients readmitted to the ICU during a hospitalization, a minimum of 40 hours was assigned to each non-ICU time period between ICU admissions. This resulted in 97.0% of PICU patients having only 1 ICU admission, and 2.3% have 2 ICU admissions, and 0.7% have 3 or more. For the rare patient that had more than 5 ICU admissions (0.13%), the ICU admissions after the 5th were not included in the ICU admission.
Length of ICU stay and time between ICU admissions for those patients with multiple ICU admissions are shown in the table below.

|                              | Median LOS (hours) | IQR (hours) | 25%-75% (hours) |
|------------------------------|-------------------|-------------|-----------------|
| First ICU Admission          | 59                | 142         | 21 - 163        |
| Second ICU Admission         | 38                | 128         | 10 - 138        |
| Third ICU Admission          | 60                | 175         | 10 - 185        |
| Time between First and Second ICU Admission | 181              | 297         | 104 - 401       |
| Time between Second and Third ICU Admission | 186              | 262         | 118-330         |

These data are consistent the published literature.2,3

**Descriptive Data of Hospitals Included in this Report:**

All 274 hospitals included in this analysis met inclusion criteria of donating pediatric inpatients with medication data. Descriptive data of these hospitals are included in the table below.

| Hospital Characteristics   | Number of Patients |
|-----------------------------|--------------------|
| Bed Size1                   |                    |
| >500                        | 289,050            |
| 300 – 499                   | 236,219            |
| 200 – 299                   | 176,947            |
| 100 – 199                   | 96,511             |
| <100                        | 94,566             |
| Census Region               |                    |
| South                       | 110                |
| Midwest                     | 66                 |
| West                        | 49                 |
| Northeast                   | 49                 |
| Teaching Hospital           |                    |
| Yes                         | 650486             |
| No                          | 242807             |

1. Bed size refers to total number of hospital beds and is not specific to pediatric bed availability. Details about pediatric bed numbers were not available in the Health Facts® database.
Health Facts® Laboratory and Clinical Events (Vital Signs, Respiratory) Data:

Laboratory, vital sign, and respiratory data were assessed for measurement units and each test and its specific measurement units were assessed with descriptive statistics and data distributions. Units such as missing or null were combined with the appropriate data when the assessment of the data values, descriptive statistics, and data distributions indicated the identical measurement unit. Laboratory data with several units of measurement were converted to the standard units and combined. This is described in detail in Appendices C and D.

Health Facts® Medication Data: The dataset contains the drug name (generic and brand), national drug code (NDC), medication volume, administration times, and administration frequency that were requested and dispensed from the pharmacy. Medications were assumed to be administered during the times the pharmacy dispensed them to be administered. The duration of medication administration was rounded to the nearest hour. Medications administered once or for less than 1 hour were assigned an administration time of 1 hour. To assess medications by class, the medication table was linked to an industry standard for medication classification, Cerner Multum™ Solutions. Cerner Multum™ provides information about therapeutic action in three categories from general mechanism of action to a specific therapeutic category. A total of 96% of medications were classified by Cerner Multum™. The drugs not categorized by Cerner Multum™ were categorized by individual assessment by three physicians (AKP and MMP) into the pre-existing Cerner Multum™ tiered categories. This is described in detail in Appendix 2.
1. Hardin AP, Hackell JM. Age Limit of Pediatrics. *Pediatrics*. 2017;140(3):e20172151. doi:10.1542/peds.2017-2151

2. Edwards JD, Lucas AR, Stone PW, Boscardin WJ, Dudley RA. Frequency, risk factors, and outcomes of early unplanned readmissions to PICUs. *Crit Care Med*. 2013;41(12):2773-2783. doi:10.1097/CCM.0b013e31829eb970

3. Edwards JD, Lucas AR, Boscardin WJ, Dudley RA. Repeated Critical Illness and Unplanned Readmissions Within 1 Year to PICUs. *Crit Care Med*. 2017;45(8):1276-1284. doi:10.1097/CCM.0000000000002439

4. Fung KW, Kapusnik-Uner J, Cunningham J, Higby-Baker S, Bodenreider O. Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support. *J Am Med Inform Assoc*. 2017;24(4):806-812. doi:10.1093/jamia/ocx010

5. UMLS Metathesaurus - MMSL (Multum) - Synopsis. Accessed July 25, 2018. https://www.nlm.nih.gov/research/umls/sourcereleasedocs/current/MMSL/
eAppendix 2. Creation of the Medication Database

The Health Facts® database contains the drug name (generic and brand), national drug code (NDC), medication volume, administration times, and administration frequency that were requested and dispensed from the pharmacy. Infusion times were available, but sparsely recorded and were therefore not utilized. Medications were assumed to be administered to patients during the times the pharmacy dispensed them to be administered. The duration of medication administration was rounded to the nearest hour. If a single dose of medication was administered in an hour – the patient was considered to have received one hour of medication.

To assess medications by class (ie. IV Opioid medications), the medication table was linked to an industry standard for medication classification, Multum™, via the NDC number.

Multum™ provides information about medications therapeutic action in three categories from general mechanism of action to a specific therapeutic category. Table A provides a summary distribution of the first IV opioid administered in the intervention and control groups before and after propensity score matching.

Table A: First IV Opioid Medication Administered in the Control and Intervention Groups Before and After Propensity Score Matching

| First IV Opioid Medication Administered | Before Propensity Score Matching | After Propensity Score Matching |
|----------------------------------------|----------------------------------|---------------------------------|
|                                        | Control n=102,840 n (%)          | Intervention n=1,739 n (%)      |
|                                        |                                 |                                 |
| Fentanyl                               | 41,136 (40.0)                   | 682 (39.2)                      |
| Morphine                               | 43,707 (42.5)                   | 753 (43.3)                      |
| Hydromorphone                          | 17,380 (16.9)                   | 301 (17.3)                      |
| Meperidine                             | 514 (0.5)                       | 3 (0.2)                         |
| Nalbuphine                             | 103 (0.1)                       | 0 (0.0)                         |

|                                        | Control n=839 n (%)              | Intervention n=839 n (%)        |
|                                        |                                 |                                 |
| Fentanyl                               | 337 (40.2)                      | 338 (40.3)                      |
| Morphine                               | 356 (42.4)                      | 353 (42.1)                      |
| Hydromorphone                          | 144 (17.2)                      | 146 (17.4)                      |
| Meperidine                             | 2 (0.2)                         | 2 (0.2)                         |
| Nalbuphine                             | 0 (0.0)                         | 0 (0.0)                         |

p = 0.045

1. Control group includes patients who received IV opioids without IV acetaminophen.
2. Intervention group includes patients who received IV acetaminophen followed by IV opioids.
eFigure 1. Forest Plots of patients in the control (IV opioids only) and intervention (IV acetaminophen followed by IV opioids) groups pre and post propensity score matching revealing a well-balanced, matched cohort of patients post propensity score matching. Odds ratios reflect a propensity for receipt of IV acetaminophen

### 1a. Pre-Propensity Score Matching

| Baseline Characteristic       | IV Opioids Only | IV Acetaminophen and IV Opioids | Odds Ratio    | P-value |
|------------------------------|----------------|---------------------------------|---------------|--------|
| Circulatory                  | 19 (2.3%)      | 18 (2.1%)                       | 0.95 (0.49 - 1.82) | 0.8680 |
| Digestive System             | 164 (19.5%)    | 159 (19%)                       | 0.96 (0.75 - 1.23) | 0.7569 |
| Genitourinary System         | 38 (4.5%)      | 39 (4.6%)                       | 1.03 (0.65 - 1.62) | 0.9071 |
| Musculoskeletal System       | 41 (4.9%)      | 52 (6.2%)                       | 1.29 (0.84 - 1.96) | 0.2405 |
| Dermatology System           | 13 (1.5%)      | 18 (2.1%)                       | 1.39 (0.68 - 2.86) | 0.3647 |
| Nervous System               | 79 (9.4%)      | 85 (10.1%)                      | 1.08 (0.79 - 1.5)  | 0.6218 |
| Endocrine System             | 57 (6.8%)      | 47 (5.6%)                       | 0.81 (0.55 - 1.21) | 0.3113 |
| Injury and Poisoning         | 161 (19.2%)    | 175 (20.9%)                     | 1.11 (0.87 - 1.41) | 0.3931 |
| -----------------------------|----------------|---------------------------------|---------------|--------|
| **Operations**               | **n=839**      | **n=839**                       |               |        |
| Musculoskeletal System       | 98 (11.7%)     | 91 (10.8%)                      | 0.92 (0.68 - 1.25) | 0.5888 |
| Digestive System             | 69 (8.2%)      | 74 (8.8%)                       | 1.08 (0.77 - 1.52) | 0.6620 |
| Cardiovascular System        | 29 (3.5%)      | 29 (3.5%)                       | 1.0 (0.59 - 1.69)  | 1.0000 |
| Nervous System               | 22 (2.6%)      | 24 (2.9%)                       | 1.09 (0.61 - 1.97) | 0.7649 |
| Integumentary System         | 24 (2.9%)      | 17 (2%)                         | 0.76 (0.37 - 1.32) | 0.2684 |
| Genitourinary System         | 23 (2.7%)      | 17 (2%)                         | 0.73 (0.39 - 1.38) | 0.3370 |
| Respiratory System           | 22 (2.6%)      | 15 (1.8%)                       | 0.68 (0.35 - 1.31) | 0.2445 |
| Endocrine and Lymphatic System| 19 (2.3%)      | 11 (1.3%)                       | 1.10 (0.47 - 2.61) | 0.8262 |

--- Less likely --- More likely ---
| Baseline Characteristic       | IV Opioids Only | IV Acetaminophen and IV Opioids | Odds Ratio | P-value |
|------------------------------|-----------------|---------------------------------|------------|---------|
| Circulatory                  | 2540 (2.5%)     | 39 (2.2%)                       | 0.91(0.66 - 1.25) | 0.5447  |
| Digestive System             | 1633 (15.9%)    | 34 (19.3%)                      | 1.31(1.16 - 1.47) | <.0001  |
| Genitourinary System         | 3884 (3.8%)     | 74 (4.3%)                       | 1.15(0.9 - 1.43)  | 0.2997  |
| Musculoskeletal System       | 4316 (4.2%)     | 120 (7.2%)                      | 1.84(1.54 - 2.21) | <.0001  |
| Dermatologic System          | 3258 (3.2%)     | 36 (2.1%)                       | 0.65(0.46 - 0.9)  | 0.0093  |
| Nervous System               | 6852 (6.7%)     | 163 (9.4%)                      | 1.45(1.23 - 1.71) | <.0001  |
| Endocrine System             | 4250 (4.1%)     | 98 (5.6%)                       | 1.39(1.13 - 1.7)  | 0.0019  |
| Injury and Poisonings        | 31193 (30.3%)   | 341 (19.6%)                     | 0.56(0.5 - 0.63)  | <.0001  |
| Operations                   | 102840          | 1739                            |             |         |
| Musculoskeletal System       | 8857 (8.6%)     | 205 (11.8%)                     | 1.42(1.22 - 1.64) | <.0001  |
| Digestive System             | 9508 (9.2%)     | 160 (9.2%)                      | 0.99(0.84 - 1.17) | 0.9491  |
| Cardiovascular System        | 8734 (8.5%)     | 71 (4.1%)                       | 0.46(0.36 - 0.58) | <.0001  |
| Nervous System               | 5198 (5.1%)     | 57 (3.3%)                       | 0.64(0.49 - 0.83) | 0.0008  |
| Integumentary System         | 4518 (4.2%)     | 4 (2.4%)                        | 0.55(0.4 - 0.73)  | 0.0001  |
| Genitourinary System         | 3608 (3.5%)     | 50 (2.9%)                       | 0.96(0.73 - 1.28) | 0.7928  |
| Respiratory System           | 3368 (3.3%)     | 40 (2.3%)                       | 0.70(0.51 - 0.95) | 0.0232  |
| Endocrine and Lymphatic System | 956 (0.9%)   | 17 (1%)                         | 1.05(0.65 - 1.7)  | 0.8363  |

| Baseline Characteristic       | IV Opioids Only | IV Acetaminophen and IV Opioids | Odds Ratio | P-value |
|------------------------------|-----------------|---------------------------------|------------|---------|
| Admit Year                   | 102840          | 1739                            |             | <.0001  |
| 2011                         | 17651 (17.2%)   | 59 (3.4%)                       | 0.10(0.08 - 0.13) | .       |
| 2012                         | 477 (0.5%)      | 2 (0.1%)                        | 0.10(0.03 - 0.51) | .       |
| 2013                         | 25275 (27.5%)   | 381 (21.9%)                     | 0.46(0.34 - 0.47) | .       |
| 2014                         | 2817 (27.4%)    | 568 (32.7%)                     | 0.96(0.52 - 1.7)  | .       |
| 2015                         | 20308 (19.7%)   | 465 (26.7%)                     | 0.99(0.59 - 0.98) | .       |
| 2016                         | 7908 (7.7%)     | 264 (15.2%)                     | Reference   | .       |
| Census Region                | 102840          | 1739                            |             | <.0001  |
| Midwest                      | 1911 (18.4%)    | 210 (12.1%)                     | 1.27(1.06 - 1.52) | .       |
| North                        | 19776 (19.2%)   | 625 (35.9%)                     | 3.61(1.33 - 4.15) | .       |
| South                        | 31166 (31%)     | 621 (35.7%)                     | 2.22(1.83 - 2.56) | .       |
| West                         | 32287 (31.4%)   | 283 (16.3%)                     | Reference   | .       |
| Bed Size Range               | 102840          | 1739                            |             | <.0001  |
| >100                         | 8539 (8.3%)     | 110 (6.3%)                      | 1.55(1.23 - 1.96) | .       |
| 200-299                      | 24004 (23.9%)   | 182 (10.5%)                     | 0.89(0.73 - 1.09) | .       |
| 300-499                      | 16692 (16.2%)   | 283 (16.3%)                     | 2.04(1.7 - 2.44)  | .       |
| >900                         | 28484 (27.7%)   | 906 (51.2%)                     | 4.05(3.48 - 4.72) | .       |
| ≤100                         | 24321 (23.8%)   | 204 (11.7%)                     | Reference   | .       |
| Teaching Facility            | 102222          | 1727                            |             | <.0001  |
| Yes                          | 68515 (67%)     | 1489 (85.7%)                    | 2.95(2.58 - 3.38) | .       |
| No                           | 33707 (33%)     | 248 (14.3%)                     | Reference   | .       |
### 1b. Post-Propensity Score Matching

| Baseline Characteristic | IV Opioids Only | IV Acetaminophen and IV Opioids | Odds Ratio | P-value |
|-------------------------|----------------|--------------------------------|-----------|---------|
| **Age Group**           | n=839          | n=839                          |           |         |
| age <2 years            | 102 (12.2%)    | 83 (9.9%)                      | 0.71 (0.49 - 1.02) | 0.2750 |
| age ≥ 3 - 22 years      | 503 (60%)      | 493 (58.8%)                    | 0.85 (0.66 - 1.09) |        |
| age ≥ 3 - 5 years       | 82 (9.8%)      | 88 (10.5%)                     | 0.95 (0.64 - 1.55) |        |
| age ≥ 6 - 13 years      | 152 (18.1%)    | 175 (20.9%)                    | Reference  |        |
| **Race**                | n=839          | n=839                          |           |         |
| African American        | 202 (24.1%)    | 206 (24.6%)                    | 1.07 (0.74 - 1.54) |        |
| Caucasian               | 484 (57.7%)    | 477 (56.9%)                    | 0.97 (0.75 - 1.25) |        |
| Others                  | 151 (18.2%)    | 156 (18.6%)                    | Reference  |        |
| **Gender**              | n=839          | n=839                          |           |         |
| Female                  | 388 (46.2%)    | 408 (48.6%)                    | 1.10 (0.91 - 1.33) |        |
| Male                    | 451 (53.8%)    | 431 (51.4%)                    | Reference  |        |
| **Ventilation Group**   | n=839          | n=839                          |           |         |
| Mechanical Ventilation  | 19 (2.3%)      | 12 (1.4%)                      | 0.63 (0.3 - 1.3)  |        |
| Non-Invasive Mechanical Ventilation | 1 (0.1%) | 5 (0.6%) | 4.98 (0.38 - 42.74) |        |
| no                      | 819 (97.6%)    | 822 (98.6%)                    | Reference  |        |
| **InitialTemperature Group** | n=839 | n=839 |  |         |
| InitialTemperature <58  | 766 (91.3%)    | 766 (91.3%)                    | 0.91 (0.56 - 1.49) |        |
| InitialTemperature >58.5| 39 (4.6%)      | 38 (4.5%)                      | 0.89 (0.46 - 1.72) |        |
| Temperature 38-38.5     | 32 (3.8%)      | 35 (4.2%)                      | Reference  |        |
| **Diagnosis**           | n=839          | n=839                          |           |         |
| Congenital              | 145 (17.3%)    | 128 (15%)                      | 0.85 (0.65 - 1.1)  | 0.2075 |
| Neoplasms               | 61 (7.3%)      | 59 (7%)                        | 0.96 (0.47 - 1.9)  | 0.8497 |

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| Baseline Characteristic | IV Opioids Only | IV Acetaminophen and IV Opioids | Odds Ratio | P-value |
|------------------------|-----------------|--------------------------------|------------|---------|
| Circulatory            | 19 (2.3%)       | 18 (2.1%)                      | 0.95 (0.49 - 1.82) | 0.8480 |
| Digestive System       | 164 (19.5%)     | 159 (19%)                      | 0.96 (0.75 - 1.23) | 0.7569 |
| Genitourinary System   | 38 (4.5%)       | 39 (4.6%)                      | 1.05 (0.65 - 1.62) | 0.9071 |
| Musculoskeletal System | 41 (4.9%)       | 52 (6.2%)                      | 1.29 (0.84 - 1.96) | 0.2405 |
| Dermatology System     | 13 (1.5%)       | 18 (2.1%)                      | 1.39 (0.68 - 2.86) | 0.3647 |
| Nervous System         | 79 (9.4%)       | 85 (10.1%)                     | 1.08 (0.79 - 1.5)  | 0.6218 |
| Endocrine System       | 57 (6.8%)       | 47 (5.6%)                      | 0.81 (0.55 - 1.21) | 0.3113 |
| Injury and Poisonings  | 161 (19.2%)     | 175 (20.9%)                    | 1.11 (0.87 - 1.41) | 0.3931 |
| Operations             | n=839           | n=839                          |            |         |
| Musculoskeletal System | 98 (11.7%)      | 91 (10.8%)                     | 0.92 (0.68 - 1.25) | 0.5888 |
| Digestive System       | 65 (8.2%)       | 74 (8.8%)                      | 1.08 (0.77 - 1.52) | 0.6620 |
| Cardiovascular System  | 29 (3.5%)       | 29 (3.5%)                      | 1.09 (0.79 - 1.53) | 1.0000 |
| Nervous System         | 22 (2.6%)       | 24 (2.9%)                      | 1.09 (0.61 - 1.97) | 0.7649 |
| Integumentary System   | 24 (2.9%)       | 17 (2%)                        | 0.70 (0.47 - 1.13) | 0.2684 |
| Genitourinary System   | 23 (2.7%)       | 17 (2%)                        | 0.73 (0.45 - 1.20) | 0.3370 |
| Respiratory System     | 22 (2.6%)       | 15 (1.8%)                      | 0.68 (0.35 - 1.35) | 0.2445 |
| Endocrine and Lymphatic System | 10 (1.2%) | 11 (1.3%)                  | 1.10 (0.47 - 2.61) | 0.8262 |

| Baseline Characteristic | IV Opioids Only | IV Acetaminophen and IV Opioids | Odds Ratio | P-value |
|------------------------|-----------------|--------------------------------|------------|---------|
| Admin Year             | n=839           | n=839                          |            |         |
| 2011                   | 28 (3.5%)       | 31 (3.7%)                      | 0.93 (0.54 - 1.62) | 0.4624 |
| 2013                   | 201 (24%)       | 214 (25.3%)                    | 0.90 (0.67 - 1.21) | 0.5976 |
| 2014                   | 485 (53%)       | 397 (47.3%)                    | 0.75 (0.59 - 0.96) | 0.0935 |
| 2015                   | 1 (0.1%)        | 2 (0.2%)                       | 1.68 (0.15 - 18.72) | 0.3603 |
| 2016                   | 164 (19.5%)     | 195 (23.2%)                    | Reference   |         |
| Census Region          | n=839           | n=839                          | 0.9200      |         |
| Midwest                | 100 (11.9%)     | 105 (12.5%)                    | 1.07 (0.74 - 1.53) | 0.6324 |
| North                  | 279 (33.3%)     | 268 (31.9%)                    | 0.97 (0.73 - 1.3)  | 0.7000 |
| South                  | 319 (38%)       | 327 (39%)                      | 1.04 (0.79 - 1.38) | 0.7984 |
| West                   | 141 (16.8%)     | 139 (16.6%)                    | Reference   |         |
| Bed Size Range         | n=839           | n=839                          | 0.9820      |         |
| <100                   | 100 (12%)       | 49 (5.8%)                      | 0.88 (0.55 - 1.42) | 0.3403 |
| 200-299                | 138 (16.4%)     | 136 (16.2%)                    | 0.92 (0.64 - 1.32) | 0.7300 |
| 300-499                | 164 (19.5%)     | 167 (19.9%)                    | 0.95 (0.67 - 1.35) | 0.8200 |
| 500+                   | 387 (46.1%)     | 382 (45.5%)                    | 0.92 (0.68 - 1.26) | 0.7680 |
| <100                   | 98 (11.7%)      | 105 (12.5%)                    | Reference   |         |
| Teaching Facility      | n=839           | n=839                          | 0.7340      |         |
| Yes                    | 714 (85.1%)     | 709 (84.5%)                    | 0.95 (0.73 - 1.25) | 0.8200 |
| no                     | 125 (14.9%)     | 130 (15.5%)                    | Reference   |         |