**Supplementary Tables**

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| Supplementary Table 1. Estimated mean and median cost and length of stay (LOS) derived from the 2017 National Inpatient Sample-Healthcare Cost and Utilization Project (NIS-HCUP) dataset. | | | | | | | |
| Surgery  type | Mean cost  per admission  (median) | Mean LOS in days (median) | Cost of one day less than median LOS | Cost of one day longer than median LOS | Mean  age  (years) | Age 60+ years  in % | Number of patients  with cost in NIS |
| All surgeries combined | $24,168  ($16,618) | 4.54 (3) | $3,163 | $3,365 | 61.0 | 59.6% | 467,796 |
| **By Type of Surgery** | | | | | | | |
| Gastrectomy | $17,051  ($11,252) | 3.47 (2) | $1,081 | $2,682 | 48.0 | 22.2% | 33,963 |
| Gastric Bypass | $23,002  ($14,958) | 5.13 (2) | $1,446 | $3,152 | 49.5 | 24.8% | 14,012 |
| Colon Resection | $28,906  ($19,603) | 8.56 (6) | $1,826 | $2,321 | 62.9 | 62.0% | 39,479 |
| Knee Arthroplasty | $16,590  ($14,540) | 2.33 (2) | $1,412 | $2,011 | 66.6 | 77.2% | 161,189 |
| CABG | $49,830  ($41,514) | 9.84 (8) | $2,995 | $2,358 | 66.1 | 75.0% | 40,117 |
| Spinal Fusion | $32,756  ($25,745) | 4.09 (3) | $4,916 | $4,664 | 59.6 | 53.7% | 88,874 |
| Chole-cystectomy | $18,113  ($12,883) | 4.88 (3) | $1,881 | $1,954 | 54.7 | 43.9% | 67,277 |
| Abdominal Repair | $26,116  ($15,567) | 7.24 (4) | $2,046 | $2,328 | 59.0 | 51.3% | 33,259 |

CABG: coronary artery bypass graft.

The unweighted means from the 2017 National Inpatient Sample (NIS) sample were used for calculation of the marginal cost for each surgical types shown here. The mean cost per admission was estimated by applying each hospital’s cost-to-charge ratio to the total charges for the admission, a standard approach for summarizing HCUP data.

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| Supplementary Table 2. Estimated cost weights for opioid-induced respiratory depression events by type of surgery (in 2017 US dollars). | | | |
| Type of surgery | Median estimated OIRD cost/event | Lowest estimate: OIRD cost/event based on 15% of cost/admission | Highest estimate: OIRD cost/event based on 36.4% increased LOS |
| Mean for all surgeries | $4,589 | $3,625 | $5,552 |
| **By Type of Surgery** | | | |
| Gastrectomy | $2,973 | $2,558 | $3,388 |
| Gastric Bypass | $4,668 | $3,450 | $5,886 |
| Colon Resection | $5,784 | $4,336 | $7,232 |
| Knee Arthroplasty | $2,097 | $2,489 | $1,706 |
| CABG | $7,960 | $7,475 | $8,446 |
| Spinal Fusion | $5,928 | $4,913 | $6,944 |
| Cholecystectomy | $3,094 | $2,717 | $3,471 |
| Abdominal Repair | $5,026 | $3,917 | $6,135 |

CABG: coronary artery bypass graft; LOS: length of stay; OIRD: opioid-induced respiratory depression.

Based on the PRODIGY analysis, the cost of OIRD may be estimated as either 15% of the mean cost per surgery, or as the cost associated with an increase of 36.4% in hospital LOS [21]. The lowest estimate for the cost of an OIRD shown here are calculated as 15% of the cost of an admission. The PRODIGY estimate of 36.4% increase in LOS was used to calculate the highest estimate.

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| Supplementary Table 3. Health economic model cost weights for opioid-induced respiratory depression, vomiting, and somnolence inflated to 2020 US dollar costs. | | | |
| Event Type | 2020 cost weights used  for base model\* | ± 20% range for sensitivity analysis | Cost in 2017 US dollars  (low - high) |
| Respiratory depression (Low O2 saturation) | **$3,975** | $3,180 - $4,770 | $4,589  ($3,625 - $5,552) |
| Vomiting | **$1,035** | $828 - $1,242 | $1,344  ($972 - $1,716) |
| Somnolence | **$991** | $793 - $1,189 | $1,250  ($904 - $6,353) |

\*2020 costs reflect the inflated cost from the low range of the 2017 cost

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| Supplementary Table 4. Base model estimates: Summary of impact of sensitivity analyses on the base model estimates. | | |
| Input parameter varied in sensitivity analysis | Total cost savings per 1,000 treated patients | |
| Lower bound estimated effect | Upper bound estimated effect |
| Oliceridine daily cost (range: $60 to $150 per day) | $277,711 | $174,381 |
| Adverse outcomes (range: 20% lower to 20% higher)  Vomiting  O2 Saturation  Somnolence | $205,847  $187,172  $227,541 | $251,061  $269,735  $229,366 |
| Cost of additional pain medications  (range: 50% greater cost to 50% lower cost) | $230,193 | $226,714 |
| Clinical efficacy (response to oliceridine)  (range: 10% greater to 10% lower) | $220,941 | $235,967 |

Baseline estimated cost savings of the use of oliceridine rather than morphine among 1,000 patients was $228,454.

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| Supplementary Table 5. Oliceridine parameter values used in the Monte Carlo simulations (values for morphine parameters were similarly varied). | | | | |
| Model  parameter | Base model value | Low value | High value | Distribution function |
| Adverse Outcomes | | | | |
| Low O2 saturation | 8.3% | 7.5% | 9.1% | Beta |
| Vomiting | 10.1% | 9.1% | 11.1% | Beta |
| Somnolence | 1.9% | 1.7% | 2.1% | Beta |
| Costs | | | | |
| Low O2 saturation | $3,675 | $3,180 | $6,835 | Gamma |
| Vomiting | $1,035 | $828 | $1,800 | Gamma |
| Somnolence | $991 | $793 | $1,725 | Gamma |
| Antiemetic medication | $3.60 | $2.88 | $6.25 | Gamma |
| Additional pain medication | $131.40 | $105 | $230 | Gamma |