**Model development**

*Data Preparation*

The data was converted from a “long” format with every drug given a separate line within an incident/victim combination to a “wide” format where every drug had a separate column and every incident/victim combination had only one line. The resulting file had 8,369 incidents and 8,525 victims. Each victim occurred only once by Victim ID, although there may be issues with longitudinal tracking. There were 2,319 incidents with multiple victims, averaging 2.42 victims per such incident, with a range of 2-12.

Because of small cell counts, the only drugs examined specifically were HEROIN, FENTANYL and UNKNOWN. Similarly, Race was consolidated into White, Black, or Unknown/Other. The three lowest age brackets were combined into 19 or lower, and the three highest into 60 or older.

Survive had three levels – Y, N or U – so two binary outcomes were considered. Died was Survive==”N” as opposed to “Y” or “U”, and Lived was Survive ==”Y” versus “N” or “U”

*Structure of Model*

To generate a tractable model, the ‘rms’ package in R was used to identify consistent features for a logistic regression model. The original model had the form:

***Died = f(Naxalone.Administered x [ HEROIN x (FENTANYL+UNKNOWN) + Age.Range + Race +Ethnicity.Desc+Day)])***

which allowed for Naxalone to interact with all variables and included Ethnicity and Day.

The reduced model had the structure

***Died =f(Naxalone.Administered x [ HEROIN x (FENTANYL) + Age.Range)]) +UNKNOWN +Race***

where Ethnicity and Day fell out and so did interaction between Naxalone and Race or UNKNOWN drug. Performance of this reduced model was good – AUC of 0.804, 0.800 after optimism correction. Calibration curves also matched the ideal performance between 0 and 80% probability of death.

Using the ‘lmerTest’ package, the logistic regression model was adjusted by first adding a random intercept per county to allow for variations in death rate, then by further adding a random slope so that each county might have varying efficacy with Naxalone. Changes in AIC suggested that the random slope+intercept model was the best to use. After being developed for Died as an outcome, it was also calculated for Lived as an outcome. As expected, the predictors had comparable effects in opposite directions. The ICC for the two models was < 0.10, suggesting that the county-level effect only accounted for less than 10% of the outcome variation.

*Model Predictions*

The ‘ggeffects’ packages was used to create marginal model estimates for Naxalone vs HEROIN/FENTANYL combinations and for Naxalone vs Age bracket. The model predictions were very close to the percentages calculated directedly from raw data; where there was a differential, it was that the model predictions had a stronger effect for Naxalone, suggesting that there was some case-mix element within the raw groups that the model prediction accounted for.

For odds of death, the raw data indicates that the odds ratio for Naxalone was 0.31 if neither HEROIN nor FENTANYL were reported present, 0.11 if HEROIN alone was present, and 0.06 if FENTANYL was present with or without HEROIN. Similarly, Naxalone improved odds of living with an odds ratio of 1.32 if neither HEROIN nor FENTANYL were reported, 5.09 if HEROIN alone was present, and 10.78 or 11.33 for FENTANYL in the absence or presence of reported HEROIN. The effect of Naxalone was also consistently larger in older patients, who would in fact have been at higher risk of death without it.

The plot of random effects indicates that in general, the random intercept and the random slope canceled out – if the county had a higher risk of death without Naxalone, it had a higher benefit from Naxalone, and vice versa. However, inspection of random effects for both the models with outcome of death and outcome of lived show that a handful of counties broke this pattern. Based on the confidence intervals for random effects, Adams County (code 001) and Lycoming (081) had consistently better odds of survival without Naxalone and improved response from Naxalone, while Crawford (039) and Monroe (089) had both poorer odds of survival without Naxalone and poorer response from it. This may simply be a statistical artifact, or it may be worth further investigation.