Hannam, Borrat *et al*., A model for propofol-remifentanil respiratory depression, *J Pharmacol Exp Ther.*, 12 June 2015.

## Supplemental Data.

## Table S1: Summary of model development

Model development stages are ranked based on the absolute decrease in -2LL according to the model structure (i.e. system parameters, drug parameters, covariates).

| Description | + n | ΔOBJ | *P* |
|---|---|---|---|
| **System** | | | |
| + IIV on $K_{mod}$ | +1 | -8917.55 | \*\*\*< 0.001 |
| + modulator compartment (using $K_{mod}$) | +1 | -635.10 | \*\*\*< 0.001 |
| + unfix α parameter | +1 | -336.489 | \*\*\*< 0.001 |
| **Remifentanil** | | | |
| Linear remifentanil effect (3 parameters) | | | |
| Fractional remifentanil effect (3 parameters) | | -2377.09 | \*\*\*< 0.001 |
| + IIV on $IC_{50R}$ | +1 | -19255.5 | \*\*\*< 0.001 |
| + $I_{MAX,R}$* | +1 | -1001.13 | \*\*\*< 0.001 |
| + effect compartment (using $k_{e0}$) | +1 | -531.56 | \*\*\*< 0.001 |
| + γ (slope parameter) remifentanil | +1 | -99.73 | \*\*\*< 0.001 |
| **Propofol** | | | |
| + propofol effect on $K_{mod}$ | +1 | -2586.43 | \*\*\*< 0.001 |
| + $I_{MAX,P}$ ‡ | +1 | -1069.24 | \*\*\*< 0.001 |
| **Covariates** | | | |
| + Age cov effect on $IC_{50P}$ † | +1 | -265.55 | \*\*\*< 0.001 |
| + Age cov effect on $k_{e0R}$ † | +1 | -201.01 | \*\*\*< 0.001 |
| + Age cov effect on $IC_{50R}$ | +1 | -191.08 | \*\*\*< 0.001 |
| + NOX cov effect on $K_{deg}$ | +1 | -117.14 | \*\*\*< 0.001 |
| + OPRM cov effect on $IC_{50R}$ | +1 | +91.23 | NS |

+n indicates the number of additional parameters to be estimated from the comparison model. OBJ is NONMEM´s objective function value and roughly equates to the -2 x log likelihood. A reduction in OBJ (ΔOBJ) greater than 3.84 between nested models is required for significance at α < 0.01. *This parameter was later removed as the estimate approached 1 and removal did not result in a significant worsening of model fit. ‡The inclusion of a maximal inhibitory effect on propofol was statistically significant but estimated a 1.0 and so not included in the final model. Significant covariates were estimated together, and those that failed to contribute to model fit removed reach final model (retained parameters indicated in table by †)

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## Supplemental Data 2. Sensitivity analysis of parameters

The impact of changes in each individual parameter on the population $pCO_2$ profile is shown, for ten minute fixed infusions of 2.0 µg/ml propofol and 2.5 ng/ml remifentanil. Simulations show the average profile for the typical population value ($\Theta_{TV}$), and the 5% and 95% confidence interval values as calculated from the standard errors provided by NONMEM.