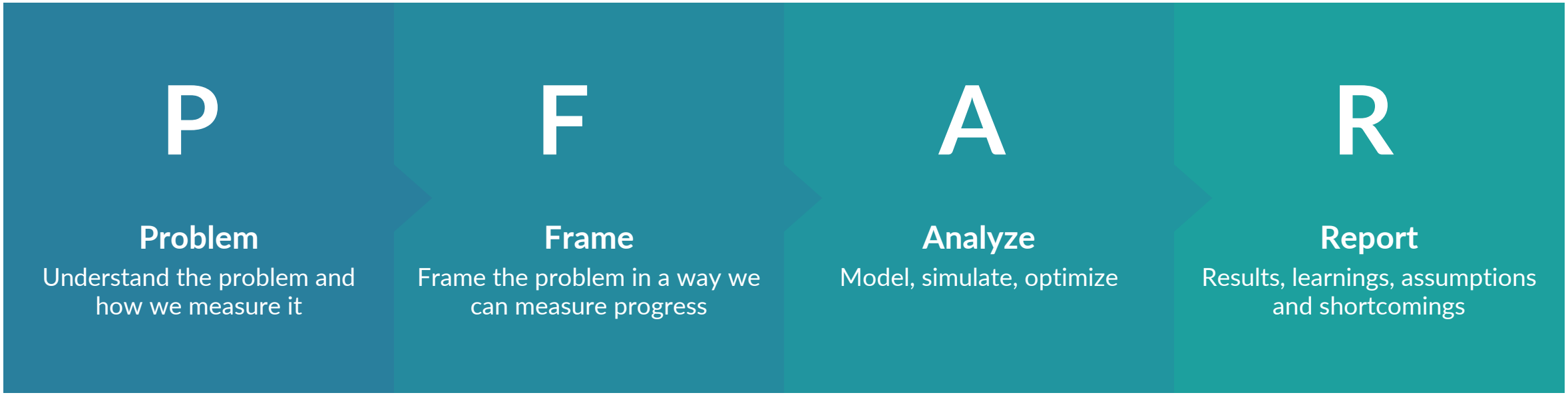
# Adaptive Buprenorphine Dose Simulations

## In Infants with NOWS

# Contents



"If you don't know where you are going, you'll end up someplace else." – Yogi Berra



# P

## Problem

Understand the problem and
how we measure it

# Neonatal Opioid Withdrawal Syndrome (NOWS)



NOWS is a condition seen among infants born to mothers who have used opioids during the course of their pregnancy[1]

1. Incidence has increased substantially in the setting of the opioid epidemic [1]
2. Symptoms include: autonomic instability, tremor, irritability, poor feeding, and loose stool.
3. 1/3 of infants with NOWS respond to behavioral approaches to treatment (minimization of stimulations, rooming in, breast-feeding, high cal meals. The other ~ 2/3 require pharmacologic intervention [2].
4. Standard of care includes administering an opioid for cosymptomatic control; then weaning off. Best opioid of choice is still under debate.

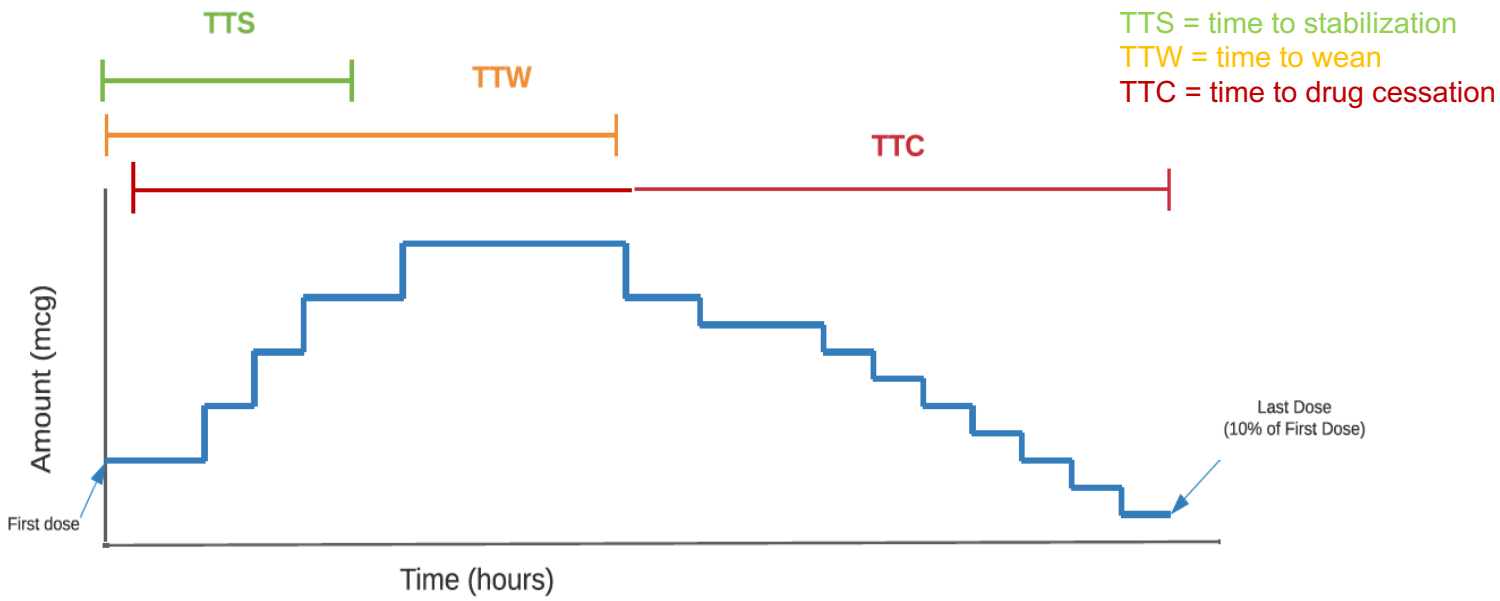

1. Weller AE, Crist RC, Reiner BC, Doyle GA, Berrettini WH. Neonatal Opioid Withdrawal Syndrome (NOWS): A Transgenerational Echo of the Opioid Crisis. Cold Spring Harb Perspect Med. 2021 Mar 1;11(3):a039669. doi: 10.1101/cshperspect.a039669. PMID: 32229609; PMCID: PMC7919394.
2. Kraft WK, Adeniyi-Jones SC, Chervoneva I, *et al.* Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome. *N Engl J Med* 2017;**376**:2341–8.

# Project Objectives



## Modeling Project Objective

Use existing PK and PD models to validate and update recommendations for buprenorphine **starting dose, titration rate, and weaning rate.**




## Clinical Objective

Reduce hospital stays (weaning and time to cessation) for infants with NOWS

# F

## Frame

Frame the problem in a way we can measure progress

# Simulation Question

**What starting dose and titration rate is required to reach target exposure and full stabilization in 50% of patients, in less than 12 days?**

Target exposure 0.8 ng/mL

AUC0-inf of 40 ng-hr/mL in moderately severe NAS

12 days to reach stabilization without treatment.

# A

## Analyze

Model, simulate, optimize

# Clinical Trials



**PHASE 1**

- N = 13/13 (2008)
- MOTHER NAS N = 12/12 (2012)

## BBORN

**Blinded Buprenorphine OR Neonatal morphine solution (2017)**

N = 33 / 30 per group

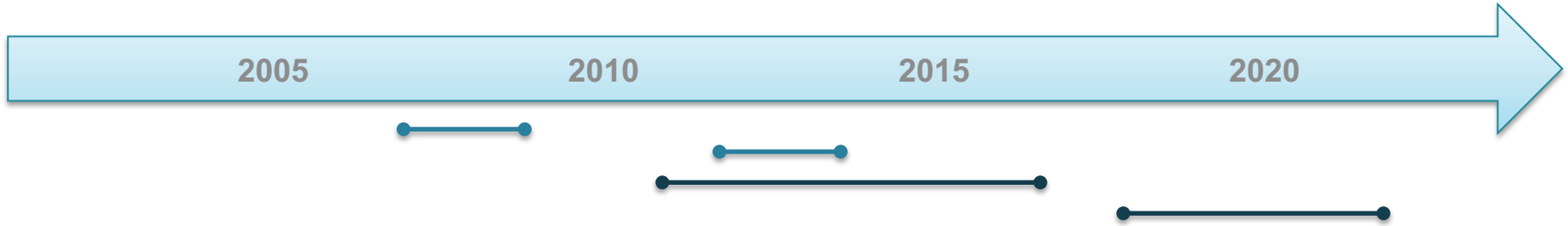
**Start Dose:** 15.9 ug/kg SOC morphine
**Response:** MOTHER NAS
**Outcome:** Buprenorphine reduced hospital stay by median 12 days, relative to morphine (median 23.8 days)

## BPHORE

**Buprenorphine Pharmacometric Open Label Research study of Drug Exposure (2021)**

N = 10

**Start Dose:** 24 ug/kg
**Response:** MOTHER NAS
**Outcome:** Median observed length of treatment was 16.8 days



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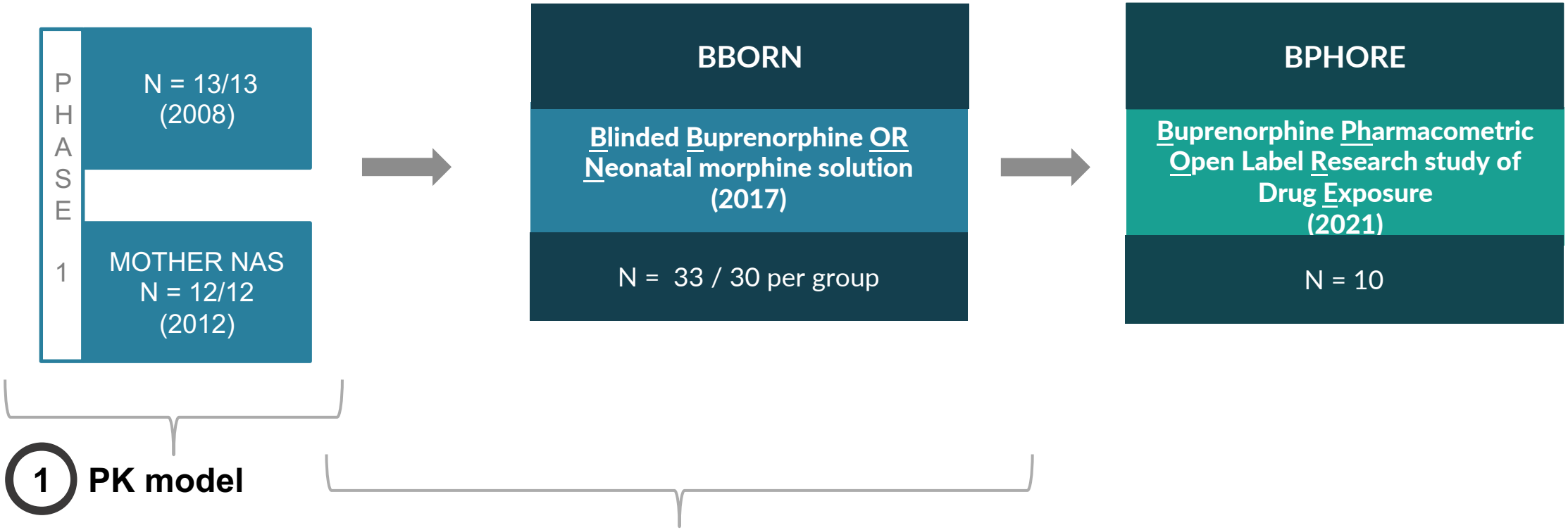
# Model Data Schematic





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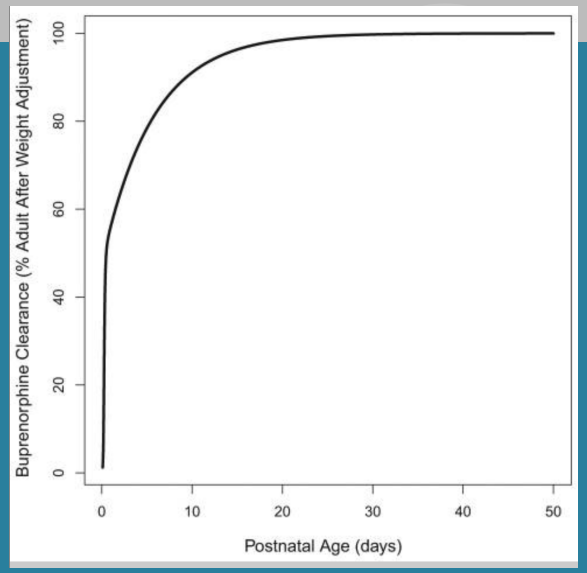
# Pharmacokinetics of sublingual buprenorphine in neonates with NAS

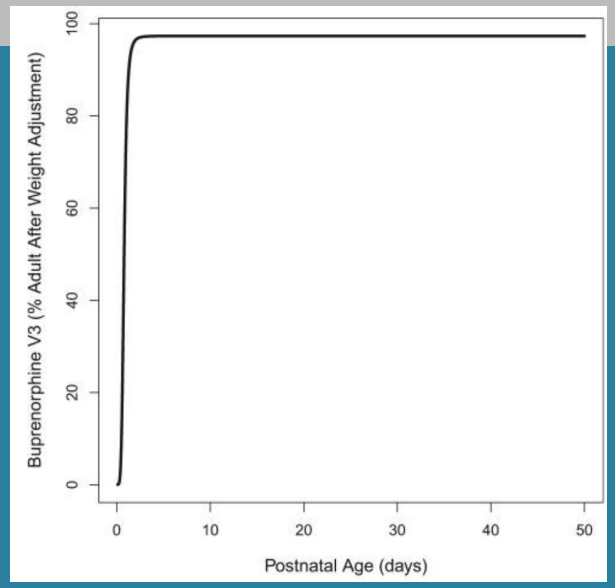
## PK Model

$$CL = \theta_{CL} \times \left( \frac{Emax \times PNA^{SLP}}{KM^{SLP} + PNA^{SLP}} \right) + (1 - Emax_{TF}) \times \left(1 - e^{-TF \times PNA}\right) \times \left(\frac{WT}{70}\right)^{0.75} \quad (1)$$

$$V3 = \theta_{V_3} \times BASE + \frac{(1 - BASE) * PNA^{SLP1}}{KM_{V3}^{SLP1} + PNA^{SLP1}} \times \left(\frac{WT}{70}\right) \quad (2)$$

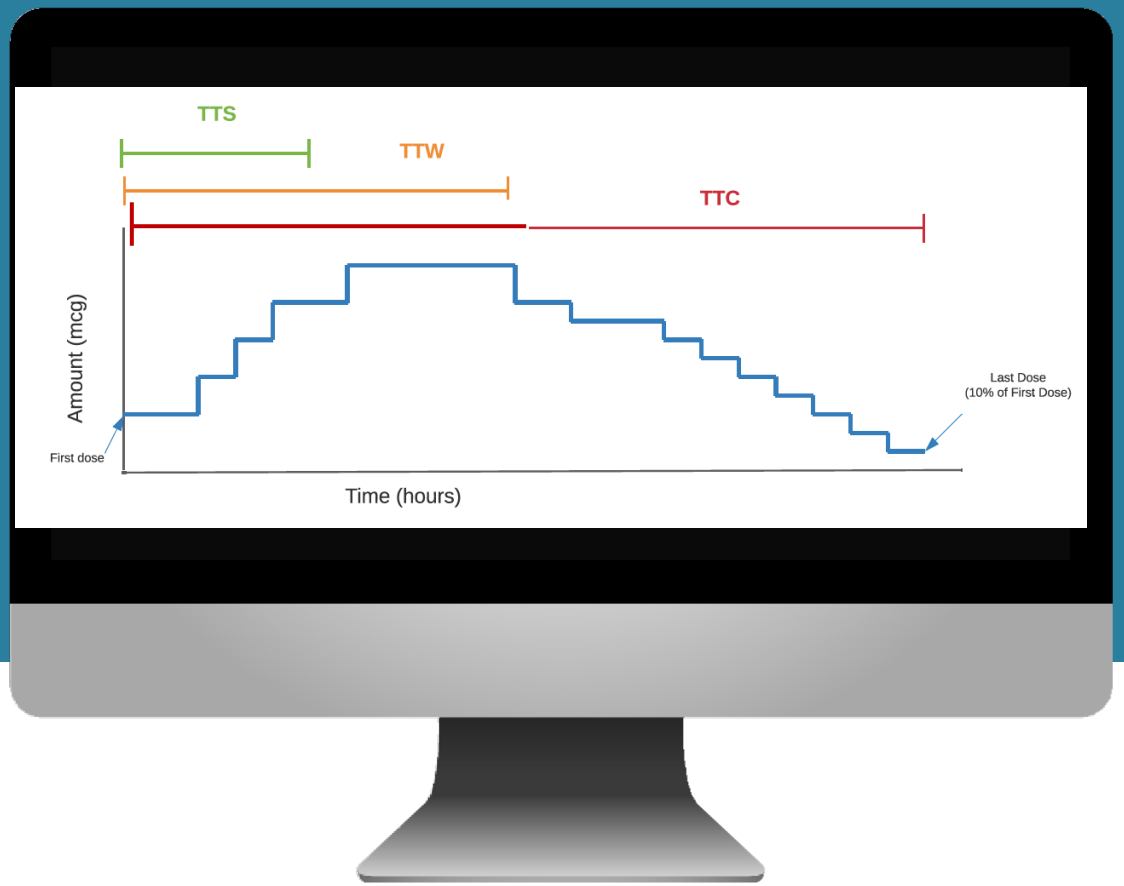
- PNA – post natal age
- SLP – hill coefficient
- Emax – max effect of PNA on CL for first pathway
- KM – half max effect of PNA on CL
- $Emax_{TF}$ – Saturation point for second PNA –dependent pathway
- TF- rate constant of saturation rate for second PNA-dependent CL pathway




Ng CM, Dombrowsky E, Lin H, Erlich ME, Moody DE, Barrett JS, Kraft WK. Population Pharmacokinetic Model of Sublingual Buprenorphine in Neonatal Abstinence Syndrome. Pharmacotherapy. 2015 Jul;35(7):670-80. doi: 10.1002/phar.1610. Epub 2015 Jul 14. PMID: 26172282; PMCID: PMC5119858.

# BBORN




## Dosing Scheme:

Starting dose: 15.9 ug/kg/day

Max daily dose: 60 ug/kg/day

Up-titration rate: 25% q8hr

Max number of up-titrations: 6

Wean rate: 10% q8hr

Cessation: < 10% of starting dose

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# MOTHER NAS

Based on Finnegin neonatal abstinence scoring system

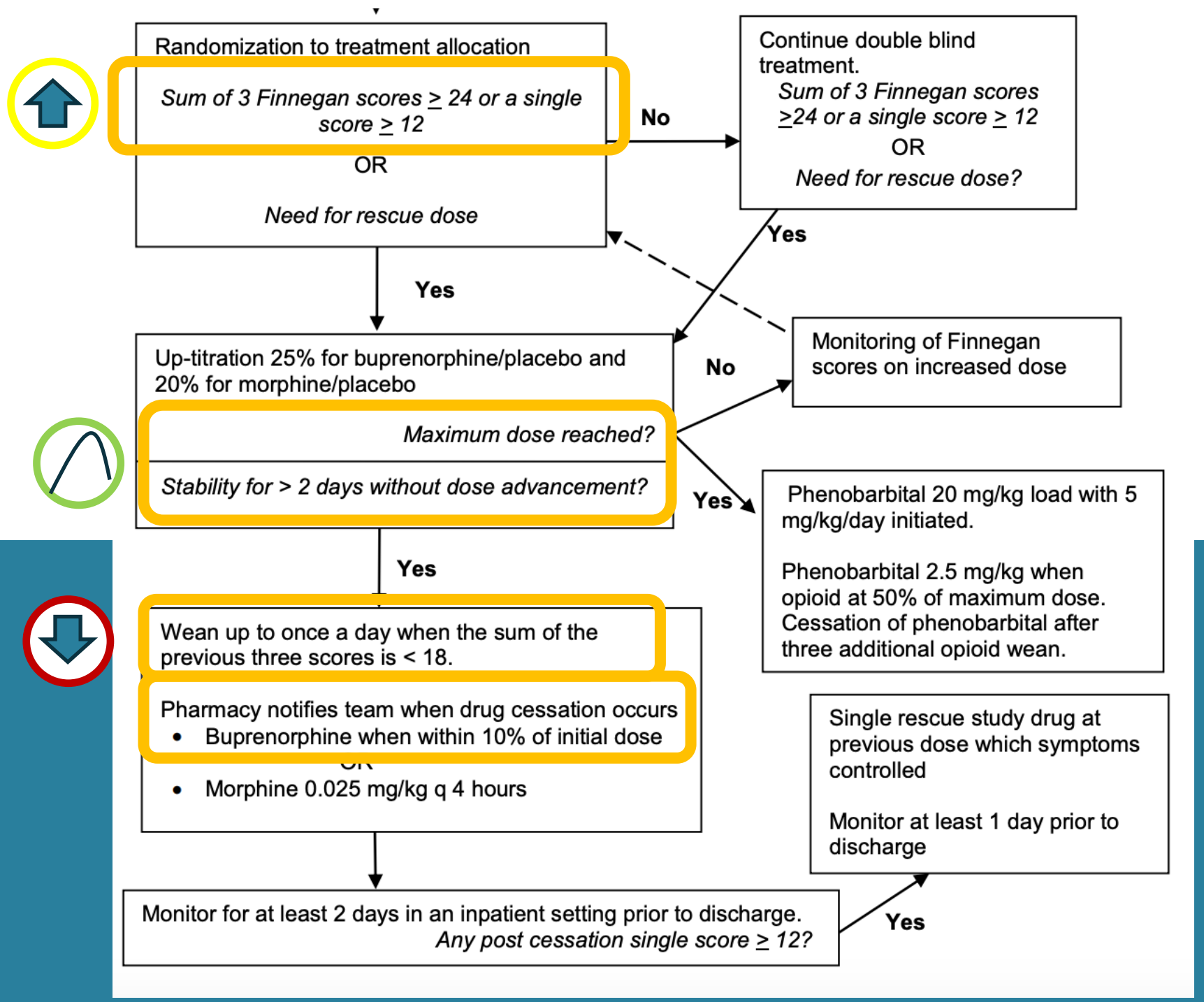


| **Scored Elements** | |
|---|---|
| *Signs and Symptoms* | *Score* |
| Crying: Excessive high pitched<br>Crying: Continuous high pitched | 2<br>3 |
| Sleeps < 1 hours after feeding<br>Sleeps < 2 hours after feeding<br>Sleeps < 3 hours after feeding | 3<br>2<br>1 |
| Hyperactive Moro Reflex<br>Markedly Hyperactive Moro Reflex | 1<br>2 |
| Mild Tremors: Disturbed<br>Moderate-Severe Tremors: Disturbed | 1<br>2 |
| Mild tremors: Undisturbed<br>Moderate-Severe Tremors: Undisturbed | 1<br>2 |
| Increased Muscle Tone | 1-2 |
| Excoriation (Indicate specific area): | 1-2 |
| Generalized Seizure (or convulsion) | 8 |
| Fever > 37.3 C (99.2 F) | 1 |
| Frequent Yawning (4 or more successive times) | 1 |
| Sweating | 1 |
| Nasal Stuffiness | 1 |
| Sneezing (4 or more successive times) | 1 |
| Tachypnea (Respiratory Rate >60/mm) | 2 |
| Poor feeding | 2 |
| Vomiting (or regurgitation) | 2 |
| Loose Stools | 2 |
| Failure to thrive (Current weight > 10% below birth weight 90% BWT=_____<br>*(record weight in score box 1 x day)* | 2 |
| Excessive Irritability | 1-3 |
| **Total Score** | |

# Dosing Scheme

BBORN






Titration Rate | Max Dose | Wean Rate

# Pharmacodynamics

Model

WITH is time course of withdrawal as a function of PNA and rate of xenobiotic removal (DRUGK)

NASMAX = max withdrawal symptoms

$$WITHD = 1 - EXP(-DRUGK * PNA)$$

$$NAST = NASMAX * KM_{NAS}^{HILL2}/(PNA^{HILL2} + KM_{NAS}^{HILL2})$$

$$E = E2MAX * C2^{HILL}/(EC50^{HILL} + C2^{HILL}) + 1$$

$$DNAS/DT = WITHD * NAST - KNAS * NAS * E,$$

$KM_{NAS}$ age at which half max withdrawal symptoms is reached

E is drug (bup) effect

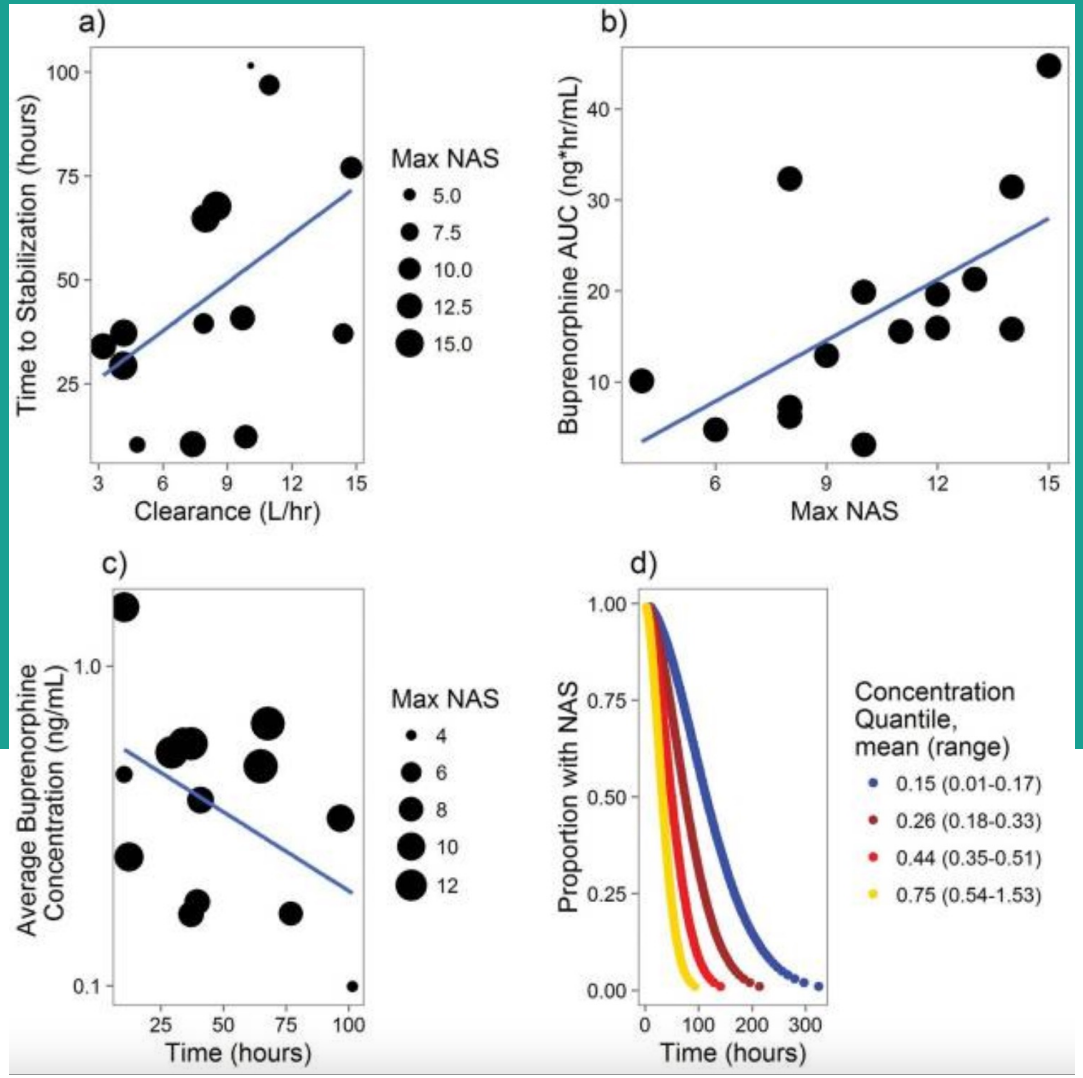
d (NAS) /dt is rate of NAS change

Moore JN, Gastonguay MR, Ng CM, Adeniyi-Jones SC, Moody DE, Fang WB, Ehrlich ME, Kraft WK. The Pharmacokinetics and Pharmacodynamics of Buprenorphine in Neonatal Abstinence Syndrome. Clin Pharmacol Ther. 2018 Jun;103(6):1029-1037. doi: 10.1002/cpt.1064. Epub 2018 Apr 28. PMID: 29516490; PMCID: PMC5992055.

# Pharmacodynamics

Observed

BBORN




- CL largest source of variability
- TTS increased with CL
- Predicted stabilization time (plot d, shown here) --> 0.8 ng/mL


Moore JN, Gastonguay MR, Ng CM, Adeniyi-Jones SC, Moody DE, Fang WB, Ehrlich ME, Kraft WK. The Pharmacokinetics and Pharmacodynamics of Buprenorphine in Neonatal Abstinence Syndrome. Clin Pharmacol Ther. 2018 Jun;103(6):1029-1037. doi: 10.1002/cpt.1064. Epub 2018 Apr 28. PMID: 29516490; PMCID: PMC5992055.

# BPHORE

## Dosing Scheme:

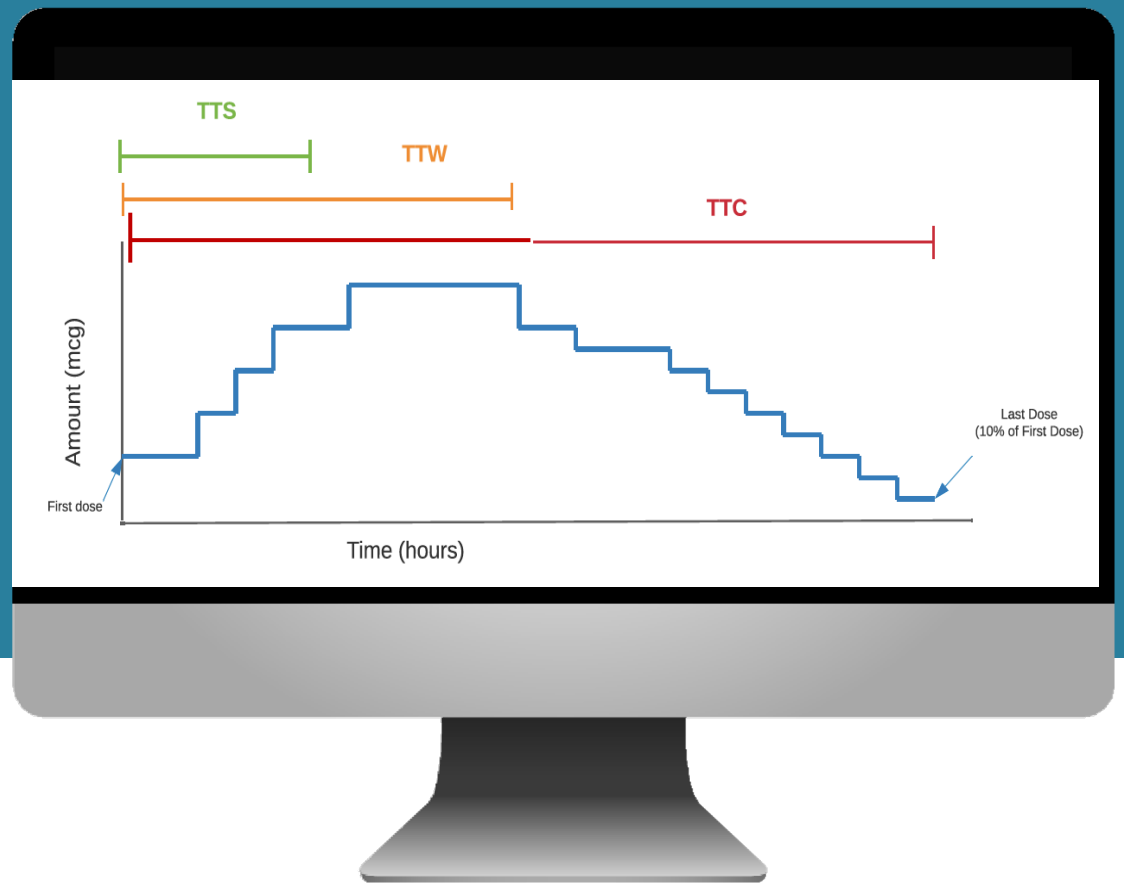



**Table S1.** Dose Regimen used for model generation (BBORN trial) and model testing (BPHORE)

| Trial | BBORN | BPHORE |
|---|---|---|
| Initial dose (mcg/kg q 8 hr) | 5.3 | 8 |
| Uptitration rate | 25% | 33% |
| Maximum number of up-titrations | 6 | 4 |
| Maximum dose (mcg/kg q 8 hr) | 20 | 25 |
| Maximum daily dose (mcg/kg) | 60 | 75 |
| Weaning rate | 10% | 15% |
| Cessation dose | ≤ 110% of initial dose | ≤ 100% of initial dose |
| Dosing interval until bottom dose (hrs) | 8 | 8 |
| Dose interval extension #1 at bottom dose (hrs) | N/A | 12 |
| Dose interval extension #2 at bottom dose (hrs) | N/A | 24 |

Starting Dose | Titration Rate | Max Dose | Wean Rate



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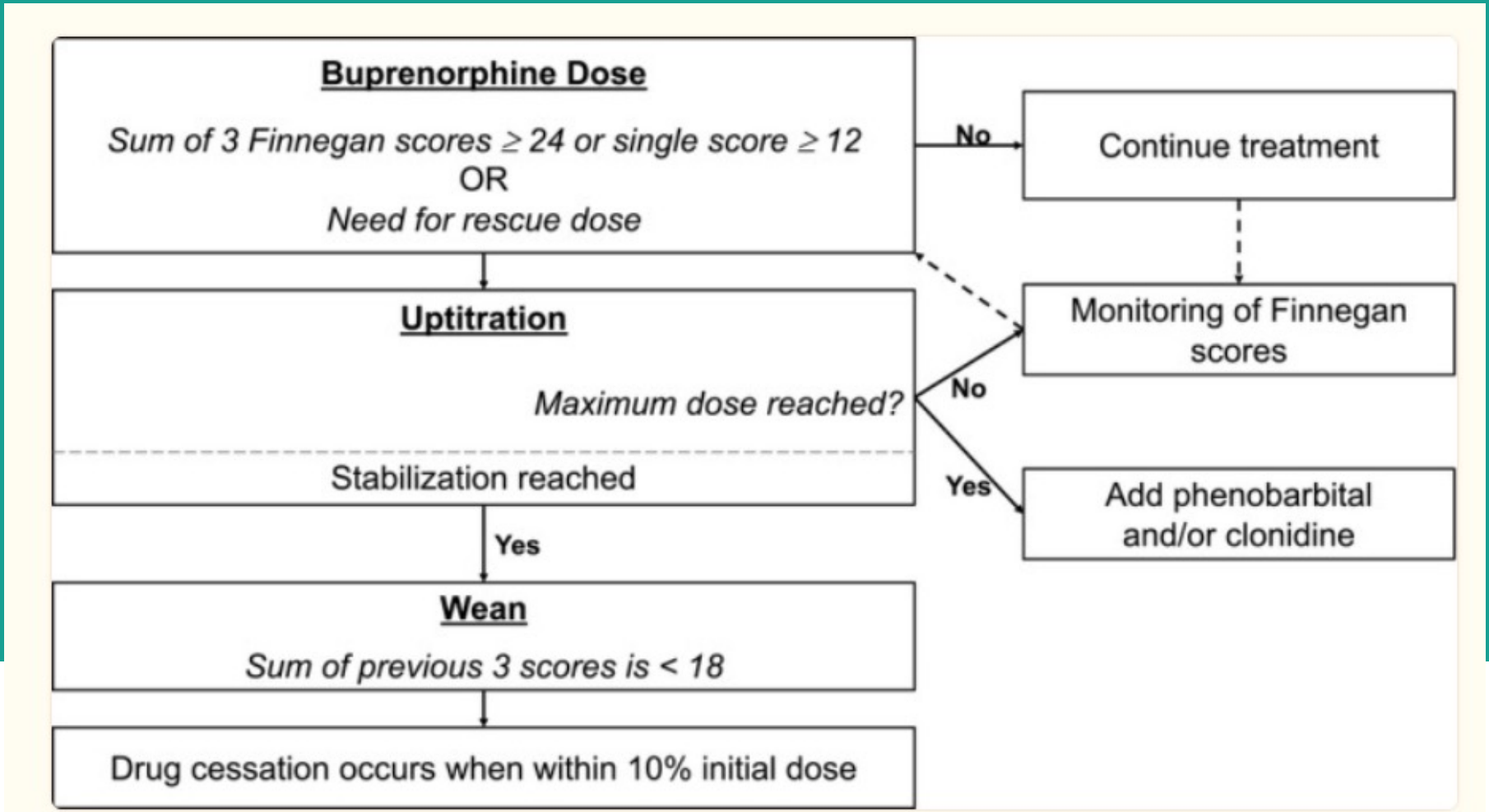
# Dosing Scheme

BPHORE



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# PD model : updated



$$NOWST = NOWSMAX * exp(-NOWSM * PNA)$$

$$EFFECT_{drug} = EMAX * C2 / (EC50 + C2) + 1$$

$$\frac{dNOWS}{dt} = K_{in} * (1 + NOWST) - K_{out} * NOWS * EFFECT_{drug}$$

$$NOWS_0 = K_{in} * (1 + NOWST)/K_{out},$$

| Parameter | Units | Estimate | 95% CI | % CV | Shrinkage (%) |
|---|---|---|---|---|---|
| NOWSMAX | score | 1.92 | (1.76, 2.08) | | |
| NOWSM | 1/day | 0.107 | (0.102, 0.112) | | |
| EMAX | unitless | 1.85 | (1.83, 1.87) | | |
| EC50 | ng/mL | 0.942 | (0.870, 1.01) | | |
| $K_{in}$ | score/hr | 0.139 | (0.128, 0.151) | | |
| $K_{out}$ | 1/hr | 0.0301 | (0.0300, 0.0302) | | |
| $\omega_{1.1}$: NOWSMAX | unitless | 1.14 | (-10.8, 13.1) | 146 | 23.8 |
| $\omega_{2.1}$: NOWSM -NOWSMAX | unitless | 0.990 | (-1.32, 3.30) | 0.778 (corr) | |
| $\omega_{2.2}$: NOWSM | unitless | 1.42 | (-4.71, 7.55) | 177 | 28.9 |
| $\omega_{3.3}$: $K_{out}$ | unitless | 0.108 | (0.0686, 0.148) | 33.8 | 9.26 |
| $\omega_{4.4}$: EMAX | unitless | 0.726 | (0.566, 0.887) | 103 | 15.6 |
| $SIGMA_{add}$ | score | 2.30 | (2.29, 2.30) | | |

# Adaptive Dose Simulations



**What mrgsolve provides that NONMEM does not in this example.**

**And NONMEM is not**

- ONE model (not a million control streams)
- Easier to *make it adaptable*
- *Rolling sum of 3 NAS scores*

# Code examples



## Header file

rollsum.h

```
1
2  #include <vector>
3  #include <iostream>
4  #include <cmath>
5
6  class roll {
7  public:
8    std::vector<double> history;
9    int n_add;
10   void reset();
11   void add(double value);
12   double sum();
13 };
14
15 void roll::reset() {
16   history.clear();
17   history.assign(3,0.0);
18   n_add = 0;
19 }
20
```

```
21
22 double roll::sum() {
23   if(n_add < 3) {
24     return -1.0;
25   }
26   double ans  = 0;
27   for(int i = 0; i < history.size(); ++i) {
28     ans = ans + history.at(i);
29   }
30   return ans;
31 }
32
33 void roll::add(double value) {
34   history[0]  = history[1];
35   history[1] = history[2];
36   history[2] = value;
37   ++n_add;
38
39 }
```

# Code examples



Model file

rollsum.cpp

Source on Save

```
1  $INCLUDE rollsum.h
2
3  $GLOBAL
4  rollsum hx;
5
6  $MAIN
7  if(NEWIND <=1) {
8    hx.reset(100);
9  }
10
11 $CMT FOO
12
13 $TABLE
14 hx.add(TIME);
15 capture rolling_sum = hx.sum();
16
17
```

# Code examples



## Model file

RS = rolling sum (of last 3 NAS)

```
120  // Titrate
121  if(RS>=24 || LFIN >=12){
122    if(DTYPE ==0 && EVID ==1){
123      NUMTIT = LNUMTIT + 1;
124      LNUMTIT = NUMTIT;
125      TITR = 1;
126      NUMWEAN = LNUMWEAN;
127      LNUMWEAN = NUMWEAN;
128    }
129  }
130  // Wean
131  if(LFIN <=8,NUMTIT>=1 && RS<18 && DTYPE==0 && EVID ==1){
132    NUMWEAN = LNUMWEAN + 1;
133    LNUMWEAN = NUMWEAN;
134    WEAN = 1;
135    TITR = 1;
136    NUMTIT = LNUMTIT;
137    LNUMTIT = NUMTIT;
138  }
```

```
170
171  if(EVID==105) hx.add(LFIN);
172  capture RS = hx.sum();
```

# R

## Report

Results, learnings, assumptions
and shortcomings

# Survival curves



## Probability of Stabilization

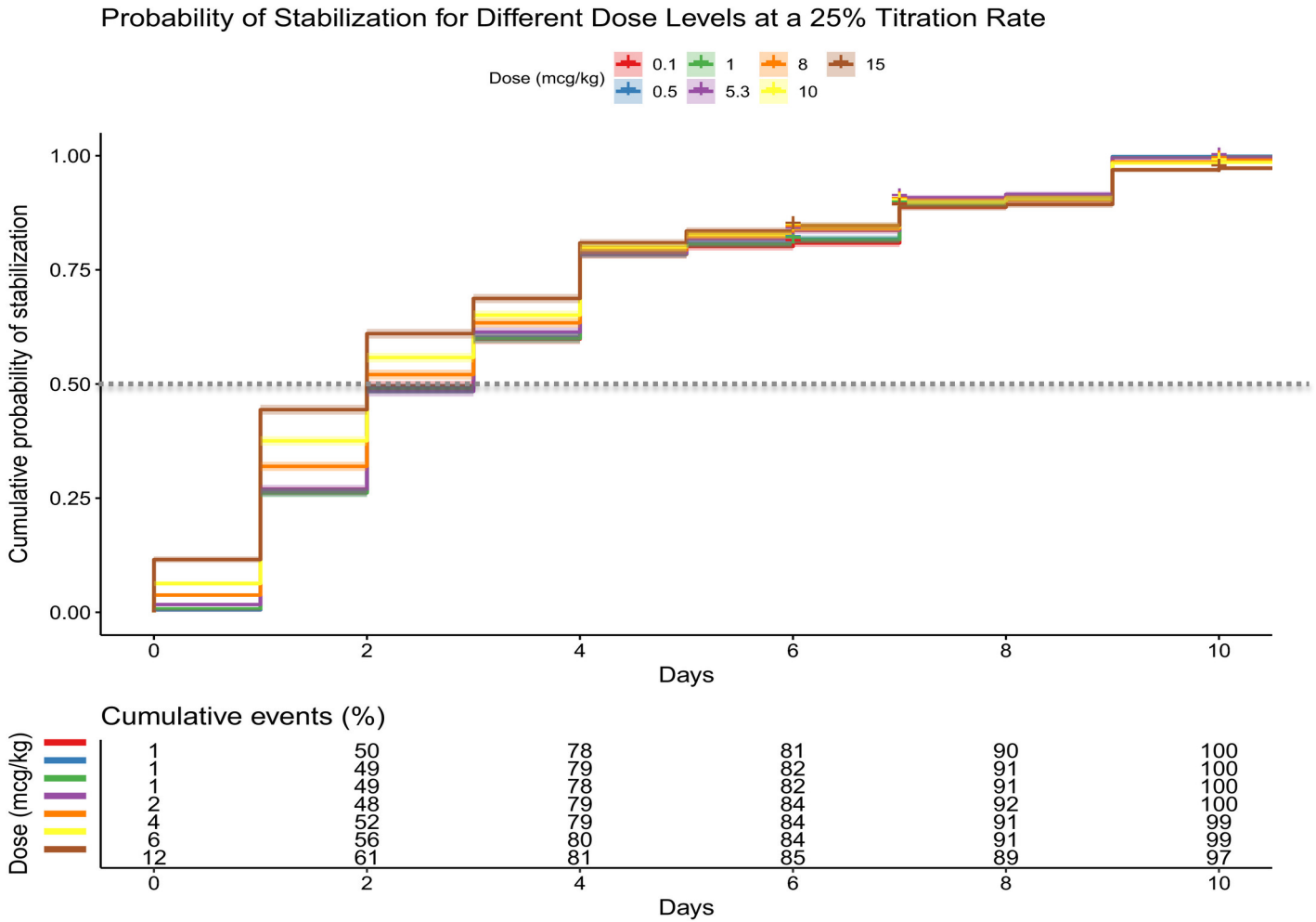
**Kaplan-Meier Plot**

Simulated time to event time to stabilization (TTS) at different initial dose levels and at a 25% up-titration rate.

\+ denotes censoring

**Summary Table**

Summary of the estimated percentage of patients who have reached stabilization, stratified by starting dose



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# Survival curves



## Probability of Weaning

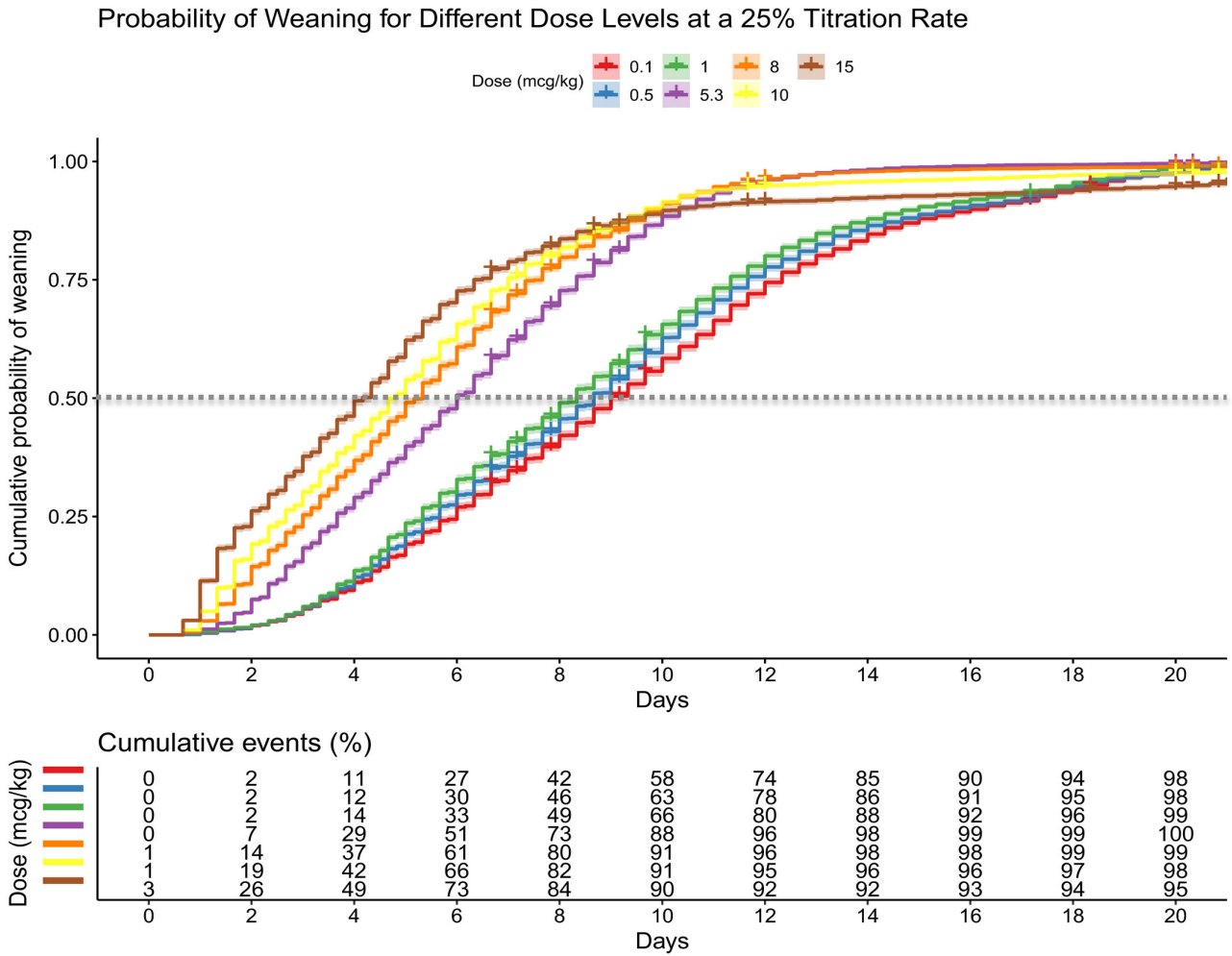
**Kaplan-Meier Plot**

Simulated time to event time to stabilization (TTS) at different initial dose levels and at a 25% up-titration rate.

\+ denotes censoring

**Summary Table**

Summary of the estimated percentage of patients who have reached weaning, by starting dose



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# Simulation Table



**TABLE 2** Simulated stabilization, weaning and cessation times (days) for probability level of at least 50% by initial dose and up-titration and wean rates

| | Titration rate (%) | | | Wean rate (%) | | |
|---|---|---|---|---|---|---|
| **Dose** | **25** | **30** | **50** | **10** | **15** | **25** |
| Time to stabilization (days) | | | | | | |
| 0.1 | 2.7 | 1.7 | 2 | | | |
| 0.5 | 2.7 | 1.7 | 2 | | | |
| 1 | 2.7 | 1.7 | 2 | | | |
| 5.3 | 2.7 | 1.7 | 2.3 | | | |
| 8 | 2.3 | 1.7 | 2 | | | |
| 10 | 2 | 1.5 | 2 | | | |
| 15 | 1.7 | 1.3 | 1.7 | | | |
| Time to weaning (days) | | | | | | |
| 0.1 | 9 | 9 | 9 | | | |
| 0.5 | 8.7 | 8.7 | 8.7 | | | |
| 1 | 8.3 | 8.3 | 8.3 | | | |
| 5.3 | 6 | 6 | 6.3 | | | |
| 8 | 5.3 | 5 | 5.3 | | | |
| 10 | 4.8 | 4.7 | 5 | | | |
| 15 | 4.2 | 4.2 | 4.3 | | | |
| Time to cessation (days) | | | | | | |
| 0.1 | | | | 22.7 | 19 | 15.3 |
| 0.5 | | | | 21.7 | 18.3 | 15 |
| 1 | | | | 21 | 17.3 | 14 |
| 5.3 | | | | 15 | 12.7 | 10 |
| 8 | | | | 12.7 | 10.7 | 8.7 |
| 10 | | | | 12 | 10 | 8 |
| 15 | | | | 10 | 8.3 | 6.7 |

*Note:* The observed time to stabilization, time to wean, and time to cessation in the Blinded Buprenorphine OR Neonatal morphine (BBORN) trial (dose = 5.3 μg/kg, 25% titration level, and 10% wean level) at the same probability was 4.92, 9.37 and 19.8 days, respectively.

# Optimized parameters


## Dosing Scheme:

8 ug/kg

Starting Dose

25-30%

Titration Rate

15-25%

Wean Rate

Max Dose

- Estimated EC50 was 0.942 ng/ml (0.870-1.01 95% CI)
- Average concentration was ~ 0.26 ng/mL for both studies
- This indicates we are having efficacy at the low end of the exposure-response curve and could potentially dose much higher



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# Discussion

Some of the shortcomings of the simulations



## Protocol deviations

Were at the discretion of the attending physician and cannot be mimicked completely by the simulations

## Maximum dose

Rule was not imposed in the simulations, because adjuvant therapies could not be simulated accurately

## Adjuvant therapies

50% of subjects in BPHORE reached max dose and needed phenobarbital and/or clonidine

## Titration events

Protocol stated only 1 event within 24 hours; this was not imposed in simulations.

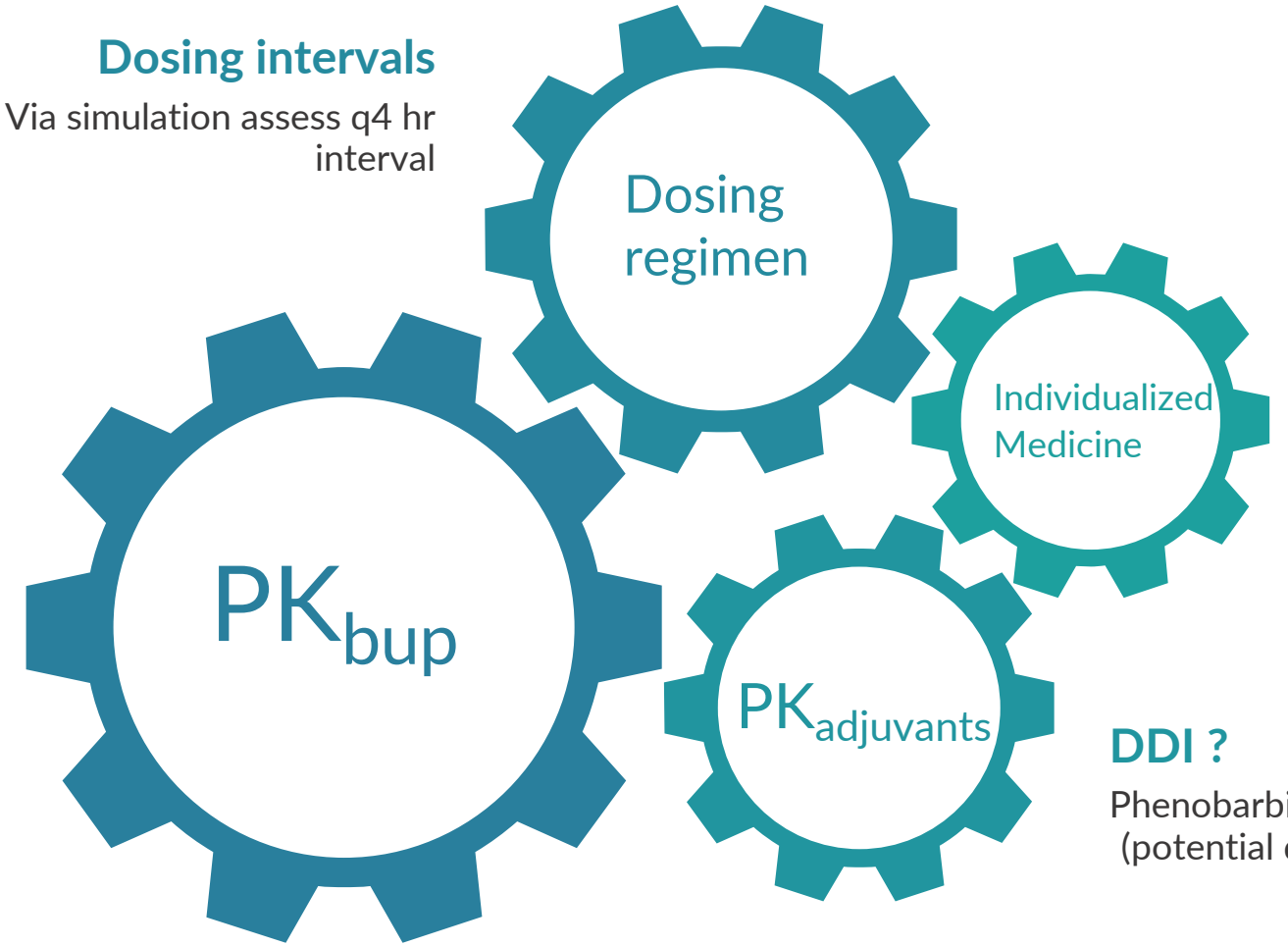
# Future Work

Still lots to do.



### Dosing intervals

Via simulation assess q4 hr interval




### Opportunities

Real-time simulations

### Parent-metabolite

Buprenorphine, norbuprenorphine, and glucuronidated buprenorphine (in urine).

### DDI ?

Phenobarbital
(potential drug-drug interaction)



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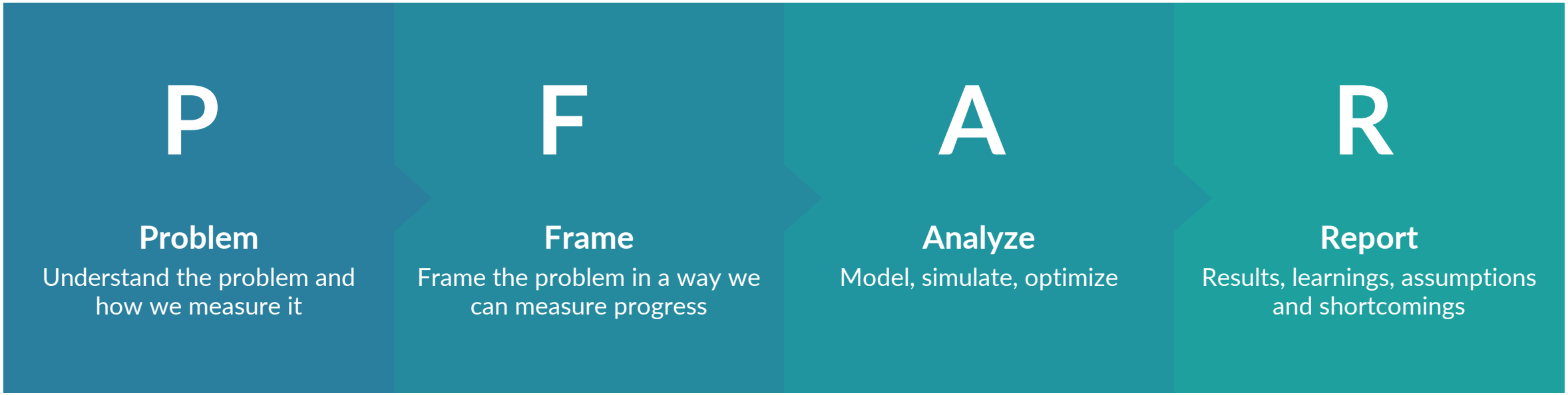
# Contents



"If you don't know where you are going, you'll end up someplace else." – Yogi Berra



# Thank you!



Dr. Kraft

Dr. Gastonguay

Dr. Ruiz-Garcia

My email:

renae@metrumrg.com

Back ups

NOWS statistics:

"In 2019, 1 in 5 women who used prescription opioid pain relievers during their pregnancy reported misuse of these medications, defined as receiving opioids from a non-healthcare source or using for a reason other than to relieve pain

Ko JY, D'Angelo DV, Haight SC, Morrow B, Cox S, Salvesen von Essen B, et al. Vital signs: prescription opioid pain reliever use during pregnancy-34 U.S. Jurisdictions, 2019. MMWR Morb Mortal Wkly Rep. 2020;69:897–903.

From 2010 to 2017, the estimated NAS rate significantly increased by 3.3 per 1000 birth hospitalizations (95% CI, 2.5-4.1), from 4.0 (95% CI, 3.3-4.7) to 7.3 (95% CI, 6.8-7.7).

Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal Abstinence Syndrome and Maternal Opioid-Related Diagnoses in the US, 2010-2017. JAMA. 2021 Jan 12;325(2):146-155. doi: 10.1001/jama.2020.24991. Erratum in: JAMA. 2021 Jun 8;325(22):2316. PMID: 33433576; PMCID: PMC7804920.

According to 2020 data from the Healthcare Cost and Utilization Project (HCUP), which is managed by the U.S. Agency for Healthcare Research and Quality, about six newborns were diagnosed with neonatal abstinence syndrome (NAS) for every 1,000 newborn hospital stays.

https://www.cdc.gov/pregnancy/opioids/data.html