RTTE modelling of opioid consumption
in postoperative pain

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Postoperative pain

A major healthcare issue
~ 230 million surgeries performed each year (in 2008)

A medical need:
Few advances despite intensive clinical research

A need to rethink how clinical trials are designed and analysed

Weiser TG, et al. 2008 Lancet
Wu CL, Raja SN. 2011 Lancet

Trial design challenges

1. Pain is subjective
2. Placebo effects
3. Ethics: Rescue medication

Rescue:
Opioids

Rescue medication: How to handle in clinical trials?

1) Handle as dropouts

✓ Controlled setting

✓ Informative dropout can be modelled

% Limited time period

2) Include rescue in analysis

✓ Setting of intended treatment

% Pain confounded by rescue medication

- **Opioid consumption used as an indirect measure of efficacy**
  - Traditionally summed at end-of-trial

M Bjornsson & USH Simonson. 2011. Br J Clin Pharmacol.
Juul, R.V., Knøsgaard, K.R., et al. 2016. The AAPS journal.
Sechzer PH. 1968. Anesthesiology

Opioid consumption in a perspective

Opioid consumption reported in **600+ trials** trials

Kissin 2009

A history of **inappropriate** analysis applications

Moore 2011

Inability to account for important **time-varying factors**, such as side-effects

McQuay 2008

Not recommended as an independent endpoint in pain trials

FDA 2014

Kissin I, 2009. Anesth Analg
Moore RA, et al 2011. Eur J Anaesthesiol
McQuay, et al 2008. Br J Clin Pharm
FDA, 2014 Guidance for industry

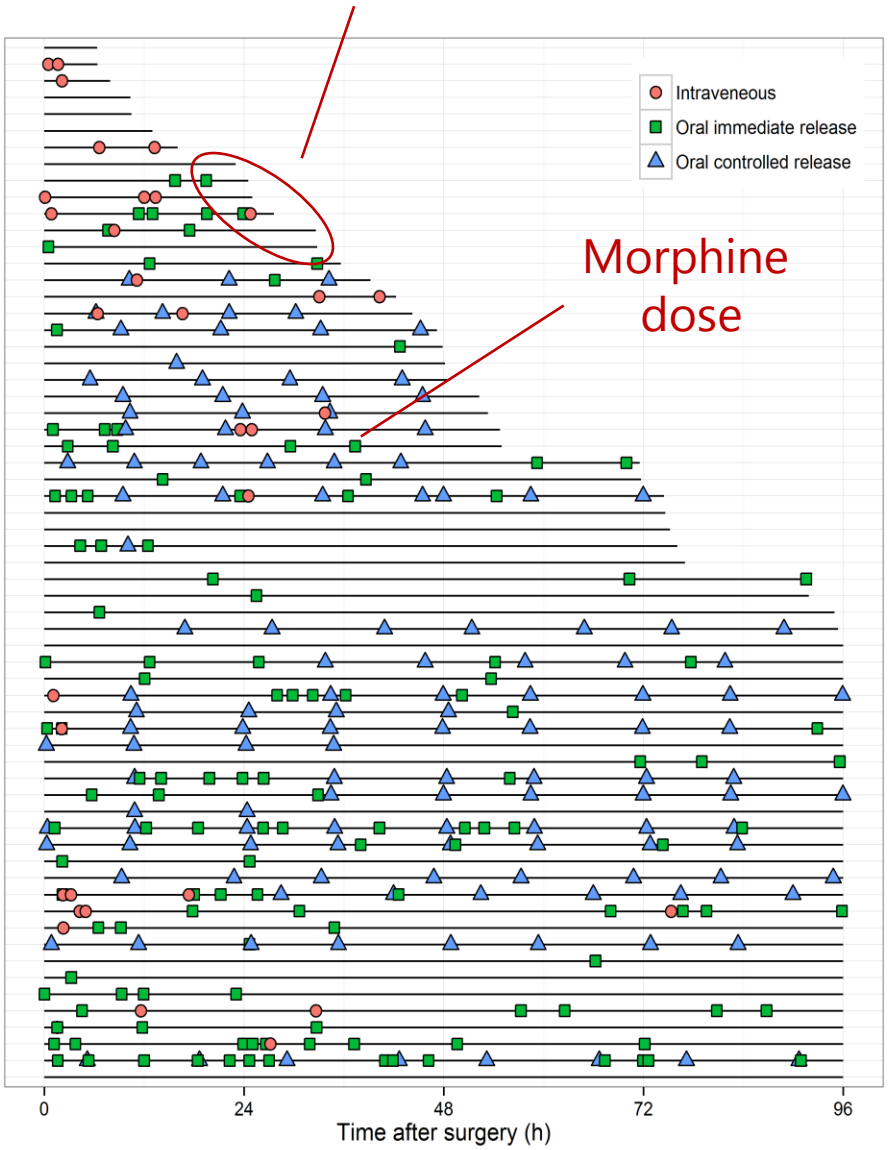
Aim

To investigate Repeated Time-to-Event (RTTE) modelling for analysis of opioid consumption in postoperative pain

Agenda

1. Illustrate RTTE in opioid consumption
2. Clinical trial simulation

Data



Morphine consumption in 63 patients undergoing hip surgery (0-96h after surgery)

Standard analgesia

- Paracetamol 4 x 1g / day
- Morphine on request

	IV	Oral IR	Oral CR
2.5mg	26	1	0
5mg	7	7	20
10mg	0	115	81
15mg	0	0	11
20mg	0	8	17
30mg	0	3	6
Sum	33	134	302

Methods: RTTE modelling

Hazard function

$$h(t) = h_0(t) \cdot e^{\eta} \cdot e^{\beta} \cdot E(C)$$

Base hazard | IIV | Covariates and drug effects

Hazards

- Expontential
- Weibull
- Gompertz

Covariates & PKPD

- Age
- Sex
- Day/Night (11pm-7am)
- Morphine PKPD*

PKPD

- Linear
- Emax
- Sigmoidal Emax
- Effect delay

Estimation

- NONMEM 7.3
- LAPLACE

Selection criteria

- OFV
- VPC

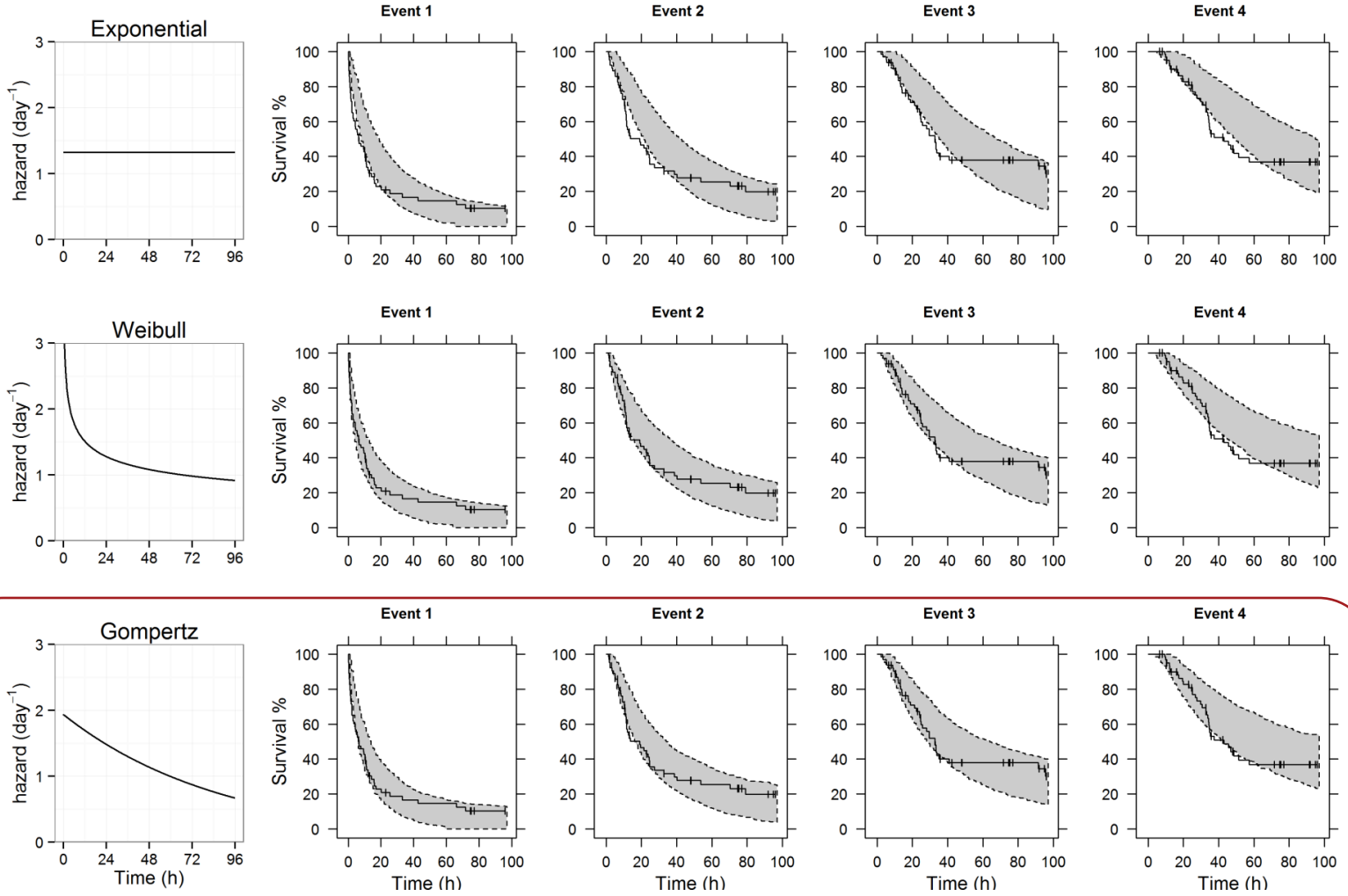
* Predicted from litterature PK model

Final model

$$h(t) = \lambda \cdot e^{\gamma \cdot t} \cdot e^{\eta} \cdot e^{\beta \cdot \mathrm{Night}} \cdot \left(1 - \frac{E_{max}{}^{Hill} \cdot C^{Hill}}{EC_{50} + C^{Hill}}\right)$$

Gompertz distribution | IIV | Day/night covariate | Morphine PKPD

Gompertz model best described dosing events



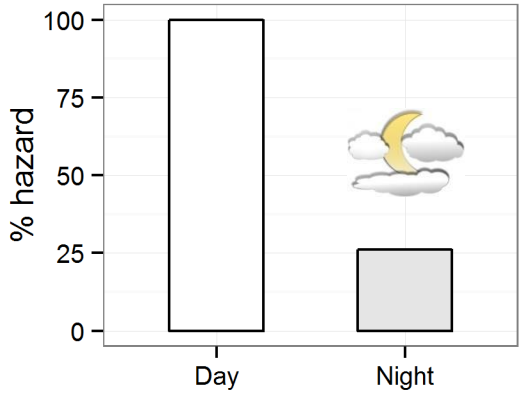
dOFV = 0

dOFV = −30.5
dDF = 1

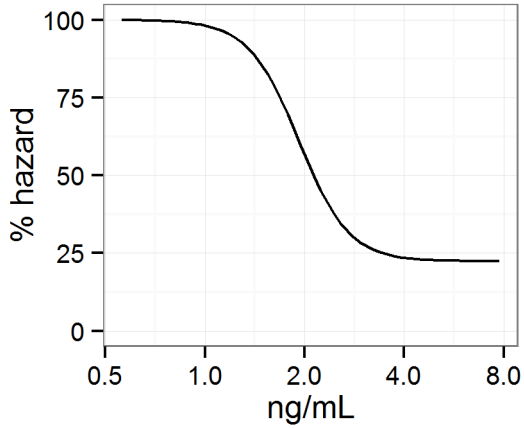
dOFV = −26.8
dDF = 1

Covariates reveal highly dynamic patterns

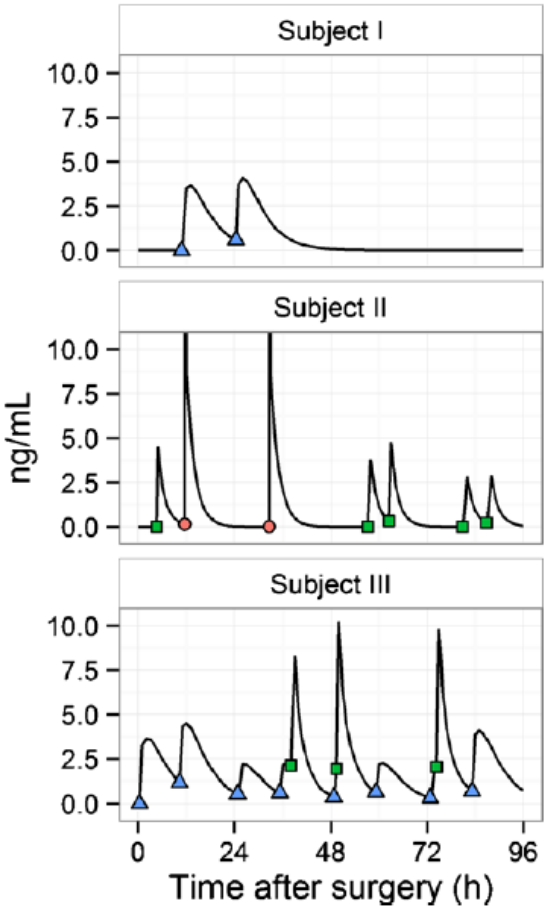
Day/Night



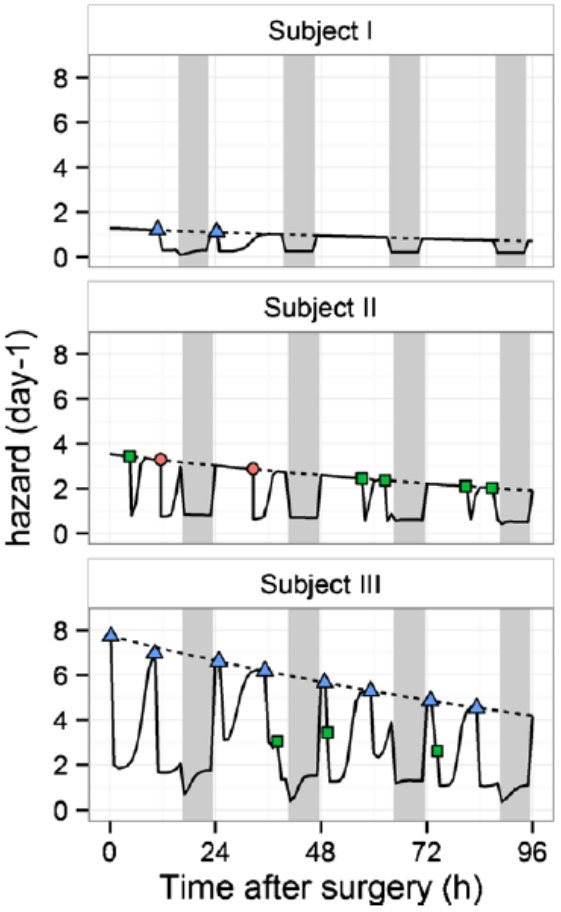
Morphine PKPD



Morphine PK



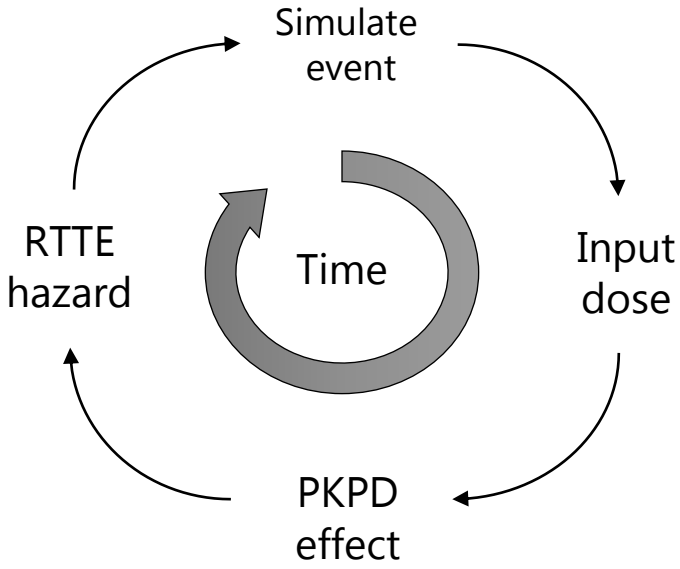
Hazard



Clinical trial simulations

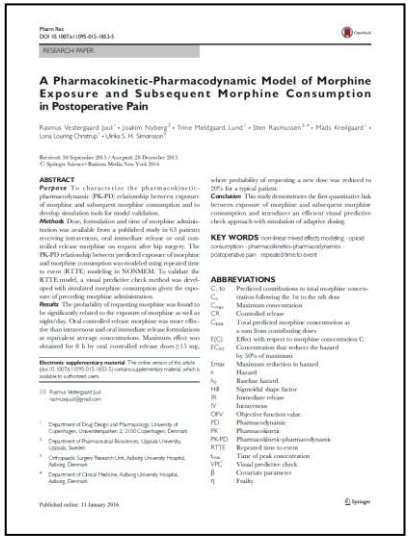
Technical challenge: Simulation opioid events

Adaptive feedback



NONMEM script features

1. Evaluate hazard
2. Simulation of event(s) in DES (no grid)
3. Simulation of dose(s) in DES
4. Superpose PK for PKPD
5. Update hazard for next step DES



A Pharmacokinetic-Pharmacodynamic Model of Morphine Exposure and Subsequent Morphine Consumption in Postoperative Pain

Juul RV et al (2016) Pharm Res

Clinical trial simulation

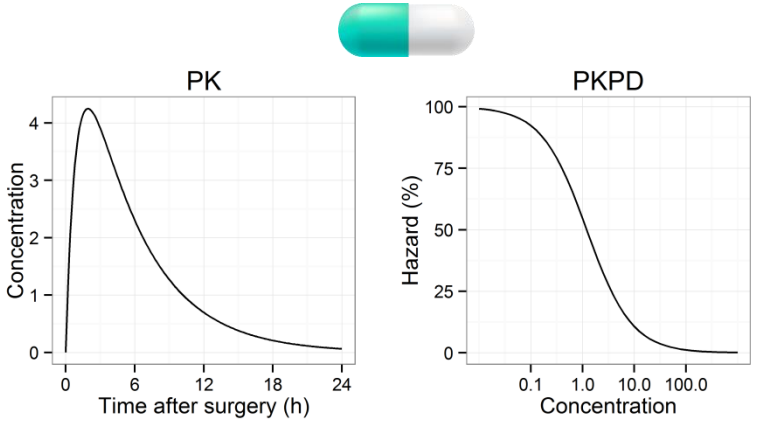
Trial design

Arm A

Morphine

Arm B

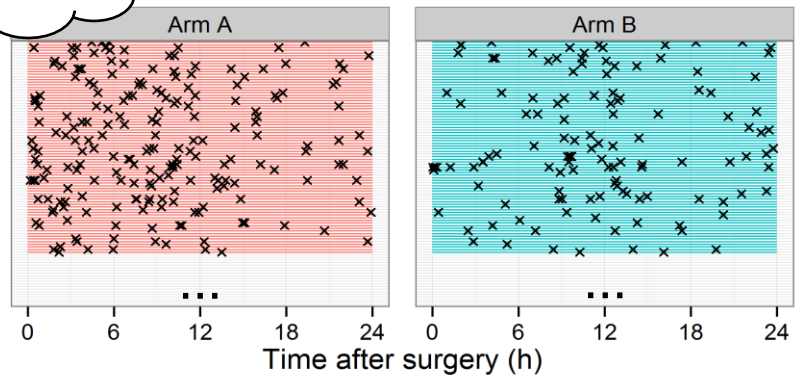
Morphine + Drug X



37 % reduction in morphine consumption

Simulations

no censoring



Power

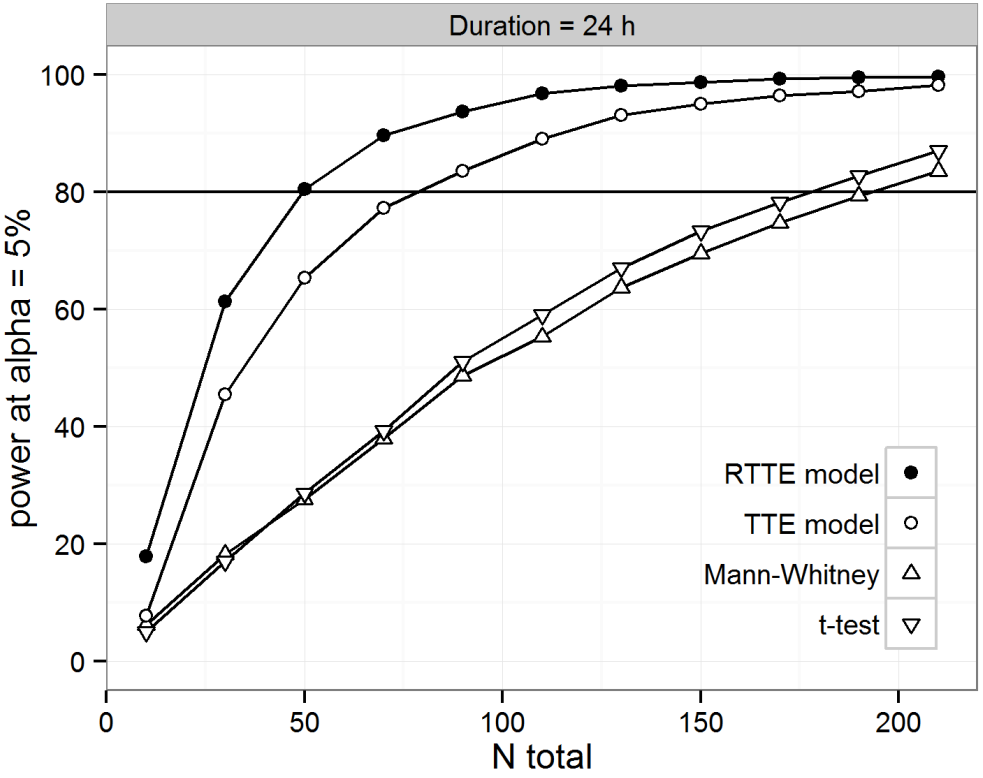
- t-test at 24 h
- Mann-Whitney rank sum at 24 h
- TTE modelling
- RTTE modelling

MCMP procedure for models

Vong C, et al. 2012 The AAPS journal

$$h = \lambda \cdot e^{\gamma \cdot t} \cdot e^{\eta} \cdot \left(1 - \frac{C_{drugX}}{EC_{50,drugX} + C_{drugX}}\right) \cdot e^{\beta \cdot \text{Night}} \cdot \left(1 - \frac{E_{max,mor}{}^{Hill} \cdot C_{mor}{}^{Hill}}{EC_{50,mor} + C_{mor}{}^{Hill}}\right)$$

RTTE modelling improves study power



Potential reduction in sample size:

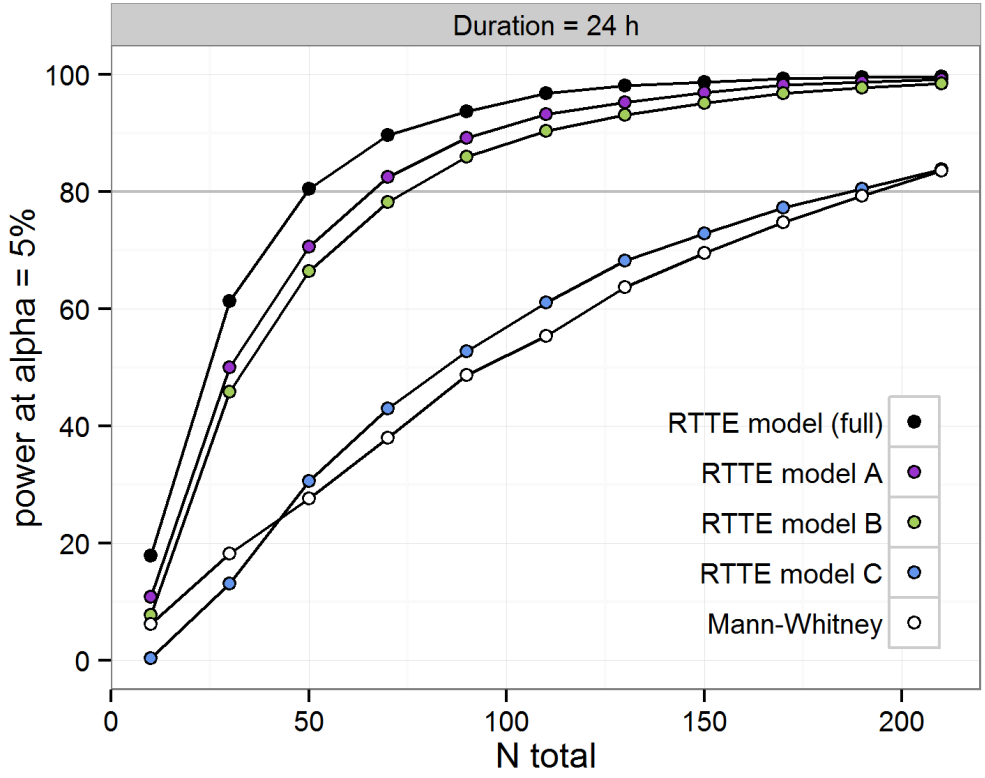
- Mann-Wh -> TTE = 2.6 fold
- Mann-Wh -> RTTE = 4.0 fold

Key assumptions

- Structural model known
- Quantification of drug X PK
- Quantification of day/night
- Quantification of morphine PK

$$h = \lambda \cdot e^{\gamma \cdot t} \cdot e^{\eta} \cdot \left(1 - \frac{C_{drugX}}{EC_{50,drugX} + C_{drugX}}\right) \cdot e^{\beta \cdot \text{Night}} \cdot \left(1 - \frac{E_{max,mor}{}^{Hill} \cdot C_{mor}{}^{Hill}}{EC_{50,mor} + C_{mor}{}^{Hill}}\right)$$

Power increased by inclusion of time-varying covariates



Full	X	X	X
A	X	X	
B	X		
C	No PK		

OBS: RTTE also handles censoring

$$h = \lambda \cdot e^{\gamma \cdot t} \cdot e^{\eta} \cdot \left(1 - \frac{C_{drugX}}{EC_{50,drugX} + C_{drugX}}\right) \cdot e^{\ldots} \cdot \left(1 - \frac{E_{max,mor}^{Hill} \cdot C_{mor}^{Hill}}{EC_{50,mor}^{Hill} + C_{mor}^{Hill}}\right)$$

Conclusion

- ✓ RTTE can appropriately describe opioid consumption data
- ✓ RTTE can model time-varying factors
  - ➢ In perspective: Pain and side-effects
- ✓ RTTE can potentially improve statistical power
  - ➢ Driven by PK/PD relationships and time-varying covariates

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