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Analysis Approaches Handling Both Event Frequency & Symptomatic Severity

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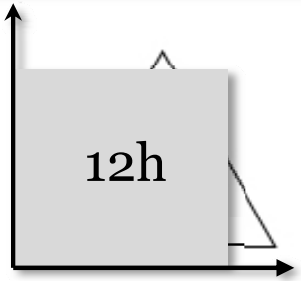
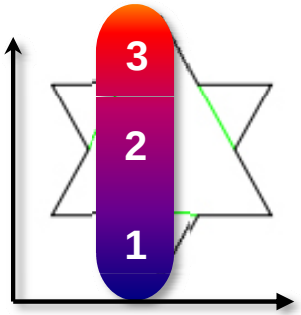
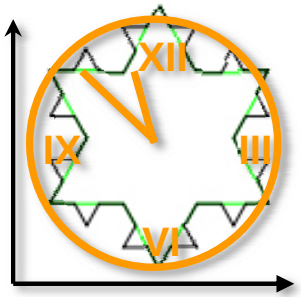
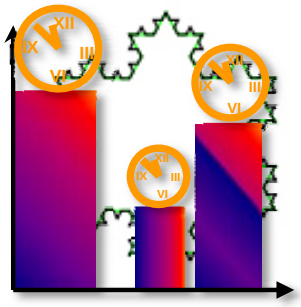
Outcome data





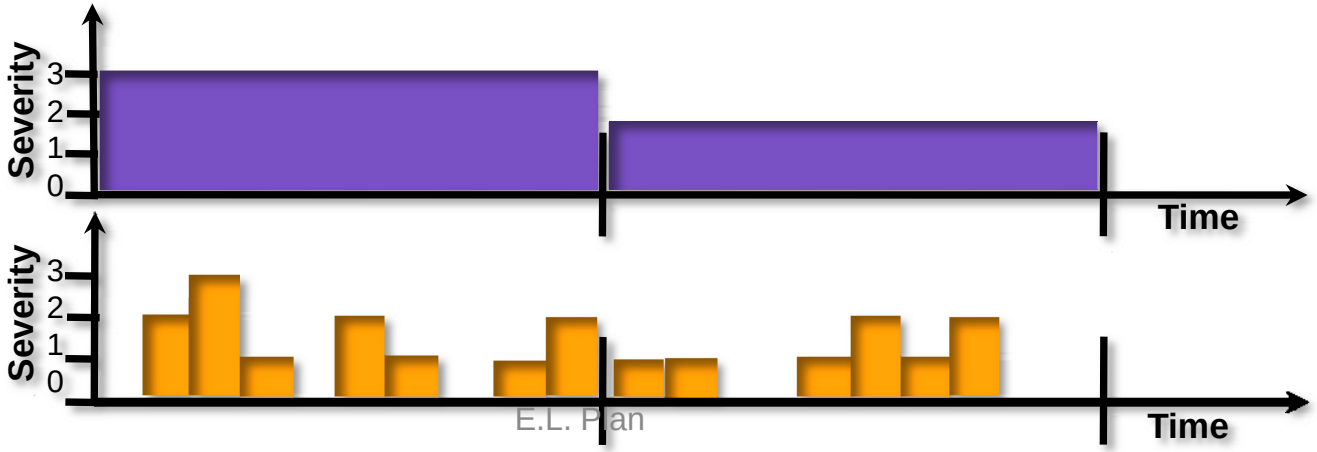




OC model

- An ordered categorical approach
  - Analgesic efficacy [0-4] pain relief index [**Sheiner, L.B.** *CPT* (1994)]
  - Intestinal toxicity [0-4] diarrhea score [**Xie, R.** *et al. CPT* (2002)]

- Pros & Cons
  - IIV, time-course, drug effect better described by use of ALL severity grades
  - Data simplification still remaining by recording only WORST diarrhea score per 3-w. course



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Rationale

- Data to model often complex:
  - ➔ Simplifications done
  - ➔ Information lost
- Last 20y, NLME approach accompanied with:
  - ↗ Computing power
  - ↗ Estimation method performance
- Models treating data in their true nature!
  - **Event at a particular time**
  - **+ of a particular severity**

= Repeated Time-To-Categorical Event (RTTCE)

Objectives

- To introduce new mixed-effects models addressing the original nature of data

- To illustrate their benefits in terms of:
  - Goodness of fit
  - Simulation properties
  - Drug effect assessment
  - Drug effect detection power

[http://www.nedarc.org/nedarc/analyzingData/index.html]

RTTCE model

- Combine Repeated Time-To-Event model
  - ***Probability (no event occurring) =***

$$h(t) = \theta_\beta \cdot e^{\eta_{\beta_i}} \cdot f(PK_i, t, X_i)$$

$$P(Y_{ij} = 0, t_j > T > t_{j+1} \mid \eta_i) = e^{-\int_{t_j}^{t_{j+1}} h(t)}$$

Y = dependent variable
t = independent variable
i = patients
j = observation point
θ = population median
η = random effect
h = hazard
PK = drug exposure
X = covariate
m = instant degree of severity

- & Ordered Categorical model
  - ***Probability (occurring event of severity m) =***

$$Logit\left[P(Y_{ij} \geq m \mid \eta_i)\right] = \theta_{\alpha_m} + \eta_{\alpha_i} + g(PK_i, t, X_i)$$

$$P(Y_{ij} \geq m \mid \eta_i) = \frac{e^{Logit\left[P(Y_{ij} \geq m \mid \eta_i)\right]}}{1 + e^{Logit\left[P(Y_{ij} \geq m \mid \eta_i)\right]}}$$

$$P(Y_{ij} = m \mid \eta_i) = \left(P(Y_{ij} \geq m \mid \eta_i) - P(Y_{ij} \geq (m+1) \mid \eta_i)\right) \cdot \left(1 - P(Y_{ij} = 0 \mid \eta_i)\right)$$

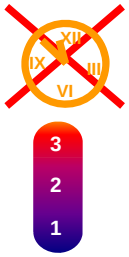
RTTCE features

- Models simultaneously two aspects of the data

- Enables drug effect on both:
  - Frequency aspect ➔ fewer events
  - Severity aspect ➔ lower proportion of severe vs mild

- Pros & Cons
  - 👍 Model treating data in their true nature!
  - 👎 Data must have been recorded as such,

  If not, if maximal events per time-intervals reported:



Repeated Categorical Event per Time-interval (RCEpT)

RCEpT model

- Combine Repeated Time-To-Event model
  - ***Probability (no event per time-interval) =***

$$h(t) = \theta_\beta \cdot e^{\eta_{\beta_i}} \cdot f(PK_i, t, X_i)$$

$$P(Y_{ij} = 0, t_j > T > t_{j+1} \mid \eta_i) = e^{-\int_{t_j}^{t_{j+1}} h(t)} = e^{-\lambda}$$

Y = dependent variable
t = independent variable
i = patients
k = observation interval
θ = population median
η = random effect
h = hazard
PK = drug exposure
X = covariate
m = max. degree of severity
n = number of Y>0 per interval

- Ordered Categorical & Count models
  - ***Probability (max m of severity of expected number of events per time-interval) =***

$$Logit\left[P(\max(Y_{ik}) \geq m \mid \eta_i)\right] = \theta_{\alpha_m} + \eta_{\alpha_i} + g(PK_i, t, X_i)$$

$$P(\max(Y_{ik}) \geq m \mid \eta_i) = \frac{e^{Logit\left[P(\max(Y_{ik}) \geq m \mid \eta_i\right]}}{1 + e^{Logit\left[P(\max(Y_{ik}) \geq m \mid \eta_i\right]}}$$

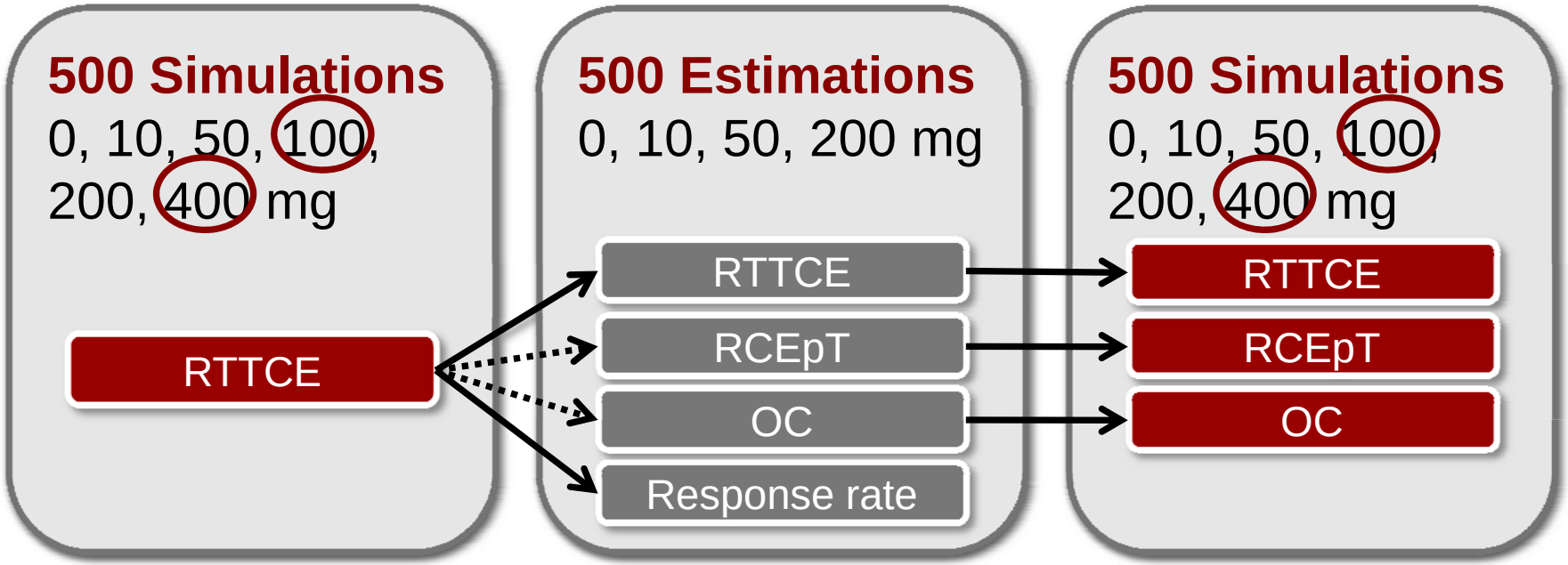
$$P(\max(Y_{ik}) = m \mid \eta_i) = \sum_{n=1}^{+\infty} \left(\frac{\lambda^n \cdot e^{-\lambda}}{n!} \cdot \left(\left(P(\max(Y_{ik}) \leq m \mid \eta_i)\right)^n - \left(P(\max(Y_{ik}) < m \mid \eta_i)\right)^n \right) \right)$$

Study design

- Mimics Phase II clinical trial
  - **72** individuals
  - **6** parallel dose arms
- Simulation of drug effect (function of C)
  - Imax on hazard
  - Linear inhibition on logit
  - Shared IIV
- Simulation of symptoms (acid refluxes)
  - **Time of symptoms:** recorded during **0-12h**
  - **Grade of symptoms: Mild, moderate or severe**

Study methodology

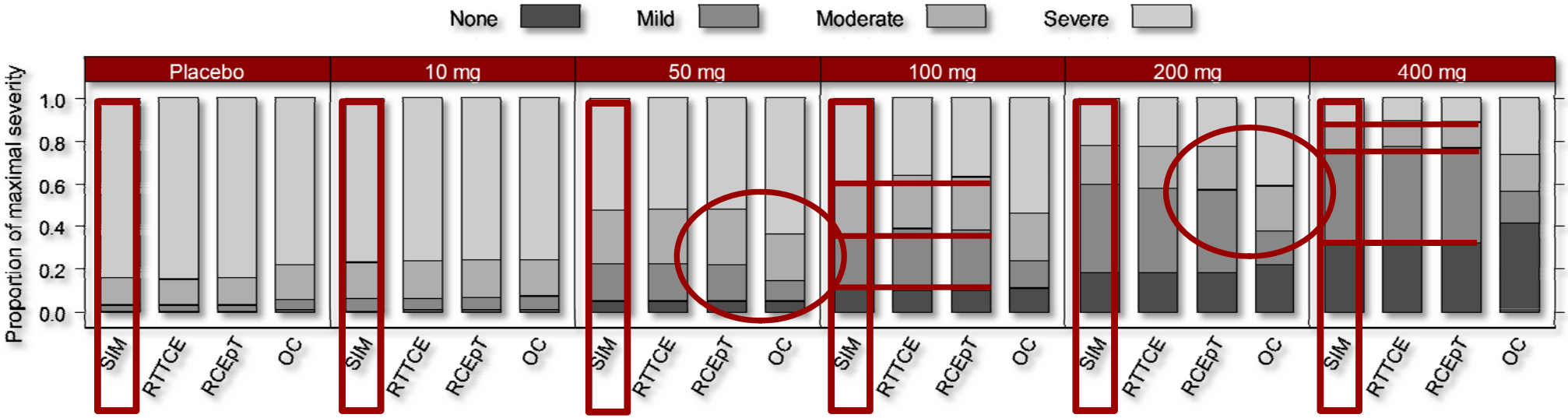
- Stochastic Simulations and Estimations (SSE)
- In NONMEM 7®, with LAPLACIAN LIKE approx.



⇢ Data simplified as max per hour

Simulation properties

- Maximal reflux grade per patient over 12h
  - Favours OC theoretically
  - Illustrates OC limitations



Proportions of none, mild, moderate and severe maximums
obtained from 100 sets of parameter estimates and simulated on a large sample

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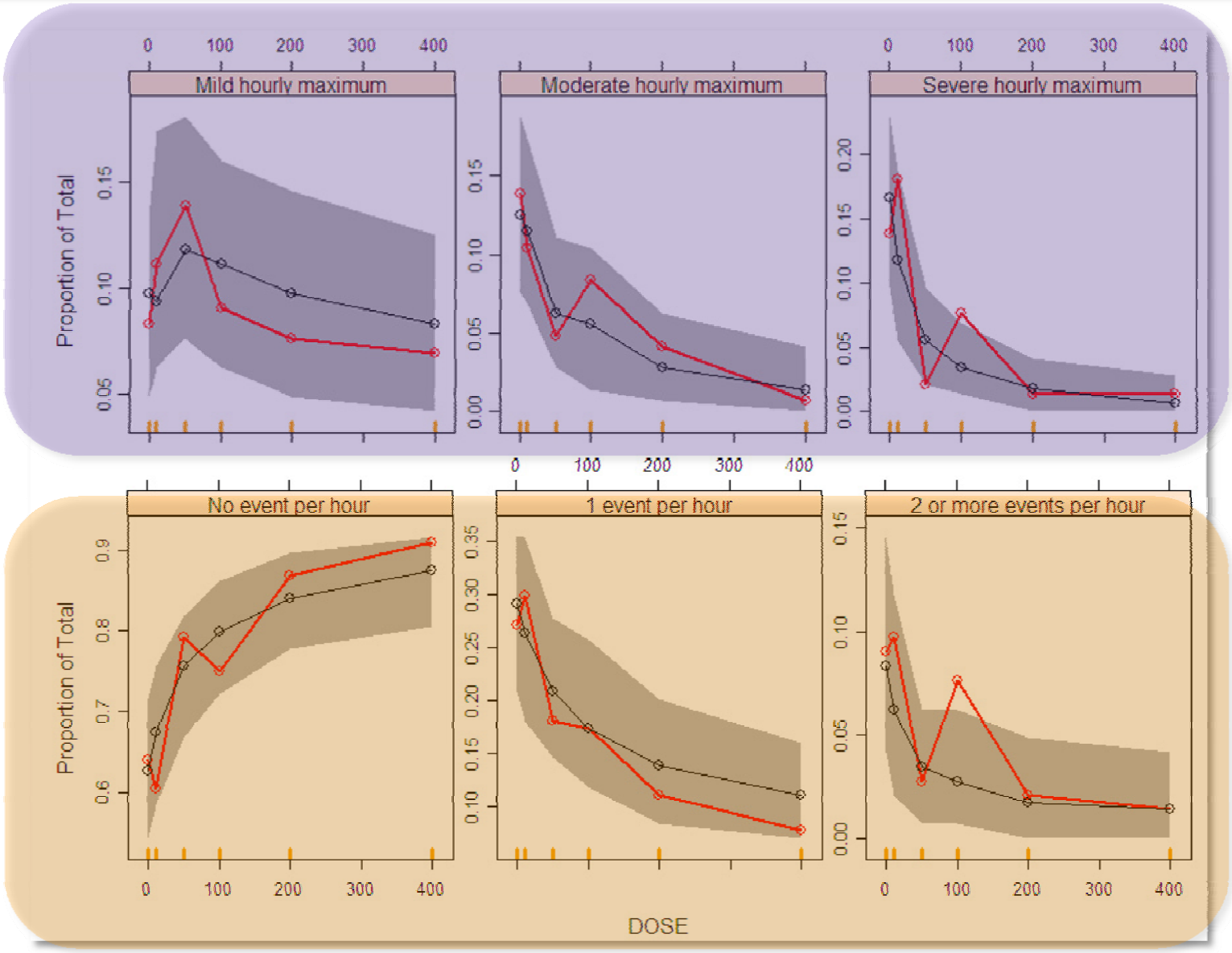
Drug effect assessment

RCEpT model

__ = median of original datasets

= 95% CI

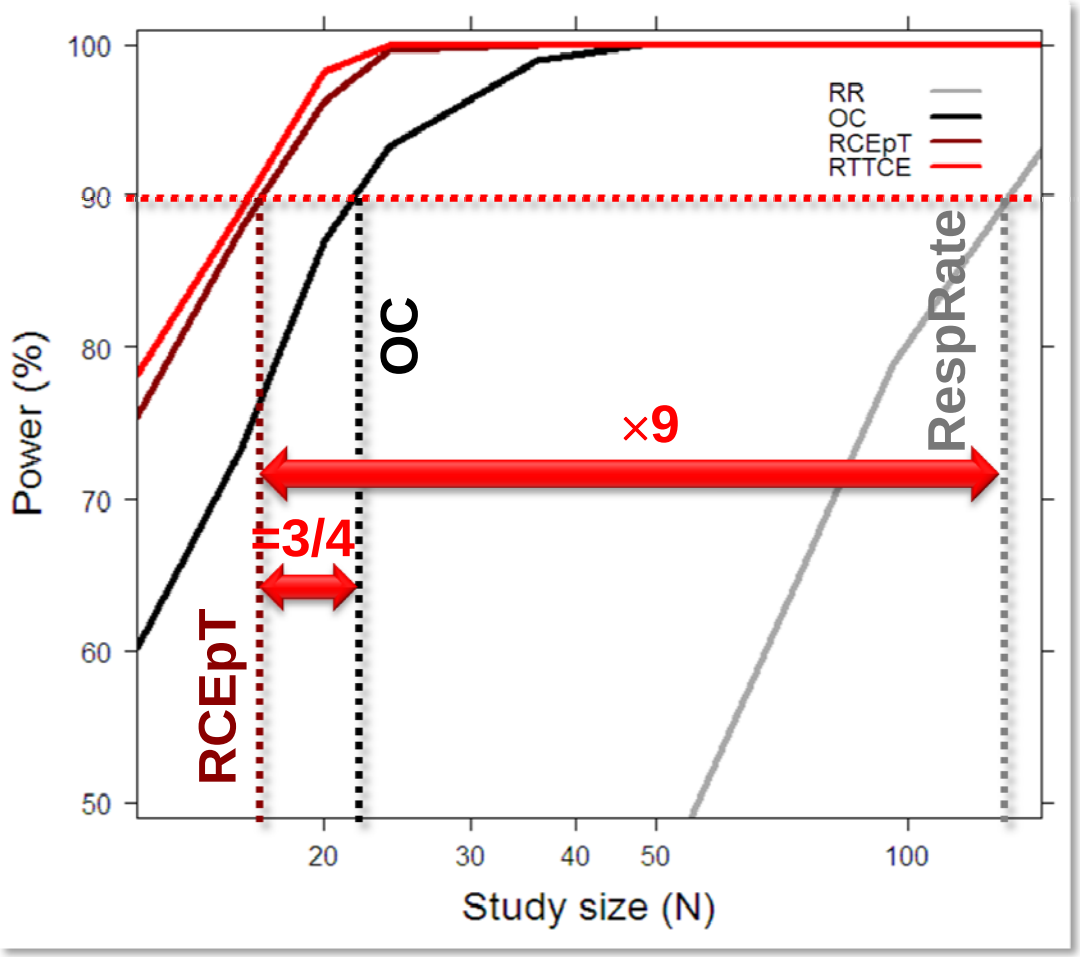
__ = median of predictions from 100 simulated samples



Drug effect detection power

- Chi square test
  p = 0.01

- For a Power = 90%:



Response rate definition = severity < 1 during 3 last h

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Summary

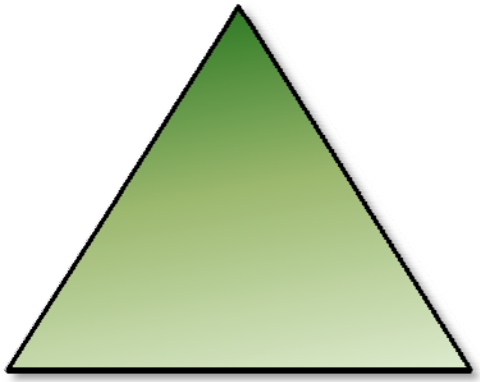
- Modeling graded symptoms with summarized information
  - ➔ poor description of the events
  - ➔ incomplete drug effect assessment
  - ➔ excessive study sizes

- Modeling simultaneously both severity and frequency of symptoms
  - ➔ good predictive performance
  - ➔ extended simulation capabilities
  - ➔ high power to identify drug effects

Outcome data

Bleeding episodes

Asthma crises



Rhinitis

http://en.wikipedia.org/wiki/Fractal

Epilepsy seizures

Nicotine craving

Sleep apnoea

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- You, for your attention

And…questions?