Simulation of popPK models

Interactive workshop

About this deck

Slides for a course about pharmacometric simulations, given at KULeuven on 14-Nov-2025. Available on github at https://github.com/rfaelens/courses/ (https://github.com/rfaelens/courses/) and live at https://rfaelens.shinyapp.io/kul2025 (https://rfaelens.shinyapp.io/kul2025)

About me

- Ruben Faelens
  - Belgian, living in Leuven
  - ruben.faelens@gmail.com (mailto:ruben.faelens@gmail.com)
- Computer Scientist, graduated 2010
- PK/PD modeling & simulation from 2012 onward
- Wrote *simulo*, a clinical trial simulation software
- Consultant for pharma industry from 2014 - 2018
- PhD in precision dosing from 2017 - 2022
- Working at J&J since Feb 2022

Medische primeur bij UZ Leuven: AI voorspelt nodige dosis medicatie na niertransplantatie beter dan artsen

I was in the news!

Een nieuw AI-model, ontwikkeld door het UZ Leuven, kan de dosis medicatie die patiënten na een niertransplantatie moeten nemen, beter voorspellen dan artsen. Dat is een medische doorbraak én een AI-primeur, want voor het eerst ter wereld is een AI-model gebruikt voor een medische ingreep zonder de tussenkomst van een arts of andere mensen. "We gaan nu

Conflict of interest

The views and opinions expressed in this course are those of the speakers and do not necessarily reflect the views or positions of their employers.

The lecturer declares no conflict of interest.

Learning objectives

- Understand the role of simulations in *Modeling & simulation*
- Know the difference between *population simulation* and *clinical trial simulation*
- Select the appropriate simulation for a given question

Contents

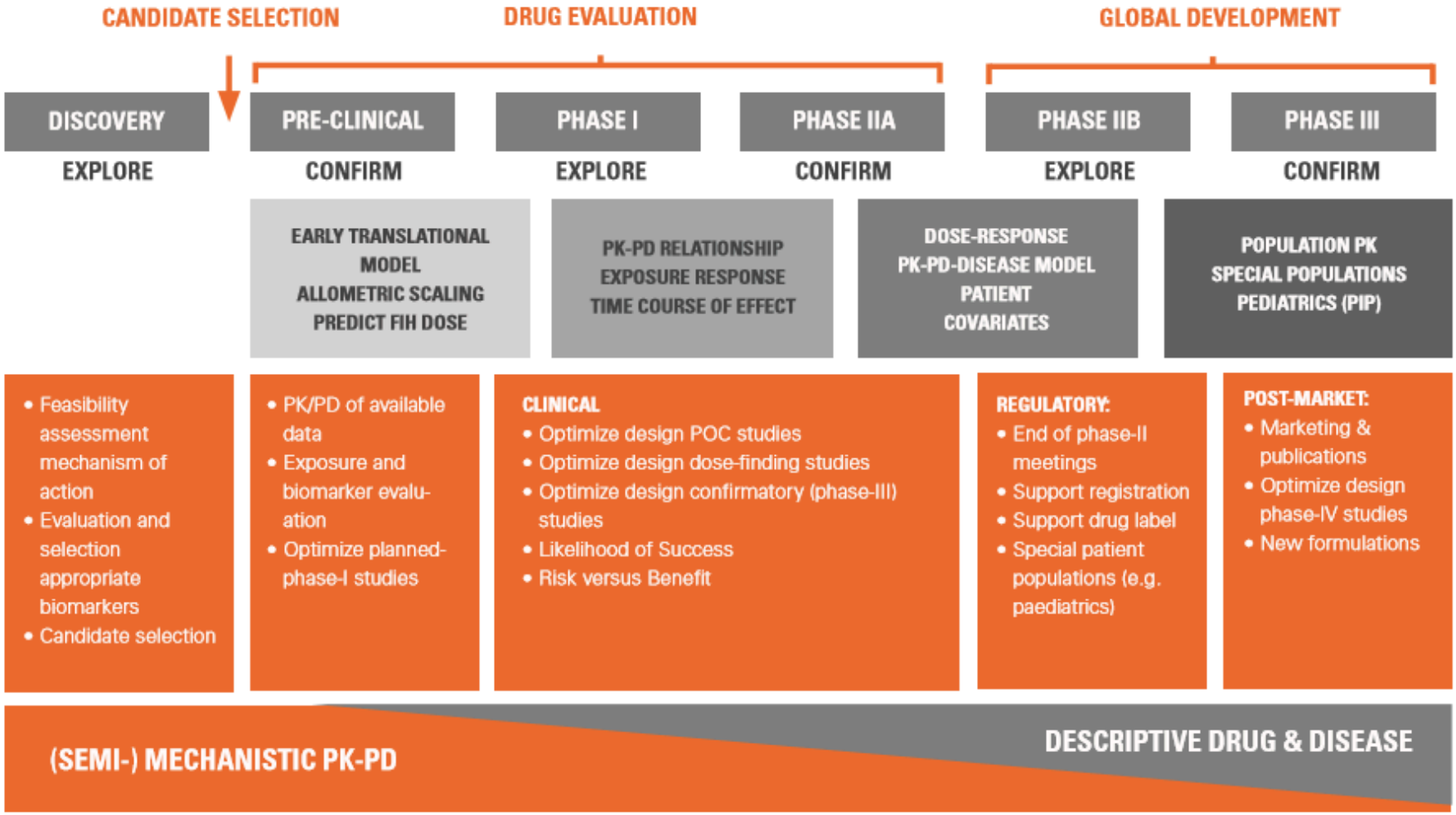
Simulation of pharmacometric models

The benefits of using modeling and simulation in drug development

Modeling & Simulation: why?

- Deeper understanding of the compound and mechanisms
- Predict candidate treatment
- Answer what-if scenario
- Predict candidate trial
- Optimize trial, minimize risk

Model-informed drug development



What kind of questions can we address?

- What is the best dose and administration interval?
- What is the best sampling schedule?
- Which protocol design will we choose?
- How many subjects do I enrol in the next phase study?
- Which proportion of my population will be well treated?
- What is the best population targeted by the drug?
- Will you continue this drug development?
- Can we look at another dosage form?
- Having information on other doses, what is the mean effect of a 100mg dose after 2 weeks of treatment?
- What is the probability of success in phase III?

Limitations

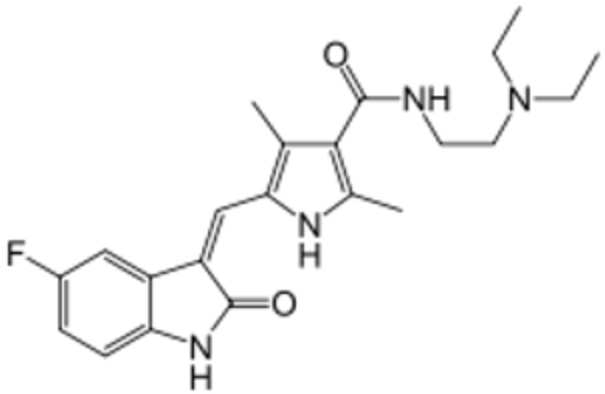
- Explain everything
- Give you the answer you want
- Find an effect where none exists
- Provide one “true” answer
- Make good studies unnecessary
- Make a silk purse out of a sow’s ear
- Make your decisions for you

A structured approach

- Modeling & Goodness of Fit
- Population simulation
- Probability of Technical Success
- Clinical trial simulation
- Probability of Study Success

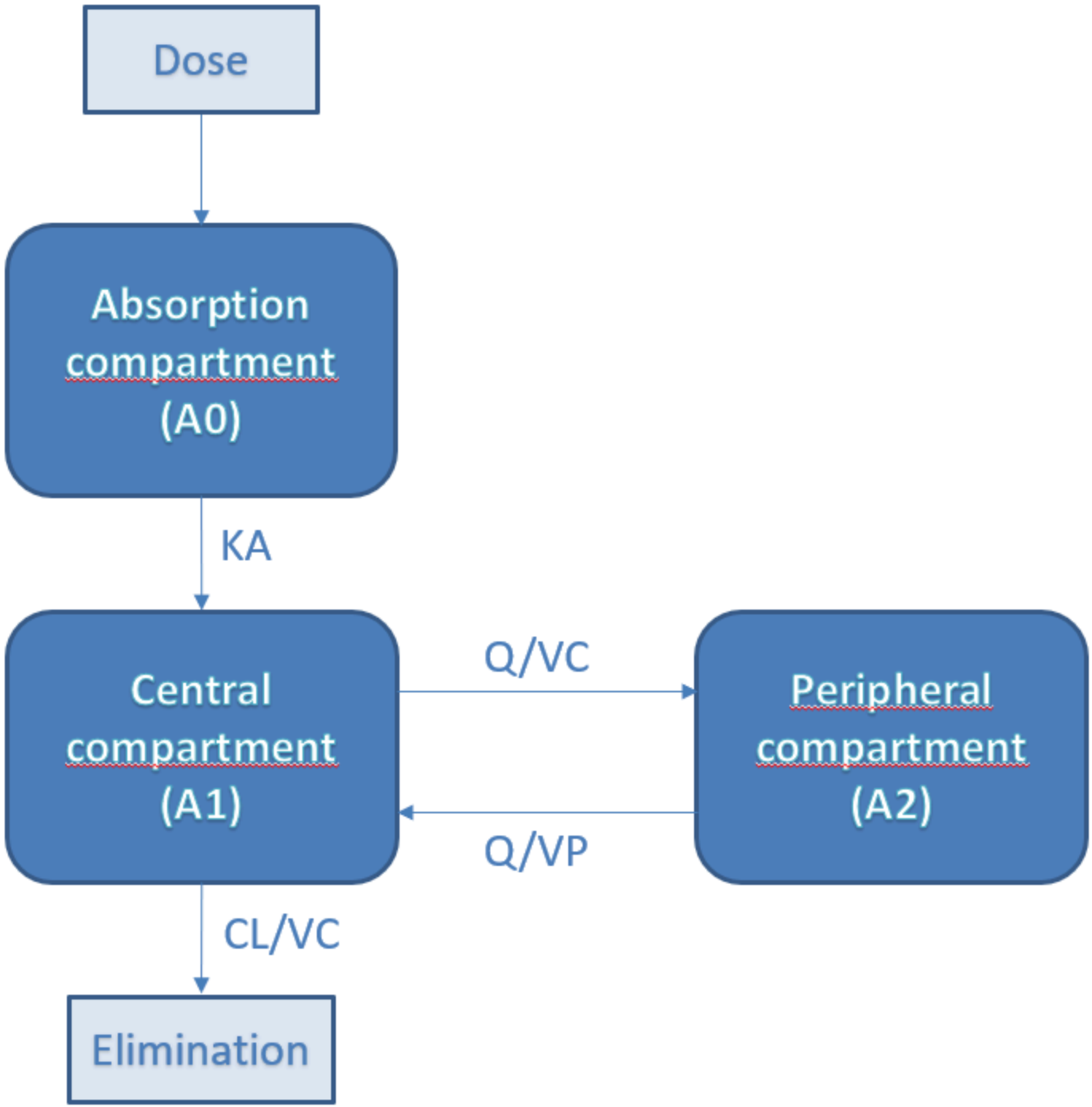
Sunitinib

Sunitinib is a multi-targeted tyrosine kinase inhibitor used in the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant/intolerant gastrointestinal stromal tumors (GIST). It gained market access in 2006.



Khosravan et al [1]

1. Reza Khosravan et al. Population Pharmacokinetic/Pharmacodynamic Modeling of Sunitinib by Dosing Schedule in Patients with Advanced Renal Cell Carcinoma or Gastrointestinal Stromal Tumor. Clin Pharmacokinet (2016) 55:1251–1269 published a model predicting PK and several PD endpoints.


Dose
Absorption compartment (A0)
KA
Central compartment (A1)
Q/VC
Q/VP
Peripheral compartment (A2)
CL/VC
Elimination

Parameter	Sunitinib
	Final model results
Population mean estimates (95 % CI)[a]	
CL/F, L/h	34.1 (32.7–35.5)
V_c/F, L	2700 (2543–2857)
K_a, h^{-1}	0.126 (0.106–0.146)
t_{lag}, h	0.527 (0.508–0.546)
V_p/F, L	774 (713–835)
Q/F, L/h	0.688 (0.651–0.725)
AGE on CL/F	−0.00702 (−0.00916 to −0.00488)
RAC on CL/F	−0.152 (−0.209 to −0.0954)
SEX on CL/F	−0.193 (−0.232 to −0.154)
TUMR on CL/F	0.293 (0.230–0.356)
BWT on V_c/F	0.281 (0.128–0.434)
SEX on V_c/F	−0.213 (−0.275 to −0.151)
TUMR on V_c/F	0.420 (0.316–0.524)
Residual variability %CV (95 % CI)[a]	
	41.7 (41.4–42.0)
Interpatient variability %CV (95 % CI)[a]	
CL/F	24.6 (22.8–26.3)
V_c/F	23.0 (20.4–25.4)
K_a	166 (146–183)

Typical value simulations

Model

```
KA=0.126;
Vc=2700;
```

These simulations predict a single profile using the typical value parameters.

Dose (mg)	Number of doses	Dosing interval	plot
50	1	24	CONC

Days

7

Keep last plot

Questions

- Change the parameter values. Predict what will happen. Do this for KA, Vc, CL, Vp, Q.
- Can you predict key PK properties? Cmax, Tmax? What is AUC for 1 dose?
- What is the steady-state concentration? What is the peak-to-trough ratio? How long is the typical washout period to have 90% eliminated?
- What dose is required for a single-dose exposure of 3000?

But is that really what would happen for the “typical patient”? Our model is not perfect. There is both *assay variability*, other sources of *variability*, and model misspecification. These are captured in *residual error*. In this model: 41.7%. What happens if we add this residual error to our model predictions?

Residual error

RE (CV%)

10

The prediction has a huge variability. Two viewpoints exist on residual error:

1. Residual error is assay error. The model prediction is the truth. Residual error should not be simulated.
2. Residual error shows uncertainty. Residual error should also be simulated. This shows what outcomes can be expected in real life situations.

Depending on the specific question, we may include or exclude residual error. What viewpoint would you defend? What other “errors” may cause residual variability?

Model

```
KA=0.126*exp(EKA);
Vc=2700*exp(EVc);
```

Population simulation

These simulations predict a virtual population. Each patient has different ETA values. The variability is determined by OMEGA.

Dose (mg)	Number of doses	plot	Days
50	1	CONC	7

Subjects	PI (%)	Ka (CV%)	CL (CV%)
50	95	166	24,6

Vc (CV%)
23

Questions

- Why are there differences between patients? What is the main driver for this variability? Explain.
- Simulate 500 patients. This shows median and 95% *prediction interval*. The prediction interval shows what variability you can expect.
- Can you predict variability on key PK properties? Cmax, Tmax? What is AUC for 1 dose?
- What is the steady-state concentration? What is the peak-to-trough ratio? How long is the typical washout period to have 90% eliminated?
- Write down the current predicted steady-state concentration Simulate 501 patients. Write down the predicted median. Why are both numbers different?
- What dose is required for a single-dose exposure of at least 3000 in 95% of individuals?

Probability of Technical Success investigates *what-if* scenarios on the overall population.

Probability of Technical Success

Case study

The sunitinib patent was granted to Pfizer in 2007. It is officially off-patent in February 2021, free for anyone to produce. We try to produce the molecule as a generic: Sunitinib Extra. To be allowed on the market, it must be *bio-equivalent* to Pfizer Sutent: median, p95 and p5 exposure should be the within 80%-125% of the exposure of Sutent (the originator). This is tested for both CMax and AUC.

Sometimes, differences in production process can lead to slightly altered pharmacokinetics. By how much can the clearance be increased or decreased before we lose bio-equivalence?

In this model, we reduce clearance by `MOD`.

Model

```
KA=0.126*exp(EKA);
Vc=2700*exp(EVc);
```

In the plot below, we show steady-state concentration after 50mg/day for 30 days. How much can you modify clearance before losing bio-equivalence on AUC? The average concentration is shown as markings on the right, the zone for concluding bio-equivalence is colored in red/green/blue.

$C_{avg} = AUC/\tau$

PI (%)	Modified clearance (%)
95	100

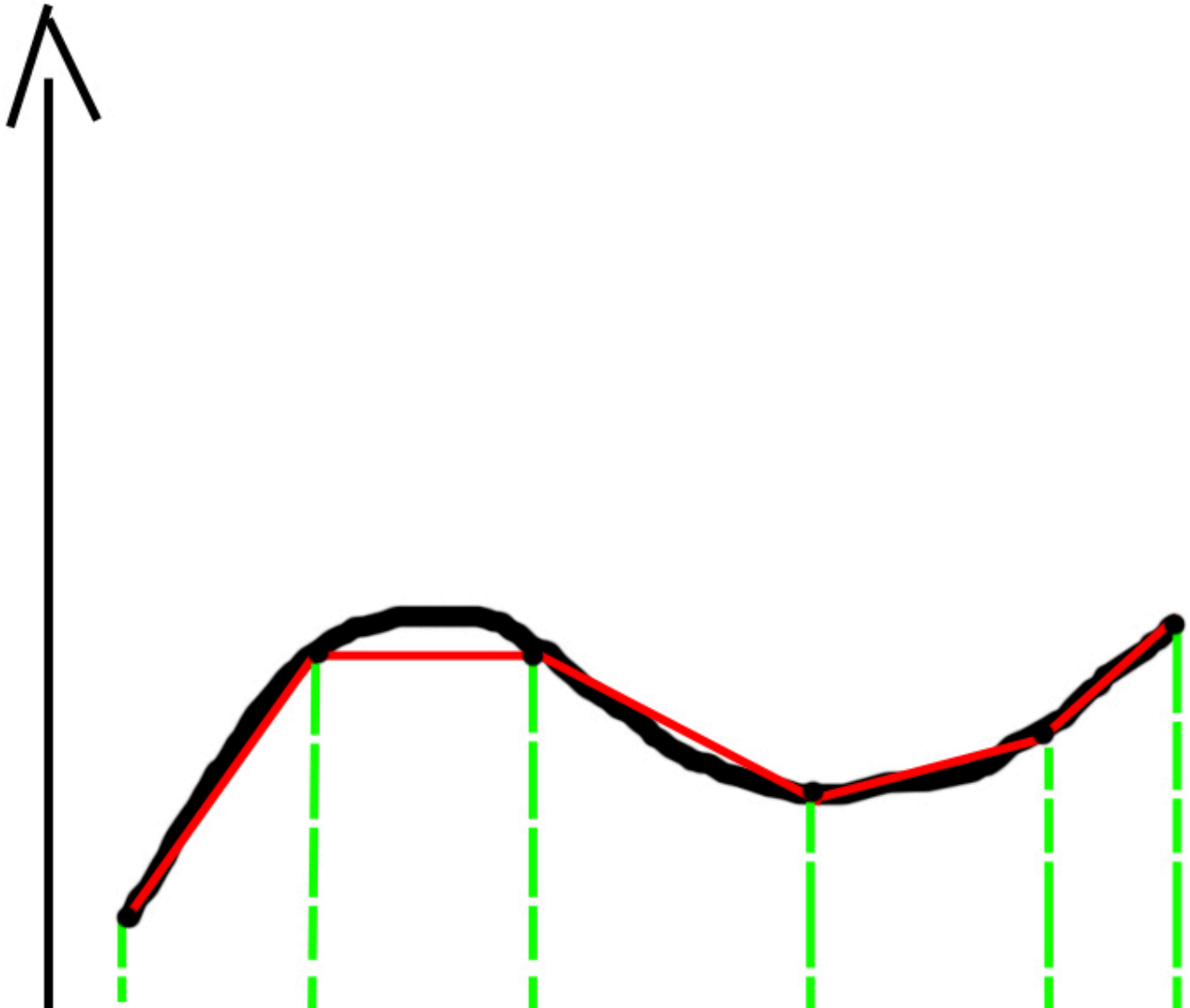
A clinical trial is limited in *number of patients*, *number of observations*, and *duration*. Furthermore, patients *drop out* and some observations will be *missing*. To combat these aspects, clinical trials are usually analyzed with *statistical methods*.

- Can you think of ways to mitigate the limitations of a clinical trial?
- When simulating a clinical trial, should we include *residual error* ?

Clinical trial simulation

Statistical analysis

We ask patients to take sunitinib for 30 days. We then ask them to come for blood sampling. We will sample blood and then use the trapezoid method to calculate AUC.



Can you optimize the number of blood samples required to determine steady-state AUC? Samples at time 0h and 24h are always taken, the rest is optional.

Schedule

0.5 1 1.5 2 2.5 3
3.5 4 4.5 5 5.5 6
6.5 7 7.5 8 8.5 9
9.5 10 10.5 11 11.5
12 12.5 13 13.5 14
14.5 15 15.5 16 16.5
17 17.5 18 18.5 19
19.5 20 20.5 21 21.5
22 22.5 23 23.5

Random Seed

1234

Can you optimize the number of blood samples required to characterize CMax after the first dose?

Schedule

1 2 3 4 5 6 7 8 9
10 11 12 13 14 15
16 17 18 19 20 21
22 23 24 25 26 27
28 29 30 31 32 33
34 35 36 37 38 39
40 41 42 43 44 45
46 47 48

Random Seed

1234

Enrollment

Every patient costs. Both in terms of money (recruitment, cost of medicine, cost of follow-up), but also in terms of time. The more patients, the longer a trial will take. And time is crucial when patents are only granted for 20 years!

Use clinical trial simulation to show 80 patients is sufficient to demonstrate bio-equivalence.

Enrollment

150

Simulate again!

The probability of study success is determined by performing `many` clinical trial simulations, and checking how many are succesful. This is the probability that a *real* trial would be succesful.

Simulations

1

Simulate!

Probability of Study Success

- Modeling & Goodness of Fit
  - Make sure your model fits the data
  - Realistic predictions
- Typical value simulation
  - Understand how the compound behaves
- Population simulation
  - Understand variability
- Probability of Technical Success
  - Explore theoretical what-if
- Clinical trial simulation
  - Real-world limitations
  - Stats analysis
- Probability of Study Success
  - Optimize a trial

Conclusion

Clinical trial simulation quantifies risk and allows up-front optimization.