Design challenges for dose-finding studies in drug development

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Part 1: Estimands and Intercurrent Events

Part 2: Finding more than the right dose

Part 1:
Estimands and Intercurrent Events

Katrin Roth

Dose Finding Studies - Introduction

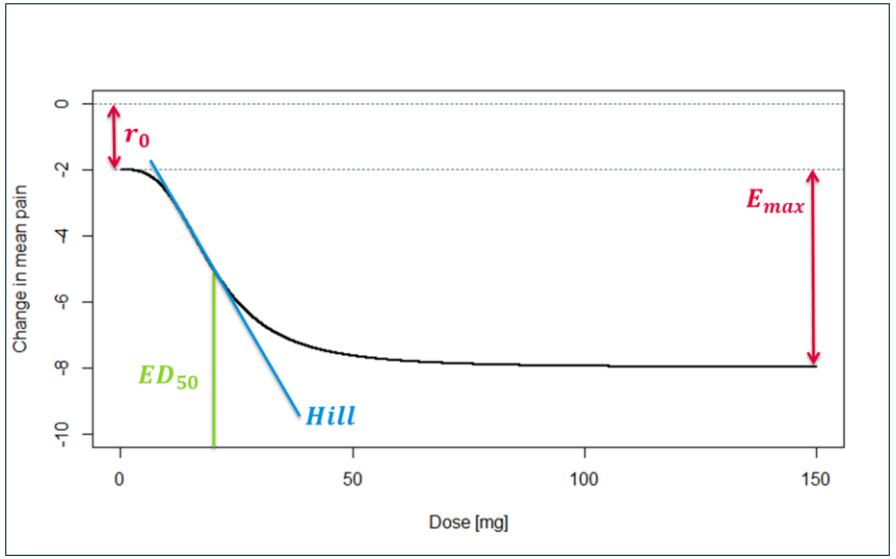
- Second phase of clinical development
- Objectives:
  - Establish a dose-response effect
  - Estimate the dose response relationship of a drug
  - Determine a therapeutic window or the therapeutic dose
- These different objectives can be addressed, e.g., by the MCP-Mod[1,2] approach
  - Testing for a dose-response effect across different candidate dose-response-relationships using a contrast test
  - Estimating the dose-response-relationship using one or several candidate shapes
  - Determining the dose achieving a pre-specified relevant effect, based on the estimated dose-response-relationship

Dose Finding Studies – Introduction and Notation

- The dose response relationship can typically be described by a function that is non-linear in the parameters of interest e.g.
  - Emax, quadratic, exponential, log-linear model
  - sigmoidal Emax model

    x = d = dose
    θ_0 = r_0 = placebo effect
    θ_1 = E_{max} = maximum effect attributable to the drug
    θ_2 = ED_{50} = dose achieving half of E_{max}
    θ_3 = Hill = “steepness”

$$f(x, \theta) = \theta_0 + \theta_1 \frac{x^{\theta_3}}{\theta_2^{\theta_3} x + x^{\theta_3}}$$

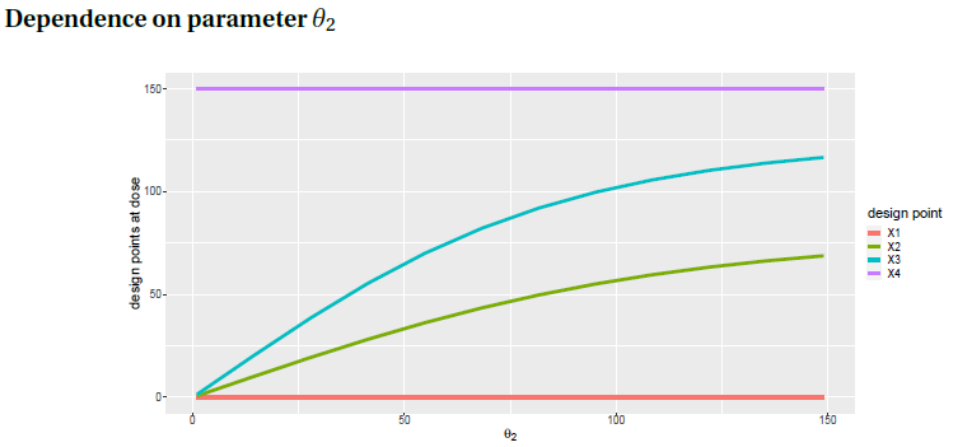


- A design for a dose finding study is defined by
  - a set of dose levels $(d_1, \dots, d_k)$
  - the number of subjects $(n_1, \dots, n_k)$ to be studied at the respective dose level

Optimal Design for a Dose Finding Study

- Different objectives require different optimality criteria
  - Estimating the overall curve – D-optimality
  - Estimating the dose that achieves a pre-specified effect – C-optimality
  - Maximizing the power of the contrast test – some kind of C-optimality? (for each model)

- Different candidate shapes lead to different D-optimal designs
  - Different number of support points, depending on the number of parameters of the model
    - E.g. 3 for Emax or quadratic model, 4 for sig-Emax or logistic model
  - Different location of the support points – in many cases strong influence of expected ED_{50}[(4)] for which there is high uncertainty



- Challenge: combine all these aspects and additional practical constraints into a good design

Application to Clinical Dose Finding Studies

Practical limitations

- The dose range is bound by 0 (i.e. placebo), upper limit is given by safety constraints
- Not every dose in this range is possible, e.g. due to available tablet strength
- The number of doses should not be too high
  - Commonly used 2-4 active doses, okay for many dose-response models as the number of parameters is limited (3-4), and the D-optimal designs are minimally supported
- The shape of the dose-response curve (i.e. the model type) and the parameter are unknown
  - Aim at finding a design that is good across a number of models and a sufficiently broad parameter range
- Patients might not be treated by the randomized dose, for the planned duration, under the planned circumstances
  - ➢ “intercurrent events” (post-randomization events, that influence the observed outcome)
  - ➢ What is the clinical question of interest, what do we really want to estimate (“the estimand”), and how do intercurrent events and their handling influence this?
  - ➢ …and **how do intercurrent events and their handling influence the optimal design of a study?**

Typical Intercurrent Events and how to handle them

- Actual dose is not the randomized dose
  - What do we estimate if we analyze the actual dose vs. the randomized dose?
- Patients are not treated for the full duration of the study
  - What observations should we use, or how should we impute the missing observations?
  - Decision could depend on the reason for missingness
- Patient receive prohibited additional medication that could influence the outcome
  - Should we use these observations? If not, what else should we do?
- Different intercurrent events can be handled by different strategies
- Common strategies
  - “treatment policy”: analyze all observed and available data irrespective of intercurrent events
  - “hypothetical”: what you would have observed if the intercurrent event had not happened
  - “composite”: the intercurrent event is included in the outcome
  - “while on treatment”: use only observations while the patient adhered to the randomized treatment

Example* - Estimand/Clinical question of interest

What is the **difference between treatment arms** (*placebo* and *1 unit, 2 units, 4 units, 8 units* of *BAY-XYZ*), estimated as **model-based means**, of the **change from baseline to *Week K*** in ***lab parameter*** in *patients with the disease of interest*, **regardless of any temporary or permanent treatment discontinuation and unplanned dose adaptations#**?

// Use the “treatment policy” strategy for all intercurrent events

but you could also ask:

What is the **difference between treatment arms** (placebo and *1 unit, 2 units, 4 units, 8 units* of *BAY-XYZ*), estimated as **model-based means**, of the **change from baseline to *Week K*** in ***lab parameter*** in *patients with the disease of interest*, **using the dose the patients reached# and remained on for the complete the full treatment period, and did not use any prohibited medication**?

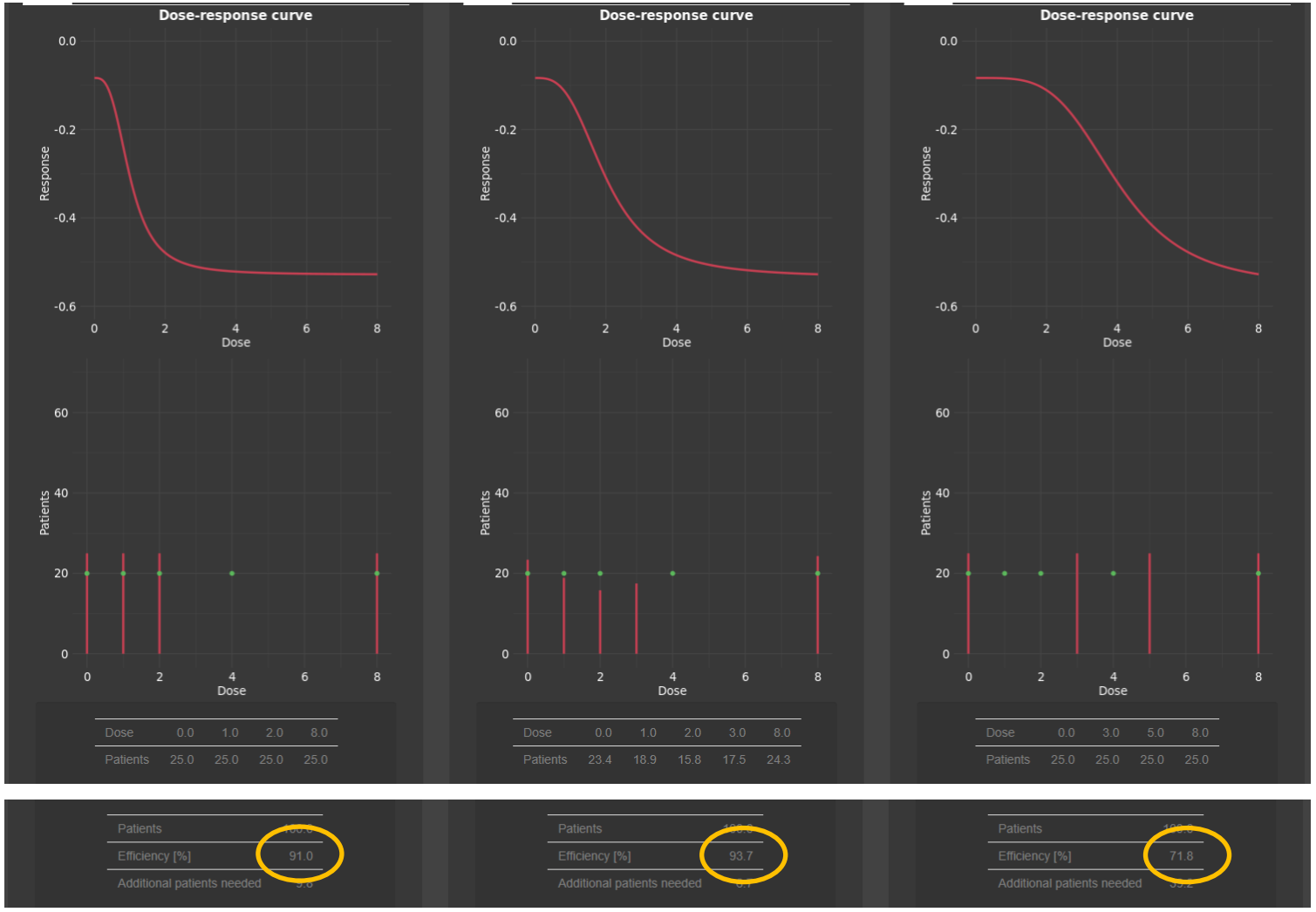
// Could use a “hypothetical” or “while on treatment” strategy, or analyze in the dose group that was actually reached

#patients receiving higher doses (4 units or more) had to be up-titrated in one or two titration steps. In case treatment was not well-tolerated, up-titration might not have been performed as planned

*for confidentiality reasons, the presented study (design/results) was changed slightly

Example* – Assumptions and Study Design

Study was planned and analyzed with (generalized) MCPMod; 5 dose levels; balanced randomization



Candidate shapes:
3 different
sigmoidal Emax
models;

Parameters:

E0=-0.0834

EMax between
-0.4451 and -0.472

ED50: 1, 2 and 4

Hill: 3, 3 and 4

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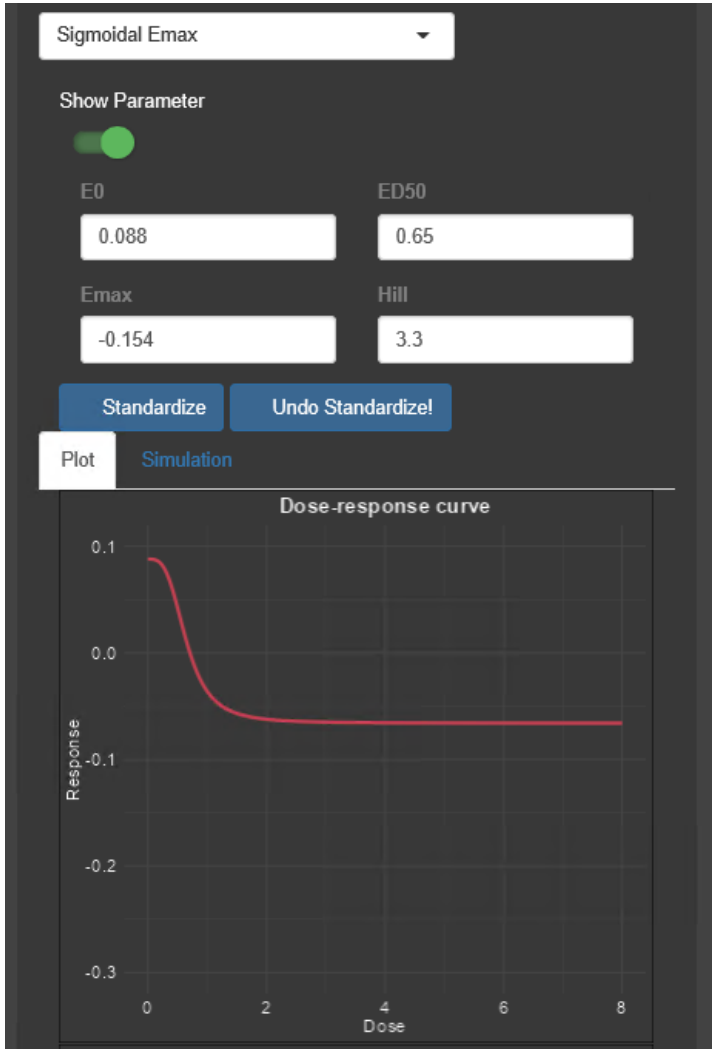
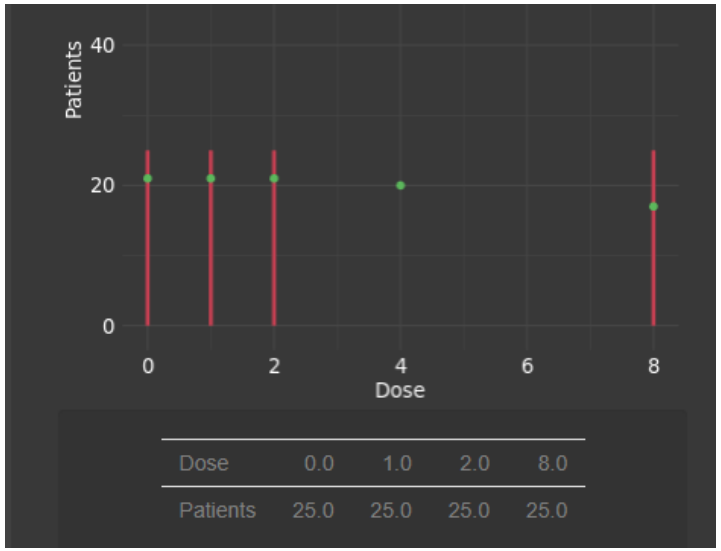
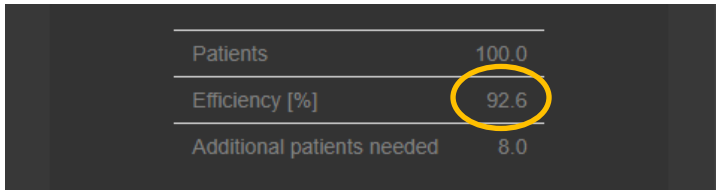
Example* – Results

Primary estimand – patients analyzed using their randomized dose







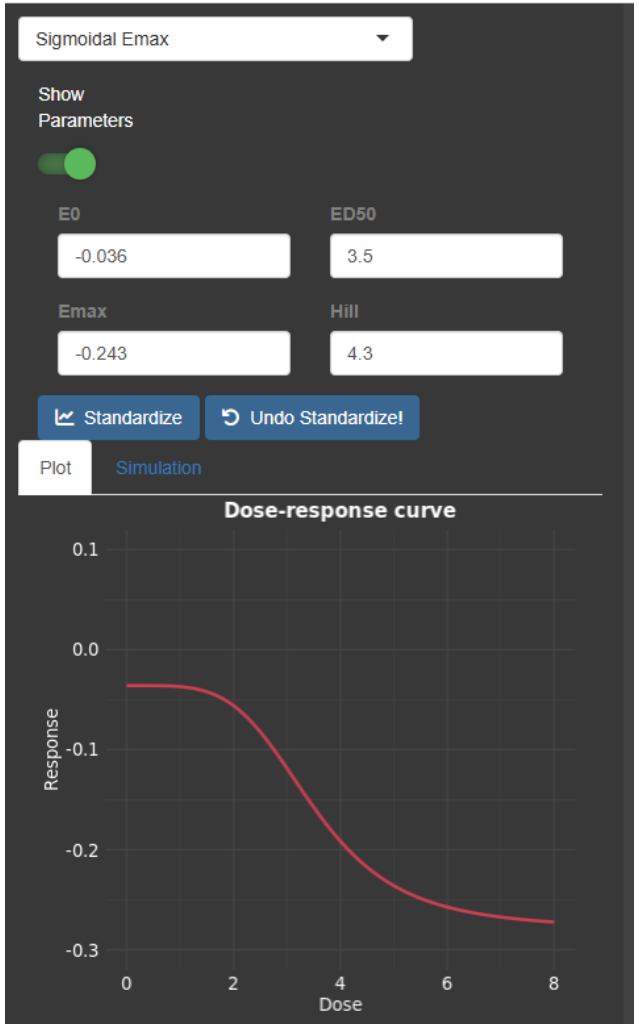
Number of (evaluable) patients per dose (%):

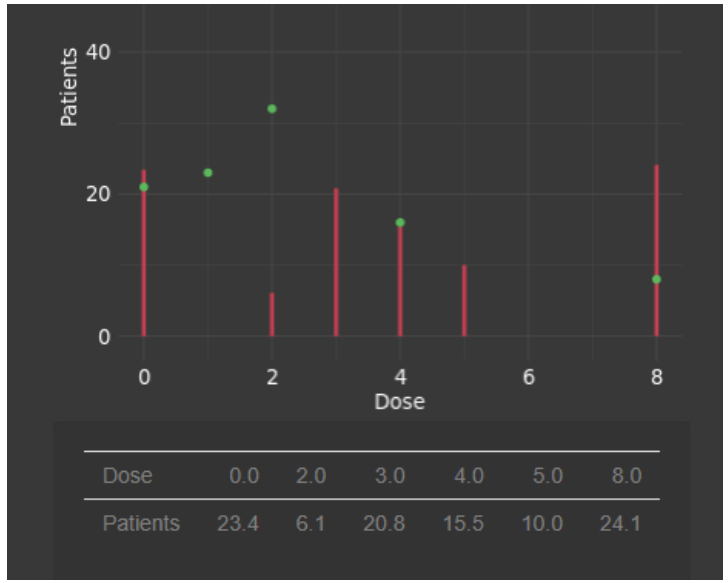
Dose	N (%)
0	21
1	21
2	21
4	20
8	17

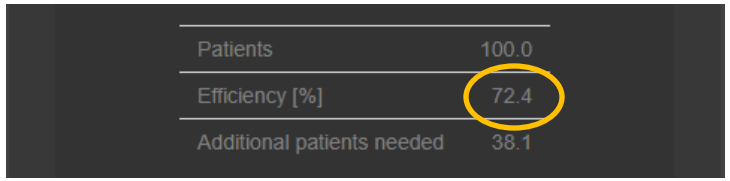
*for confidentiality reasons, the presented study (design/results) was changed slightly

Example* – Results

Supportive analysis: patients analyzed using their actual dose







Number of (evaluable) patients per dose (%):

Dose	N (%)
0	21
1	23
2	32
4	16
8	8

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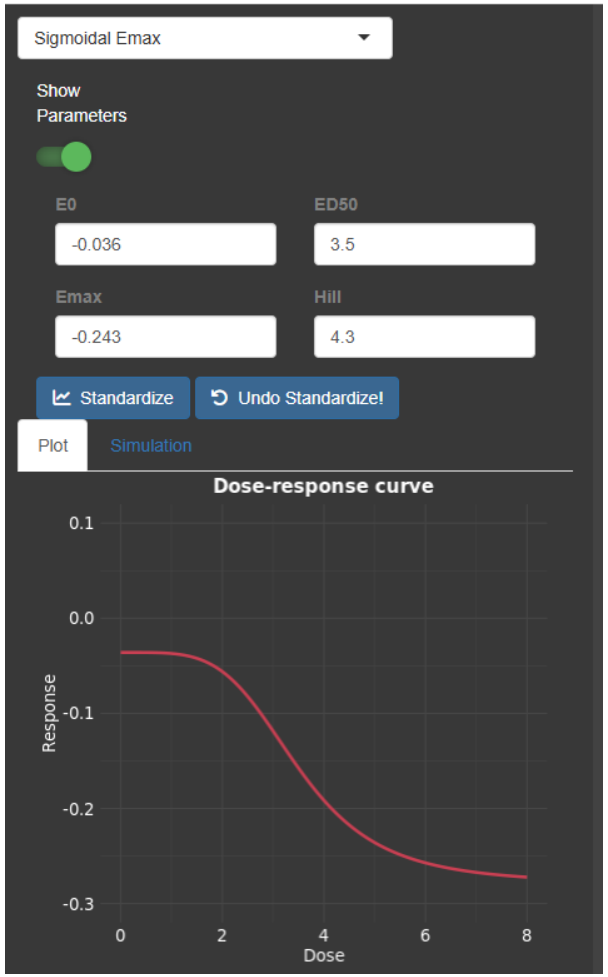
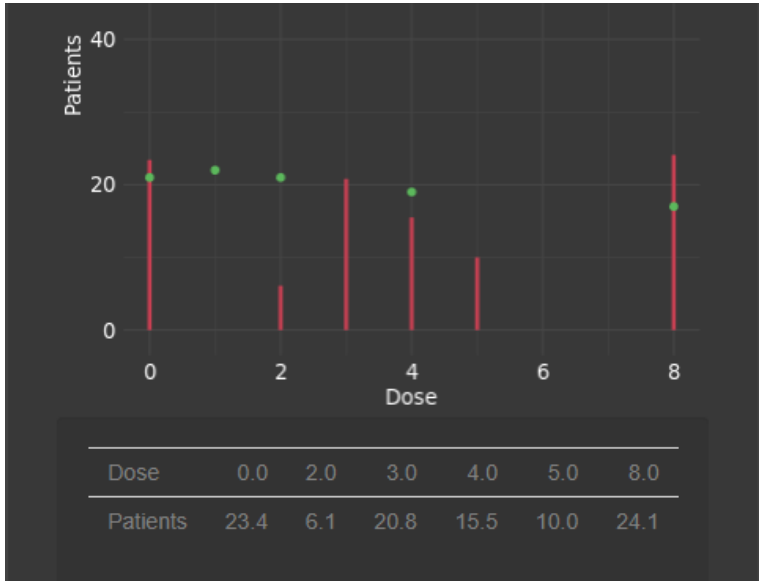
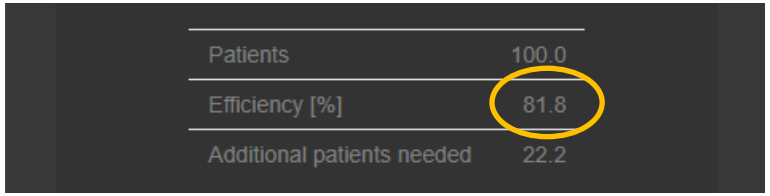
Example* – what if…

…we would have planned for some patients not reaching the planned dose and would have achieved (almost) a balanced distribution across doses ?







Number of (evaluable) patients per dose (%):

Dose	N (%)
0	21
1	22
2	21
4	19
8	17

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Summary and Conclusion

- Intercurrent Events and the chosen estimand can have a considerable influence not only on the study result, but also on the optimal study design, and should be considered at the planning stage
- Trying to consider these requires additional assumptions and increases uncertainty
- The example study was well planned with a design that was able to cover a broad range of assumptions
  - The results (ED50 and hill parameter) were in the expected range, therefore the design had high efficiency (for the primary analysis)
  - Analyzing patients based on the actual dose relevantly changed the results, and reduced the efficiency of the design
- **Learning: rather find a practicable design that has sufficient efficiency across a broad range of assumptions, than trying to focus on „the optimal design“**
- **Question: how can we better incorporate the expected effects of intercurrent events at the planning stage?**
  - Plan for imbalances in actual dose and discontinuations?
  - adaptive design that adjusts the randomization ratio based on observed intercurrent events?

Part 2: Finding more than the right dose

Thomas Schmelter

Motivating example

Development of an ophthalmology drug

- Drug will be administered by an injection into the eye
  - Treatment is expected to be „chronic“
  - Injections will be given repeatedly over many years

- Questions to be answered
  - What is the right dose?
  - What are the right intervals between the treatments?
    - Fixed intervals
    - Flexible regimen (intervals adjusted by response to treatment)

What would we usually do?

- Dose response model
  - $Y_{ij} = f(d_i, \theta) + \epsilon_{ij}$
- Design
  - $\begin{pmatrix} d_1 & d_2 & \dots & d_k \\ w_1, & w_2, & \dots, & w_k \end{pmatrix}$
- Optimize design (doses, number/proportion of patients per dose level) to
  - Best estimate the curve
  - Best estimate a certain parameter (e.g. ED50)
  - Dose response relationship not known? --> mcpMod (Bretz et al., 2005)

What now?

- Finding the right dose and the right interval
- What is a suitable model f?
  - $Y_{ij} = f(d_i, \tau_i, \theta) + \epsilon_{ij}$

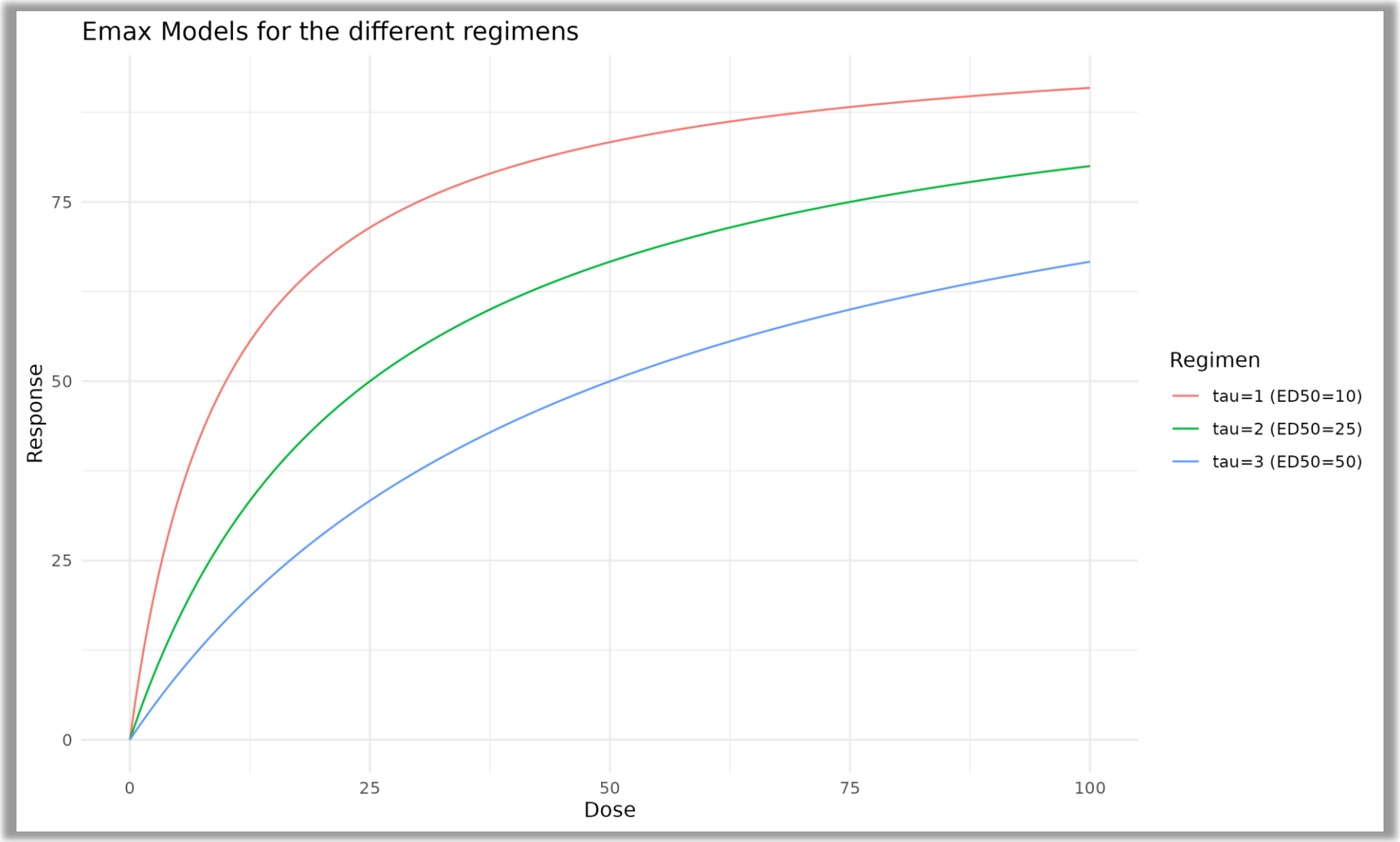
- Design space has at least one more dimension
  - interval between injections in addition to the dose
- More parameters to estimate
- More candidate models to pick from

Simple Modelling approach

Shared Model with effect of „treatment interval“ on ED_{50}

- Assume only three (discrete) options for the treatment interval
- For a given treatment interval (τ) the dose-response curve follows an Emax model
  - Only the ED_{50} differs for different treatment intervals
  - E_0 *and* E_{max} are the same regardless of the treatment interval

$$Y_i(D,\tau) = E_0 + \frac{E_{max}D}{ED_{50\_\tau} + D}$$


Emax Models for the different regimens
Response
0
25
50
75
0
25
50
75
100
Dose
Regimen
tau=1 (ED50=10)
tau=2 (ED50=25)
tau=3 (ED50=50)

Looking for optimal designs

- For a „single“ Emax model the D-optimal design is well known
- Optimal design points (with equal weights) are (e.g. Dette et al. (2010))
  - Dose 1 (Placebo): $d = 0$
  - Dose 2 (maximal dose): $d = d_{max}$
  - Dose 3 (intermediate dose): $d = d_{int} = \frac{ED_{50}\, d_{max}}{2\, ED_{50} + d_{max}}$

- Starting point for D-optimal design for shared model could have the form
  - $\xi = \begin{pmatrix} (0,1) & (d_{max},1) & (d_{max},2) & (d_{max},3) & (d_{int\,1},1) & (d_{int\,2},2) & (d_{int\,3},3) \\ w_1 & w_2 & w_3 & w_4 & w_5 & w_6 & w_7 \end{pmatrix}$

Practical example

- Dose can range from 0 (=Placebo) to 100
- Assumptions on parameters for locally optimal designs
  - $E_0 = 0,\ E_{max} = 100,\ ED_{50,1} = 10,\ ED_{50,2} = 25,\ ED_{50,3} = 50$

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  - $E_0 = 0,\ E_{max} = 100,\ ED_{50,1} = 10,\ ED_{50,2} = 25,\ ED_{50,3} = 50$

d=0, $\tau = 1$	d=100, $\tau = 1$	d=100, $\tau = 2$	d=100, $\tau = 3$	d=8.33, $\tau = 1$	d=16.67, $\tau = 2$	d=25, $\tau = 3$
w_1	w_2	w_3	w_4	w_5	w_6	w_7

Practical example

- Dose can range from 0 (=Placebo) to 100
- Assumptions on parameters for locally optimal designs
  - $E_0 = 0,\ E_{max} = 100,\ ED_{50,1} = 10,\ ED_{50,2} = 25,\ ED_{50,3} = 50$
- Numerical optimization of just the weights did not lead to a D-optimal design

d=0, $\tau = 1$	d=100, $\tau = 1$	d=100, $\tau = 2$	d=100, $\tau = 3$	d=8.33, $\tau = 1$	d=16.67, $\tau = 2$	d=25, $\tau = 3$
w_1	w_2	w_3	w_4	w_5	w_6	w_7

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  - $E_0 = 0,\ E_{max} = 100,\ ED_{50,1} = 10,\ ED_{50,2} = 25,\ ED_{50,3} = 50$

- Numerical optimization of just the weights did not lead to a D-optimal design
- Fixing only d=0 and d=100 but optimizing also the intermediate points

d=0, $\tau = 1$	d=100, $\tau = 1$	d=100, $\tau = 2$	d=100, $\tau = 3$	d=???, $\tau = 1$	d=???, $\tau = 2$	d=???, $\tau = 3$
w_1	w_2	w_3	w_4	w_5	w_6	w_7

Practical example

- Dose can range from 0 (=Placebo) to 100
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  - $E_0 = 0,\ E_{max} = 100,\ ED_{50,1} = 10,\ ED_{50,2} = 25,\ ED_{50,3} = 50$

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d=0, $\tau = 1$	d=100, $\tau = 1$	d=100, $\tau = 2$	d=100, $\tau = 3$	d=8.33, $\tau = 1$	d=25, $\tau = 2$	d=50, $\tau = 3$
0.2	0.2	0	0	0.2	0.2	0.2

Practical example

- Dose can range from 0 (=Placebo) to 100
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  - $E_0 = 0,\ E_{max} = 100,\ ED_{50,1} = 10,\ ED_{50,2} = 25,\ ED_{50,3} = 50$

Intermediate point of D-optimal design

- Numerical optimization of just the weights did not lead to a D-optimal design
- Fixing only d=0 and d=100 but optimizing also the intermediate points leads to

d=0, $\tau = 1$	d=100, $\tau = 1$	d=100, $\tau = 2$	d=100, $\tau = 3$	d=8.33, $\tau = 1$	d=25, $\tau = 2$	d=50, $\tau = 3$
0.2	0.2	0	0	0.2	0.2	0.2

Practical example

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- Numerical optimization of just the weights did not lead to a D-optimal design
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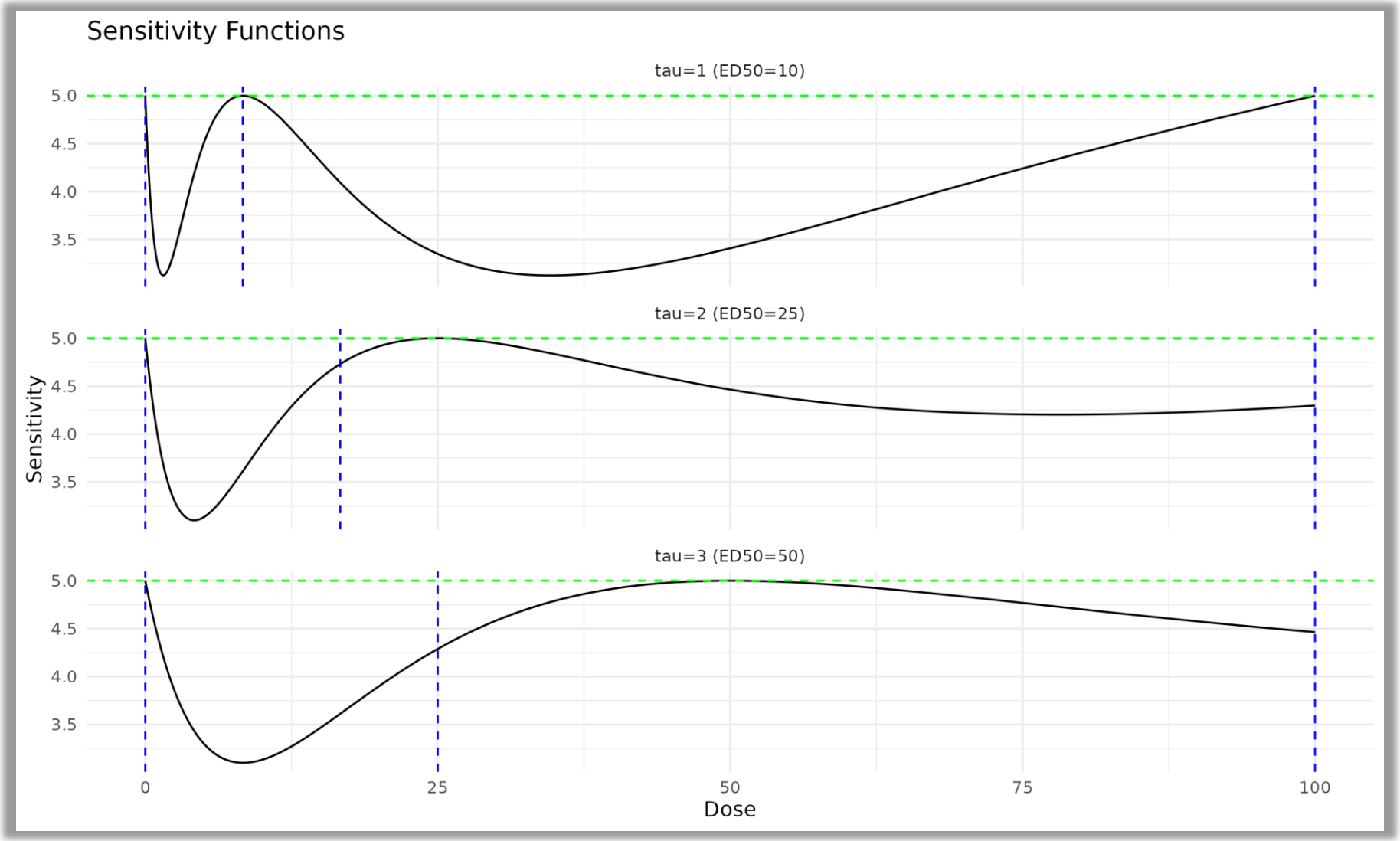
Intermediate point of D-optimal design

$ED_{50,2}$

$ED_{50,3}$

d=0, $\tau = 1$	d=100, $\tau = 1$	d=100, $\tau = 2$	d=100, $\tau = 3$	d=8.33, $\tau = 1$	d=25, $\tau = 2$	d=50, $\tau = 3$
0.2	0.2	0	0	0.2	0.2	0.2


Sensitivity Functions
tau=1 (ED50=10)
tau=2 (ED50=25)
tau=3 (ED50=50)
Sensitivity
5.0
4.5
4.0
3.5
0
25
50
75
100
Dose

Speculation

- D-optimal design for the shared Emax model (with 3 regimens) consists of
  - 5 design points
    - Placebo
    - Maximum dose in regimen with lowest assumed ED_{50}
    - Intermediate D-optimal design point from standard Emax model for regimen with lowest ED_{50}
    - Assumed ED_{50} dose in the other two regimen

- Checked for few other examples

Summary / outlook

- Often dose finding studies are aiming at more than just finding the right dose and should rather provide information on the right regimen
  - Interval between treatments
  - Titration regimens / rules
- Already in simple settings this can become challenging due to practical constraints (number of patients, number of different doses)
- Optimal design theory can help finding pragmatic approaches

Health for all, Hunger for none

Thank you!

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References and Resources

1. Bretz F, Pinheiro JC, Branson M (2005) Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics 61(3):738–748
2. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Stat Med. 2014 May 10;33(10):1646-61
3. Carolin Kirchner - Optimal design in nonlinear dose-response models (Bachelor thesis, University of Potsdam – on file)
4. dosedesignR: https://cran.r-project.org/web/packages/dosedesignR/index.html
5. Dette, H., Kiss, C., Bevanda, M., & Bretz, F. (2010). Optimal designs for the emax, log-linear and exponential models. Biometrika, 97(2), 513–518. http://www.jstor.org/stable/25734102

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Back-up

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Example - Estimand/Clinical question of interest

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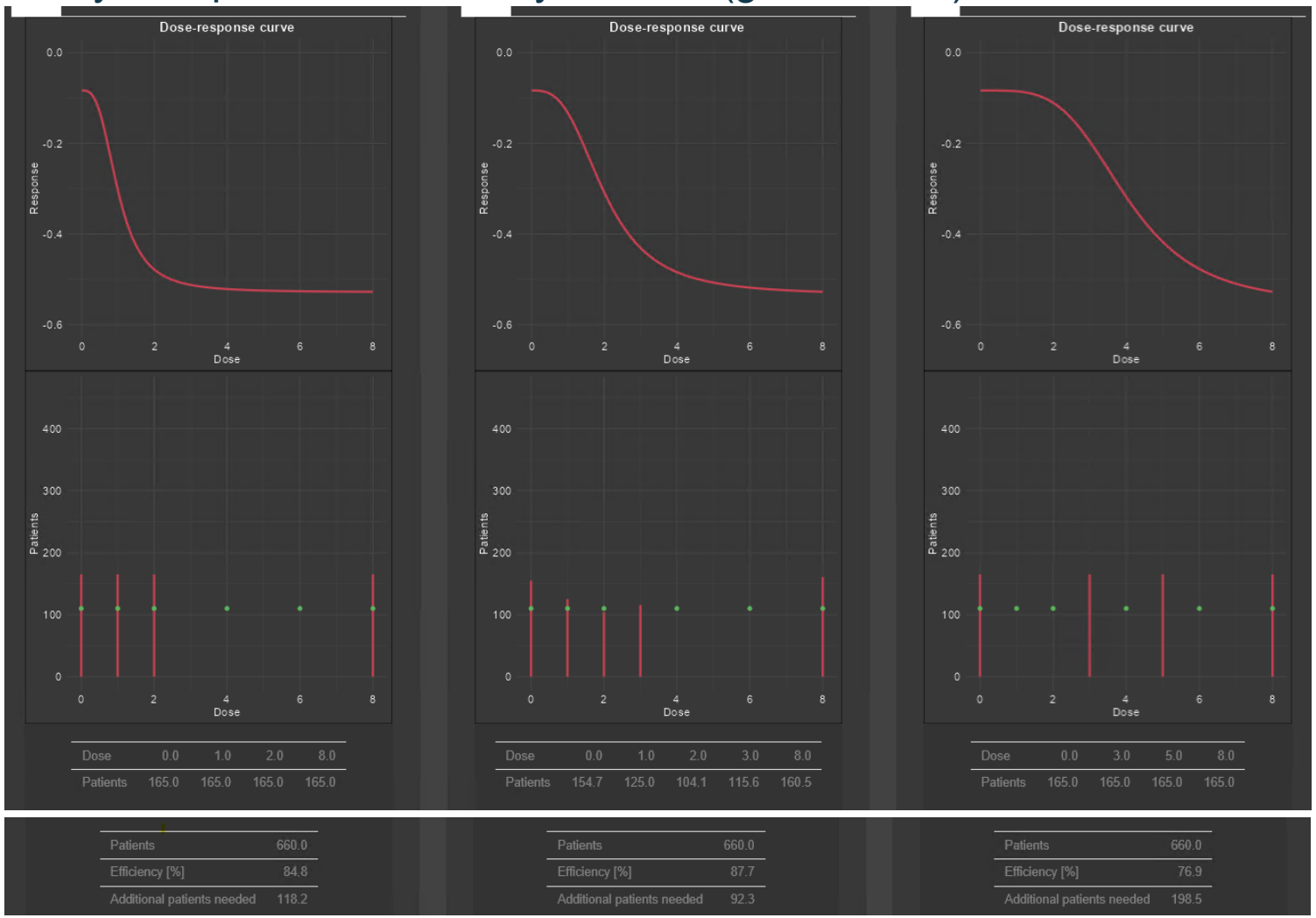
// Could use a “hypothetical” or “while on treatment” strategy, or analyze in the dose group that was actually reached

*patients receiving higher doses (4 units or more) had to be up-titrated in one or two titration steps. In case treatment was not well-tolerated, up-titration might not have been performed as planned

Example – Assumptions and Study Design

Study was planned and analyzed with (generalized) MCPMod; 6 dose levels; balanced randomization



Candidate shapes: 3 different sigmoidal Emax models;

Parameters:

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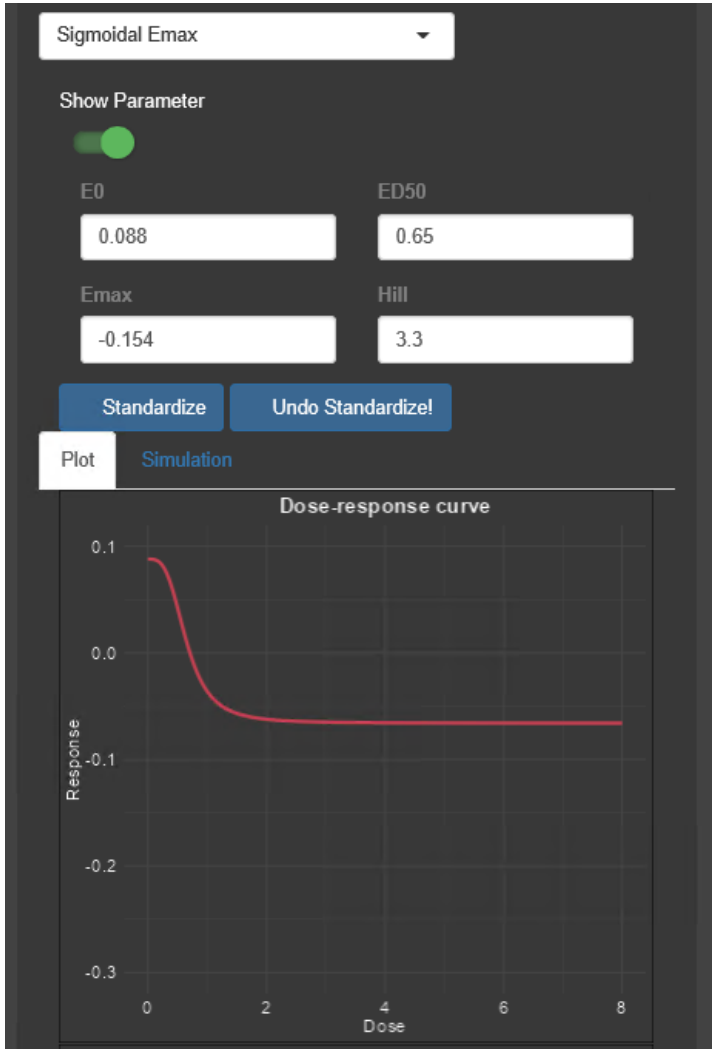
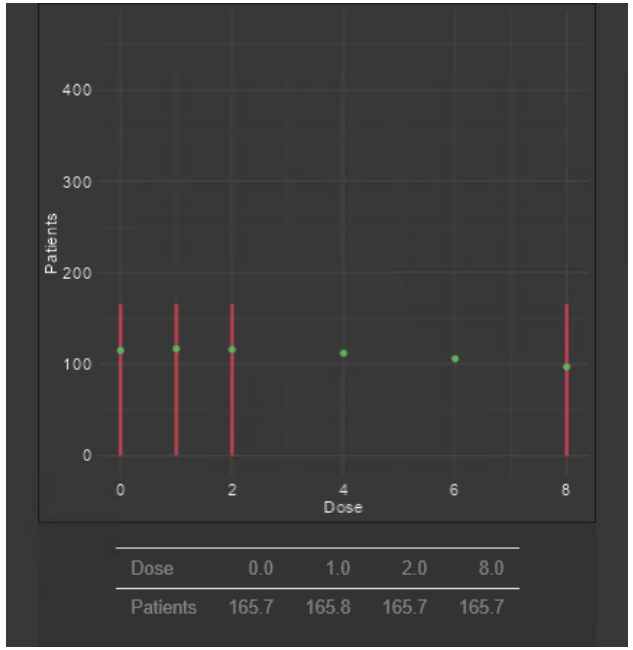
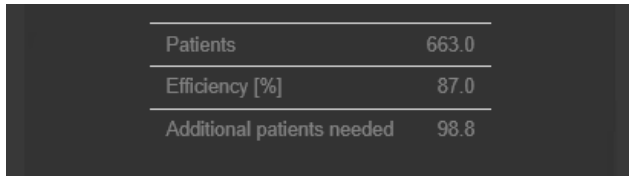
Hill: 3, 3 and 4

Example – Results*

Primary estimand – patients analyzed using their randomized dose







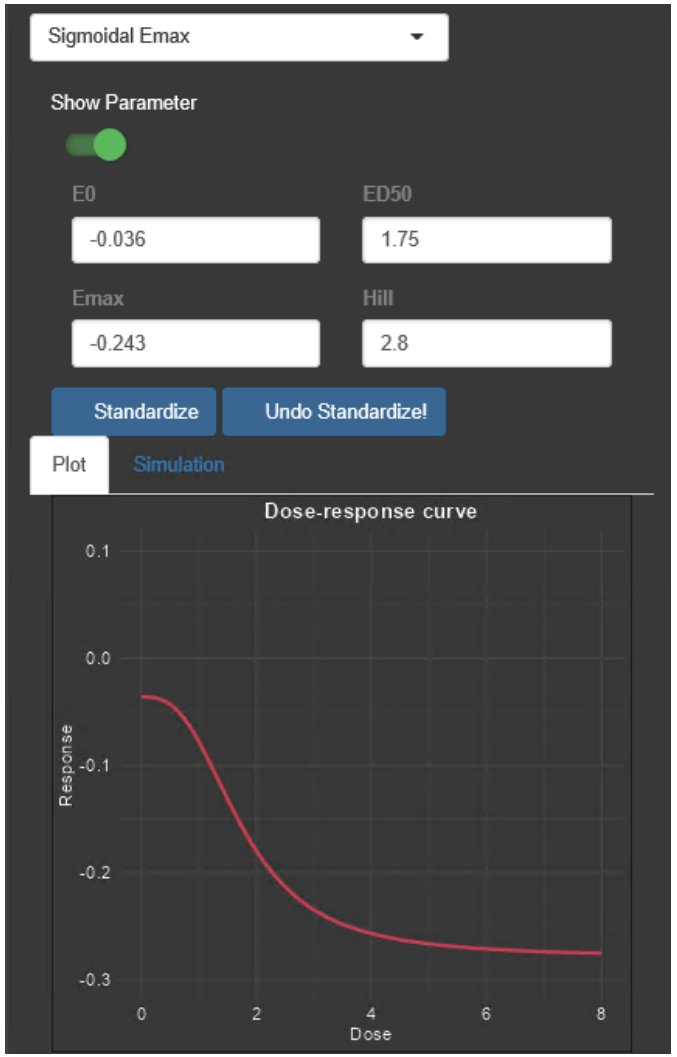
Number of (evaluable) patients per dose:

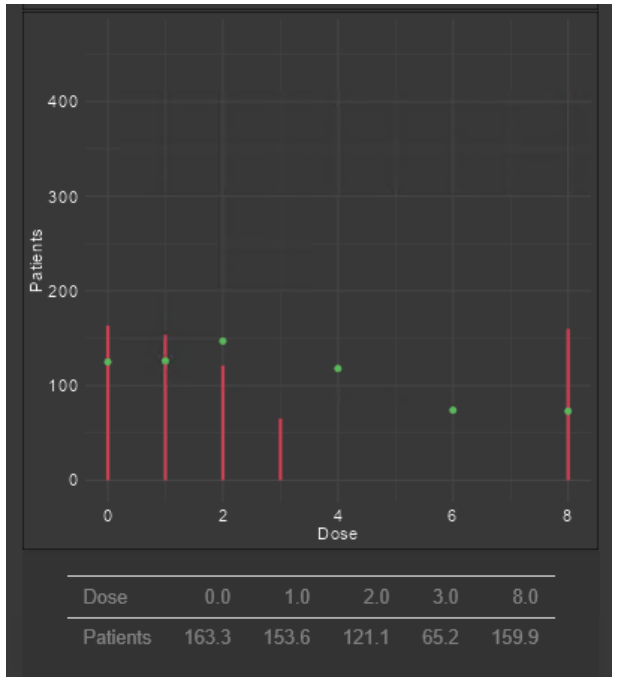
Dose	N
0	115
1	117
2	116
4	112
6	106
8	97

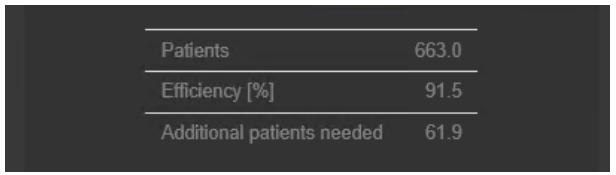
*for confidentiality reasons, the presented results are not the actual results

Example – Results*

Supportive analysis: patients analyzed using their actual dose







Number of (evaluable) patients per dose:

Dose	N
0	125
1	126
2	147
4	118
6	74
8	73

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