Challenges and pitfalls in applying optimal design theory in clinical dose finding studies

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Agenda

// Introduction to clinical dose finding studies

// Optimal designs for dose finding studies

// A recent example with some learnings (and many open questions)

Dose Finding Studies - Introduction

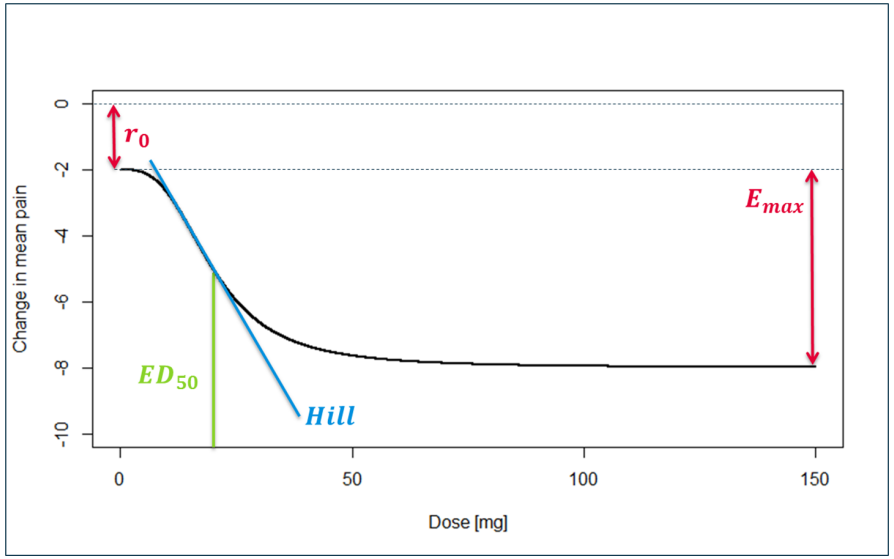
- Second phase of clinical development
- Objectives:
  - Establish a dose-response effect
  - Estimate the dose response relationship of a drug
  - Determine a therapeutic window or the therapeutic dose
- These different objectives can be addressed, e.g., by the MCP-Mod[1,2] approach
  - Testing for 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

Planning Dose Finding Studies – Workflow

// The typical interdisciplinary effort in the planning phase consists of

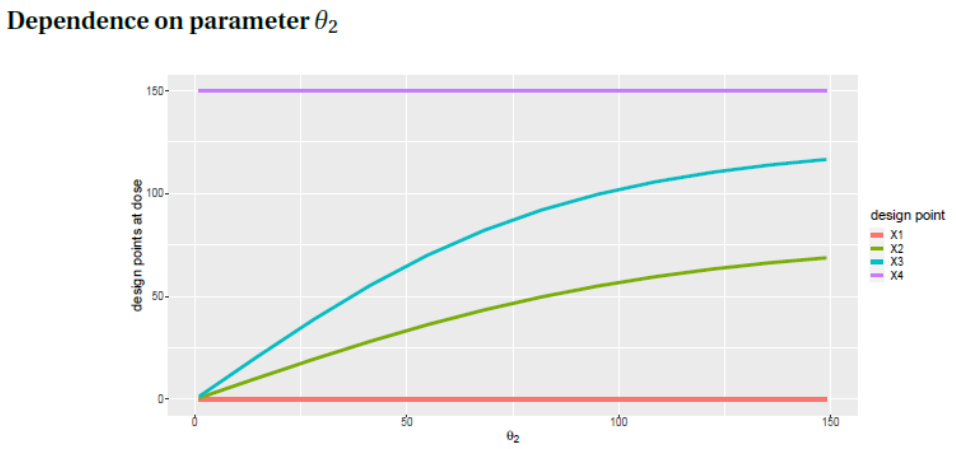
1) defining the dose range (and the specific dose levels) that can be studied,
2) discussing the outcome variable(s) and the possible/expected range for the studied dose range,
3) discussing potential shapes (functional relationship and parameters) of dose-response curves (=candidate models),
4) optimizing the designs for the different candidate models (under constraints),
5) reviewing the designs, e.g., for practicability or robustness for other candidate models.

// The last two steps can be facilitated by the *dosedesignR*[3] tool (shiny app available as R package)

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 $ED_{50}^{(3)}$ 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

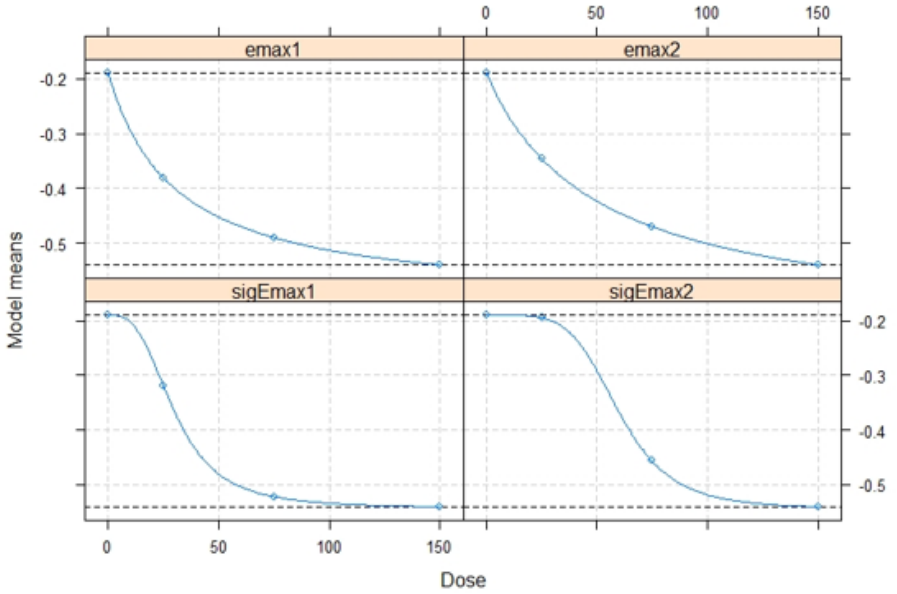
Practical limitations

- 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

Example: PAGANINI[5,6] - Dose Finding Study in Chronic Cough

Planning of the study

- Intention to analyze the study with MCP-Mod
- Dose range: placebo (0 mg) to 150 mg, smallest tablet strength available was 25 mg
- Primary endpoint:
  - Change from baseline in log(24h cough count)
  - continuous, normally distributed, with lower values being better
- A linear dose-response relationship was ruled out
- Emax and sigmoidal Emax shapes were considered plausible
- Derived candidate set (based on literature, prior studies, expert opinion):



Model	Response as function of dose d
Emax1	*-0.19 - 0.42 * d / (30 + d)*
Emax2	*-0.19 - 0.47 * d / (50 + d)*
sigmoidal Emax1	*-0.19 - 0.35 * d^3/(30^3 + d^3)*
sigmoidal Emax2	*-0.19 - 0.35 * d^5/(60^5 + d^5)*

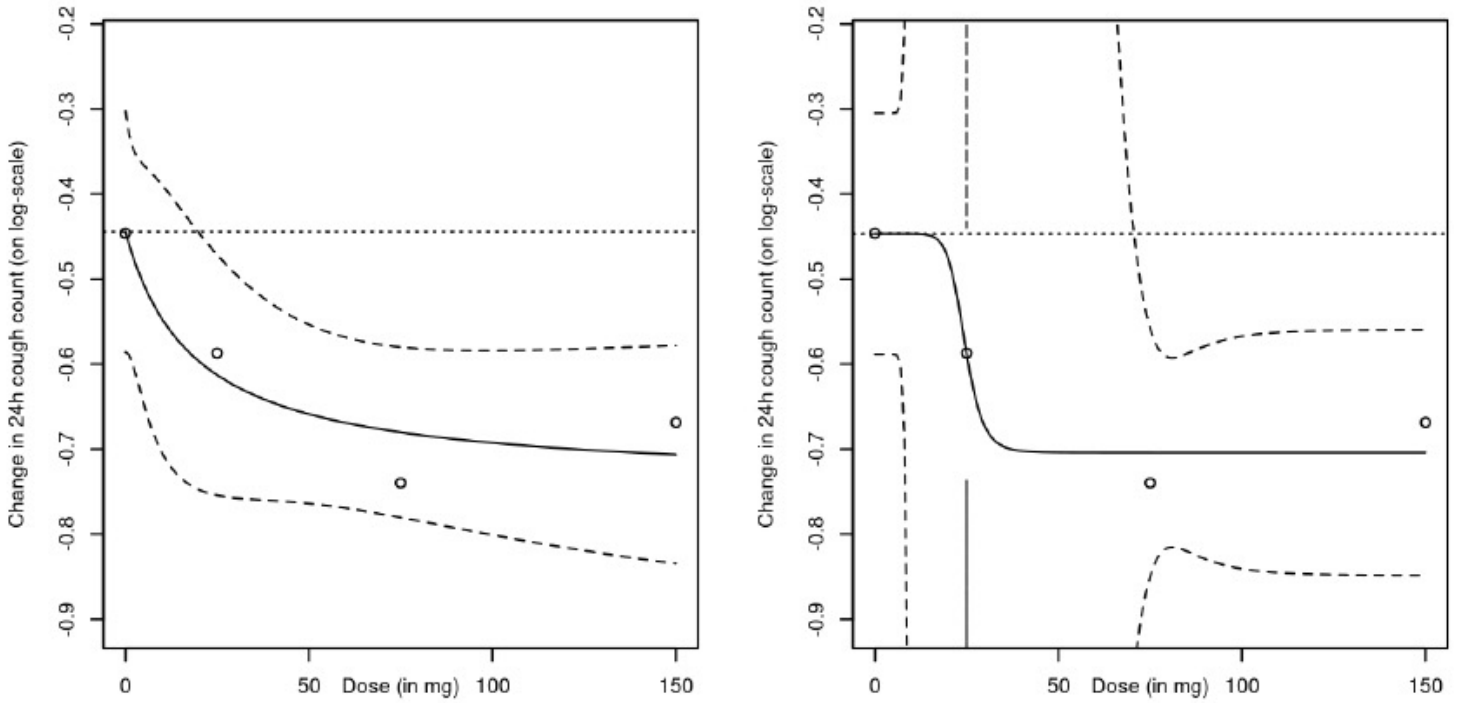
Example: PAGANINI – Final Study Design

- Selected doses: placebo, 25 mg, 75 mg, 150 mg
  - This is not the D-optimal design for any of the candidate models
  - Efficiency gets quite low:
    - compared to the optimal unrestricted design: between 89% (Emax) and 40% (2nd sigEmax)
    - compared to a “good” design with 5 realistic doses: between 99% (Emax) and 46% (2nd sigEmax)
- The design is actually good for 2 out of the 4 candidate models, okay for the 3rd, and bad for the 4th
- The choice of the design was not only based on statistical considerations
  - 25 mg was expected to have only limited efficacy
  - 75 mg was expected to give the minimum efficacy needed and to be well tolerated
  - 150 mg was expected to give maximum efficacy (a little better than 75 mg) but being less well tolerated
  - The exposures were expected to overlap, but only slightly, between the three selected doses
    - If additional doses in between (e.g. 50 mg) would have been selected, this would have resulted in a strong overlap in exposures and thus might have made it difficult to detect differences in effect between the doses

Example: PAGANINI - Results

- In the MCP part, a statistically significant dose-response was detected (all 4 tests)
- As for both candidate model types (Emax and sigEmax), the result was significant, both models were fitted
- The Emax model could be fitted without problems
- For the sigEmax model, the estimation especially of the hill parameter was difficult*

Dose-response model and target dose for the change in 24h cough count from baseline to week 12 (with 80%-CI) (per protocol set)



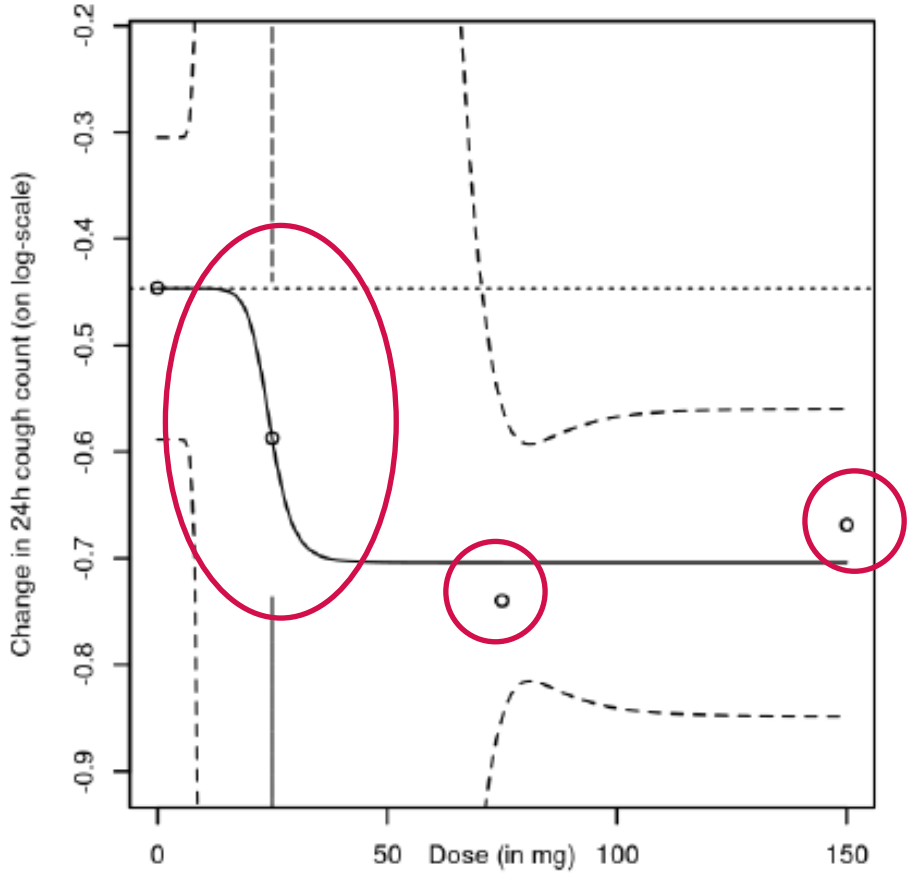
Emax model is shown on the left, sigmoidal emax model is shown on the right side

Bayer: /var/swan/root/bhc/1817080/20393/stat/main01/prod/analysis/pgms/t_14_2_1_1_adfapr_mcpmod_cclog.sas 04AUG2021 18:25

*not a new problem – see presentation of Tobias Mielke at mODa11

Example: PAGANINI – Problems with the sigEmax Model

- The observed means were non-monotone
  - Most likely due to chance, and the true response is very similar for 75 mg and 150 mg
- A good result was already observed for 25 mg (appr. half of the maximum effect)
  - ED50 was estimated close to 25 mg
  - Leading to high uncertainty on both ED_{50} and especially h
  - Extremely wide confidence intervals in the dose range up to 75 mg
- Design was completely inefficient (if the observations are reflecting the “truth”) – 2.2%
- Results from sigEmax model were not useful



Parameter	Estimate	Standard Error	Lower 95% CI Limit	Upper 95% CI Limit
e0	-0.4468	0.1106	-0.6636	-0.2300
Emax	-0.2573	0.1423	-0.5361	0.0216
ed50	24.5160	1767.8328	-3440.3726	3489.4045
h	10.0000	36913.2389	-72338.6188	72358.6188

Example: PAGANINI – Retrospective D-optimal Design

For the parameters

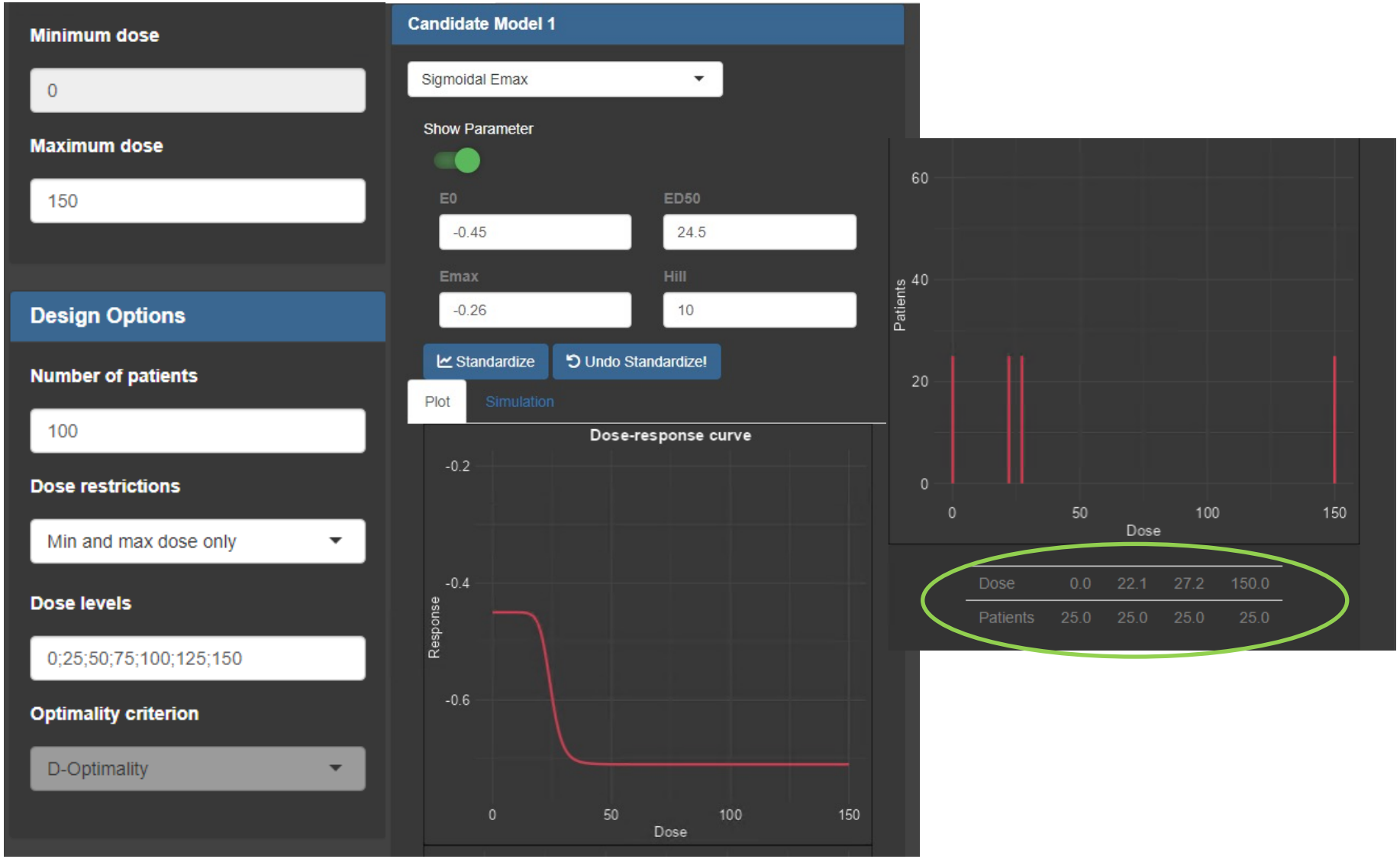
ED_{50}=24.5

and h=10,

the D-optimal design would have been:

[0, 22.1, 27.2, 150]

…but this was technically not possible!



Example: PAGANINI – Retrospective D-optimal Design

Restricted to the technically possible doses, the D-optimal design would have been:

[0, 25, 50, 150]

But this is actually highly inefficient (13.3%), compared to the unrestricted D-optimal design!

Example: PAGANINI – A Good Design

Retrospectively, what would have been a good design?

- An efficient design would have required smaller dose steps / a dose below 25mg
- As doses above 75 mg did not provide additional information, the maximum of the dose range could have been chosen to be smaller (e.g. 75 mg or 100 mg)

- If the observed result reflects the truth, a good design could have been [0,20,30,80] if tablets would have been available in 10 mg steps

- To cover a broad range of possible parameters with an ED_{50} between 25 mg and 75 mg, a good compromise would have required dose steps of 10 mg and 7 doses, e.g.

  [0,20,30,40,60,90,120] with equal weights

- Such a design has practical challenges…

Learnings and Practical Suggestions for Future Studies

- If you want to estimate a 4-parameter model and are uncertain about the ED_{50}, use more than 4 doses
- Include one less complex model in your candidate set
- Apply a design that is highly efficient across the expected parameter range
- Check what deviations from your expected parameters do to the efficiency of your design, and possibly adjust
- Question whether the available tablet strengths are granular enough
- Question whether the upper end of the dose range is too high

- Discussions on the design of the dose finding study should take place early enough so that the requirements on number of dose levels, granularity of tablet strength etc. can actually be considered

References and Resources

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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
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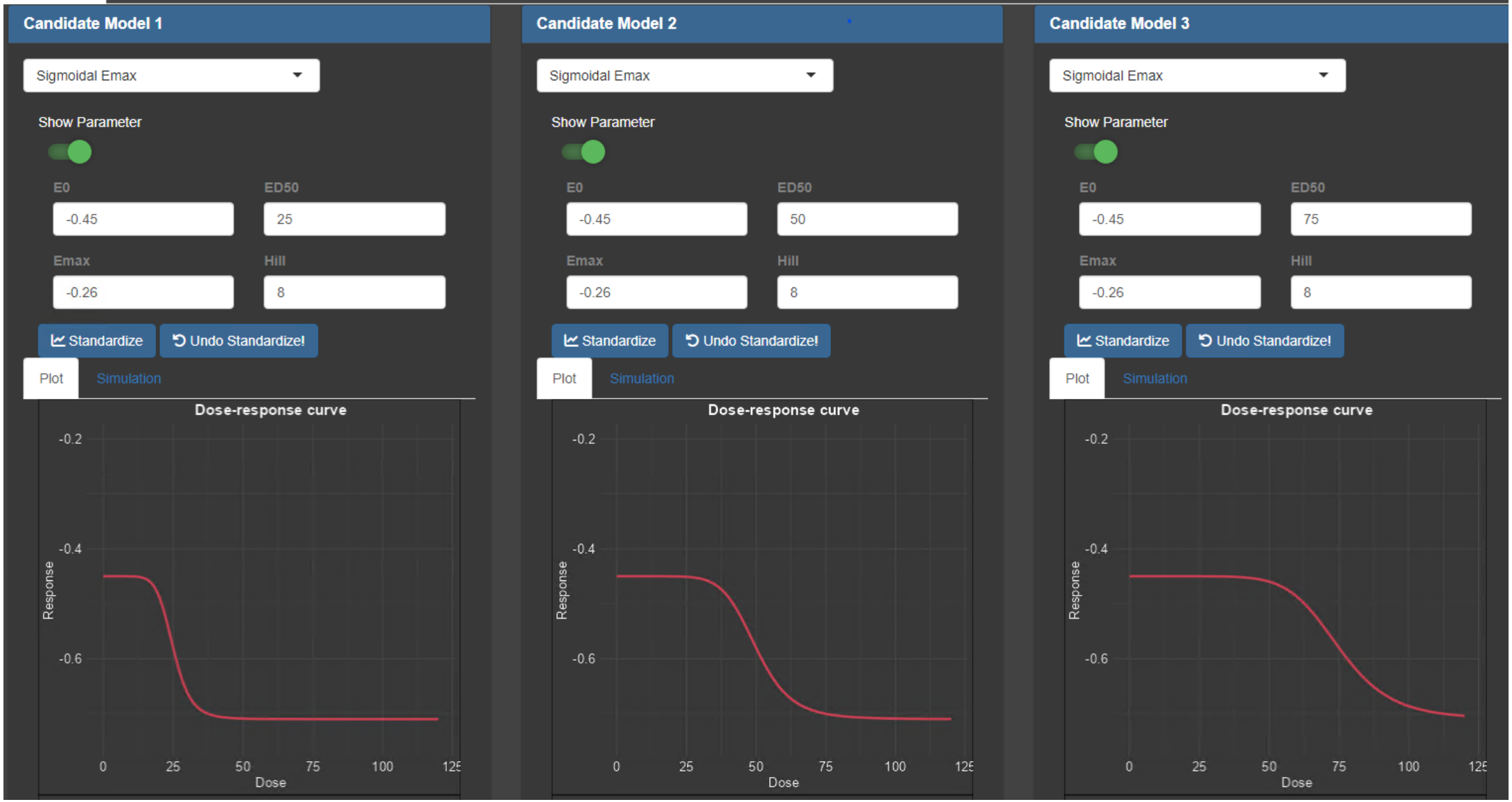
5. PAGANINI Study: https://clinicaltrials.gov/ct2/show/results/NCT04562155
6. Dicpinigaitis, P.V., Morice, A.H., Smith, J.A. et al. Efficacy and Safety of Eliapixant in Refractory Chronic Cough: The Randomized, Placebo-Controlled Phase 2b PAGANINI Study. Lung 201, 255–266 (2023). https://doi.org/10.1007/s00408-023-00621-x

Thank you!

Optimizing Across a wide Range of Possible ED_{50}s



Optimizing Across a wide Range of Possible ED_{50}s