Exposure-Response Modeling for Dose Selection Under Model Uncertainty: Extending MCPMod

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PODE Meeting – Basel, CH - September 08, 2017

Motivation

- Improper understanding of dose response (efficacy and safety), resulting in inadequate dose selection for Phase 3 programs remains a critical problem in drug development:
  - 50% of NMEs not approved when first submitted – 16% of those involved uncertainties about dose selection (Sacks et al, 2014)
  - Frequent post-marketing dosage changes – 20% of NMEs approved between 1980-1999 (Cross et al, 2002), majority dose reductions
- Some common reasons:
  - Phase 2 studies designed as mini-Phase 3 studies, using pairwise comparisons to control for dose selection
  - Few doses evaluated, often with similar efficacy (plateau of dose response profile), covering relatively small dose range
- Poor dose selection can lead to delays in, or denial of, regulatory approval, possibly preventing patients access to effective drugs

Dose finding Phase 2 studies

- Two main goals
  - Proof-of-concept (PoC): identify evidence of dose-response (DR) or exposure-response (ER) signal on efficacy
  - Dose selection: which dose(s) to take to Phase 3 program – e.g., minimum effective dose (MED), ED90 (dose producing 90% of maximum possible improvement over placebo)
- Design/analysis strategies fall into two broad classes
  - Pairwise comparisons between doses and placebo (accounting for multiplicity) with dose selection driven by hypothesis testing
  - Modeling of DR/ER relationship(s), with dose selection driven by model-based estimation (e.g., dose/exposure corresponding to target value, minimum acceptable value)

MCPMod: A unified dose finding approach

Trial Design Stage

General design considerations

Determination of suitable study population, endpoints, etc.

Set of candidate models

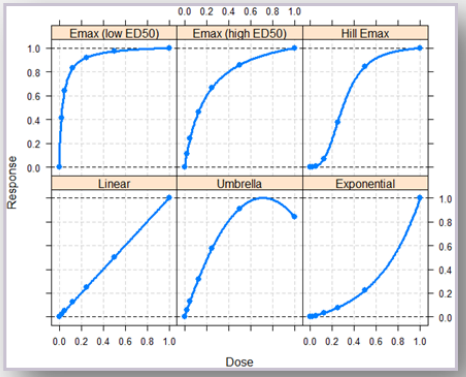
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



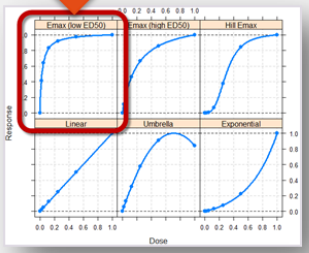
Trial conduct

$p < \alpha$?

Trial Analysis Stage

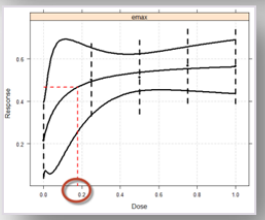
MCP step

- Assessment of dose-response signal using contrast tests
- Model selection (or model averaging) out of the set of significant models



Mod step

Dose-response and target dose estimation based on selected model(s)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/SAWP/757052/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013[1]
Start of public consultation	15 October 2013[2]
End of consultation (deadline for comments)	24 November 2013[3]
Adoption by CHMP	23 January 2014

FDA Fit-for-Purpose Determination of MCP-Mod

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

May 26, 2016

Janssen Research & Development, LLC
Attention: Purve Patel, RPh
Director, Global Regulatory Affairs
920 Highway 202, South
Raritan, NJ 088969

Dear Ms. Patel:

Please refer to the submission by Janssen Pharmaceuticals and Novartis Pharmaceuticals intended to support the use of MCP-Mod[1, 2] as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. We have completed our review of your submission and have determined it is fit-for-purpose in the context outlined in this letter.

MCPMod limitations and extensions

- Originally developed for parallel arm designs, normally distributed, homoscedastic response, with single measurement per patient, with modeling focused on DR
- gMCPMod extended use of methodology to binary, count, time-to-event, etc. response variables, possibly coupled with longitudinal data, but still focused on DR modeling only
- More recent extensions allow MCPMod with candidate families of models (without guesstimates and specific model contrasts): permutation tests and multiplicity adjusted likel. ratio tests
- Adaptive design, optimal design, Bayesian versions further extended MCPMod approach – all based on DR modeling
- Consider here initial attempt at extending methodology to ER modeling (single exposure measurement per subject)

ER extension of MCPMod

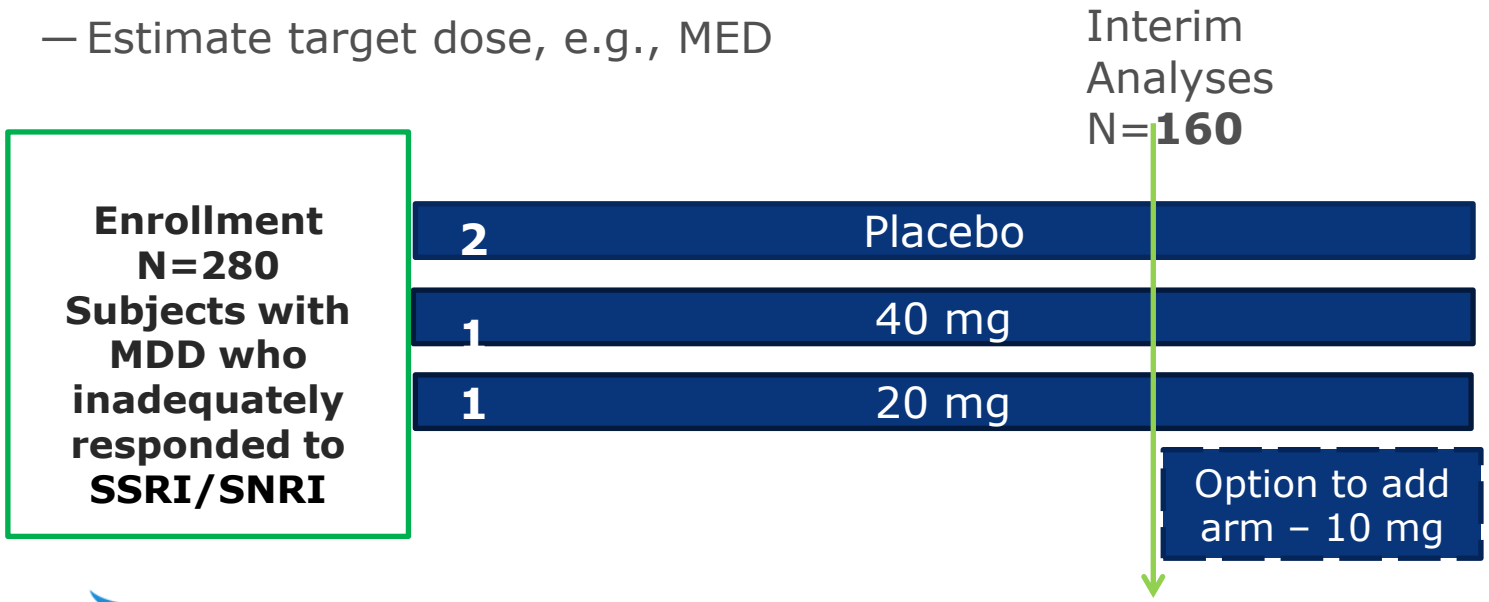
- MCPMod originally developed and extended for DR models:
  - Assumed fixed doses $d_1, \ldots, d_K$, with corresponding sample sizes $n_1, \ldots, n_K$ determined at study design
  - Optimal model contrasts and critical values for testing DR signal based on fixed doses and sample sizes, assuming underlying DR models $\mu(d) = f(d, \boldsymbol{\theta})$
- MCPMod ideas of testing and estimation under model uncertainty can be extended to ER models, requiring modifications to base methodology:
  - Exposures $\boldsymbol{x} = x_1, \ldots, x_N$ are not known before hand and there can be as many different values as the number of subjects

ER MCPMod extension (2)

- Consider first MCP-Mod for continuous response data:
  - Observed concentrations conditionally treated as doses, for which optimal (ER) model contrasts and critical values can be derived
  - Conditionally, Pr(Reject $H_0|\mathbf{x}) = \alpha(\boldsymbol{x}) = \alpha$, under null hypothesis H_0 of flat ER, ie., $\mu(\boldsymbol{x}) = c$, for all $\mathbf{x}$
  - Because observed PD response is independent of concentration under H_0, it follows $E(\alpha(\boldsymbol{x})) = \alpha$, so that conditional specification of optimal (ER) model contrasts and critical values, controls Type I error unconditionally.
- For more general types of PD response, e.g., binary, count and time-to-event, for which gMCPMod can be used:
  - bin concentrations into classes $X_1, \ldots, X_K$ with median of each class playing role of dose in the original gMCPMod specification

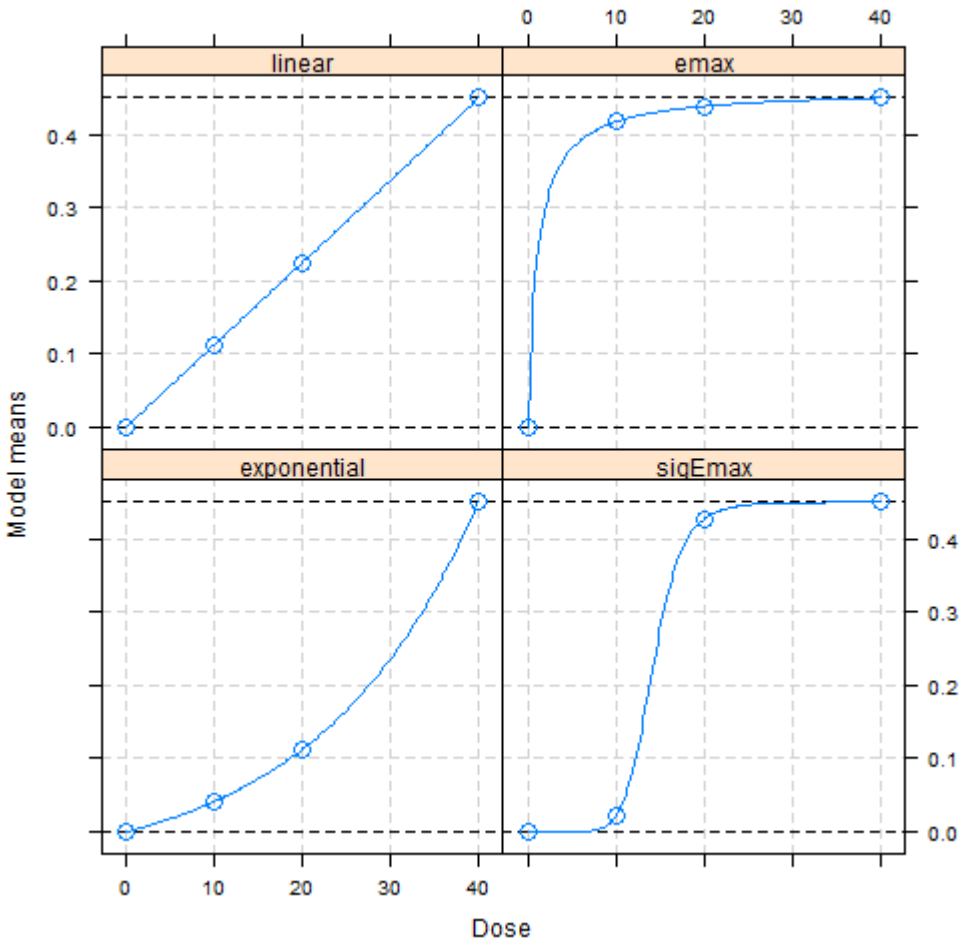
Example: Ph. 2 study in Depression

- Phase 2A/2B randomized trial in subjects with a moderate depression disorder (MDD)
- Primary endpoint: change from baseline in MADRS
- Objectives:
  - Test DR/ER signal - PoC
  - Evaluate up to 3 doses (10, 20, 40 mg) to characterize the dose-exposure-response relationship
  - Estimate target dose, e.g., MED

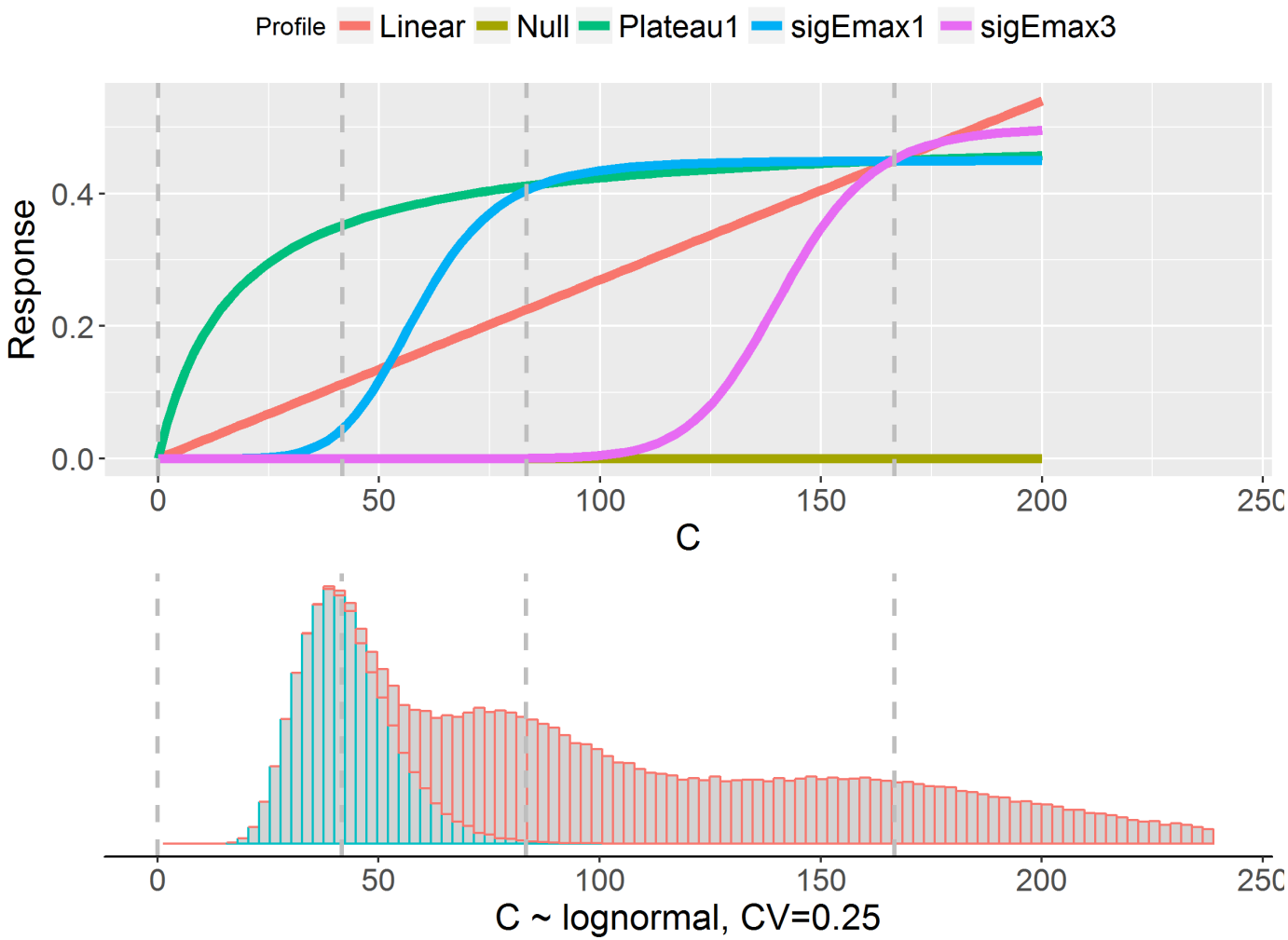


MCPMod: Candidate Models

- MCPMod: primary analysis approach for interim and final analysis (DR & ER)
- DR candidate models for IA: “linear”, “emax” and “exponential”
- For final analysis, candidate set extended with sigmoidal shape if 10 mg is added at IA
- All four shapes included in ER candidate set (final)

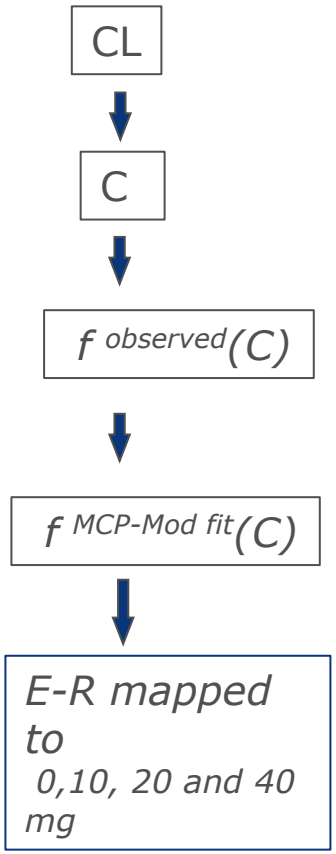


Simulation Scenarios for ER

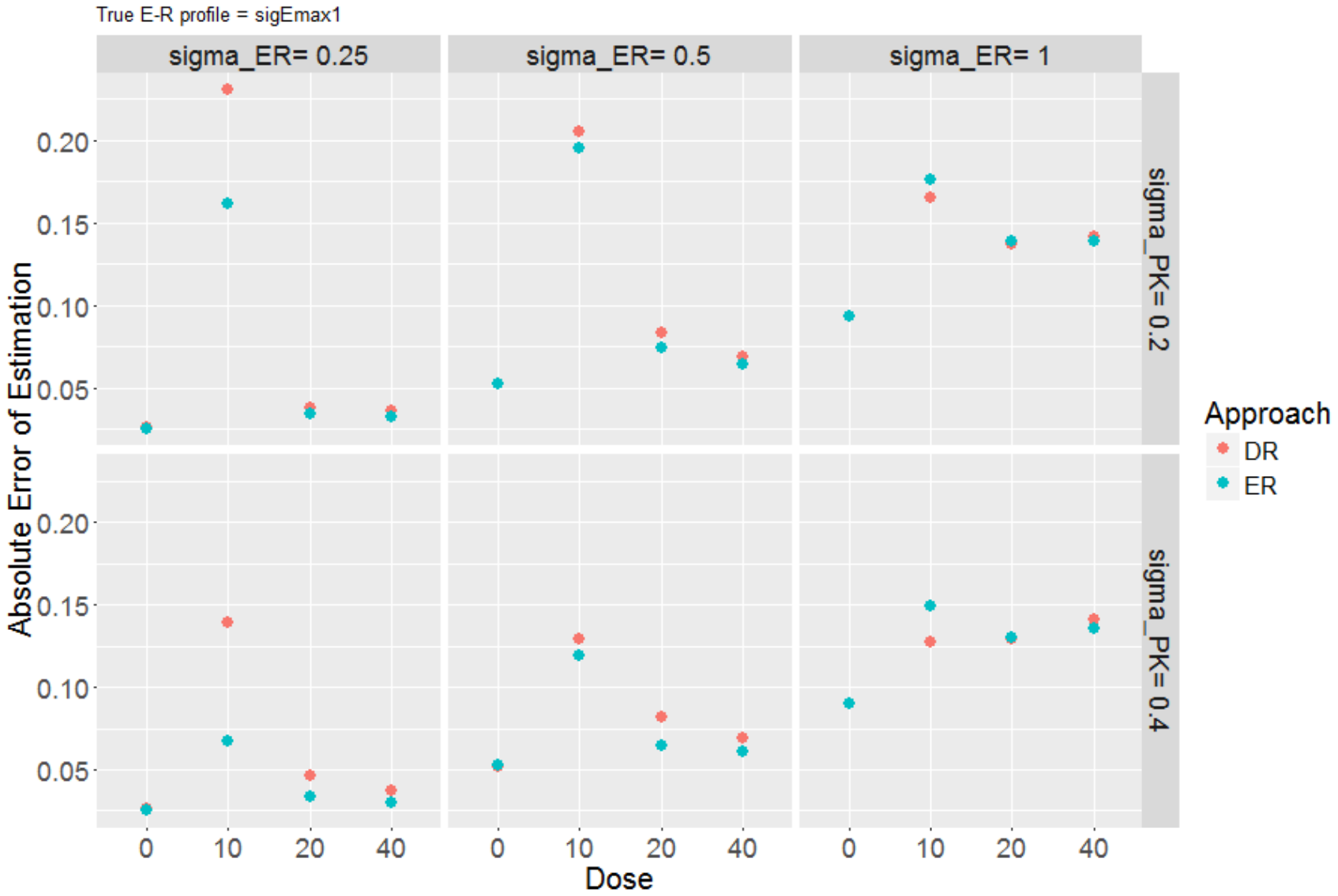


Simulation algorithm to generate ER data

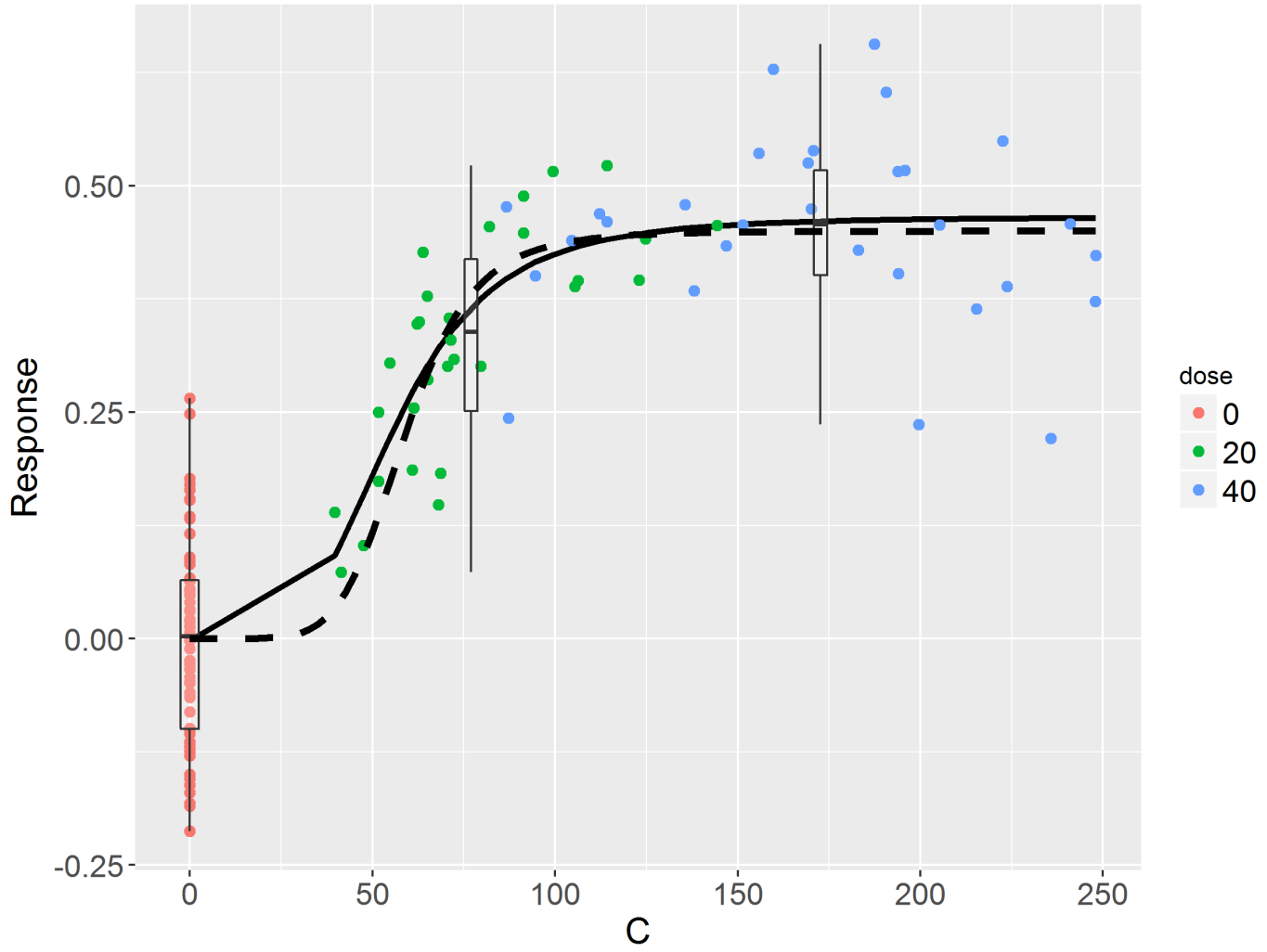
1. Simulate clearance, CL, as lognormal variable with *log-mean* CL_{tv} *= 10 L/h, CV =30%*
2. Set concentration, *C = Dose/CL * 1000/24*,
   - *C* is the average steady-state concentration over 24 h
   - Tested doses are 0, 20 mg, and 40 mg
3. Simulate response using true model with mean $f^{true\ E\text{-}R}(C)$; normal errors with $SD=\sigma_{ER}$ (variability of MADRS change from baseline)
4. Fit MCPMod on *C*-scale, i.e., estimate *f(C)*
5. Map ER to DR by averaging $f(C_j)$ across each dose (need to simulate C for 10 mg)



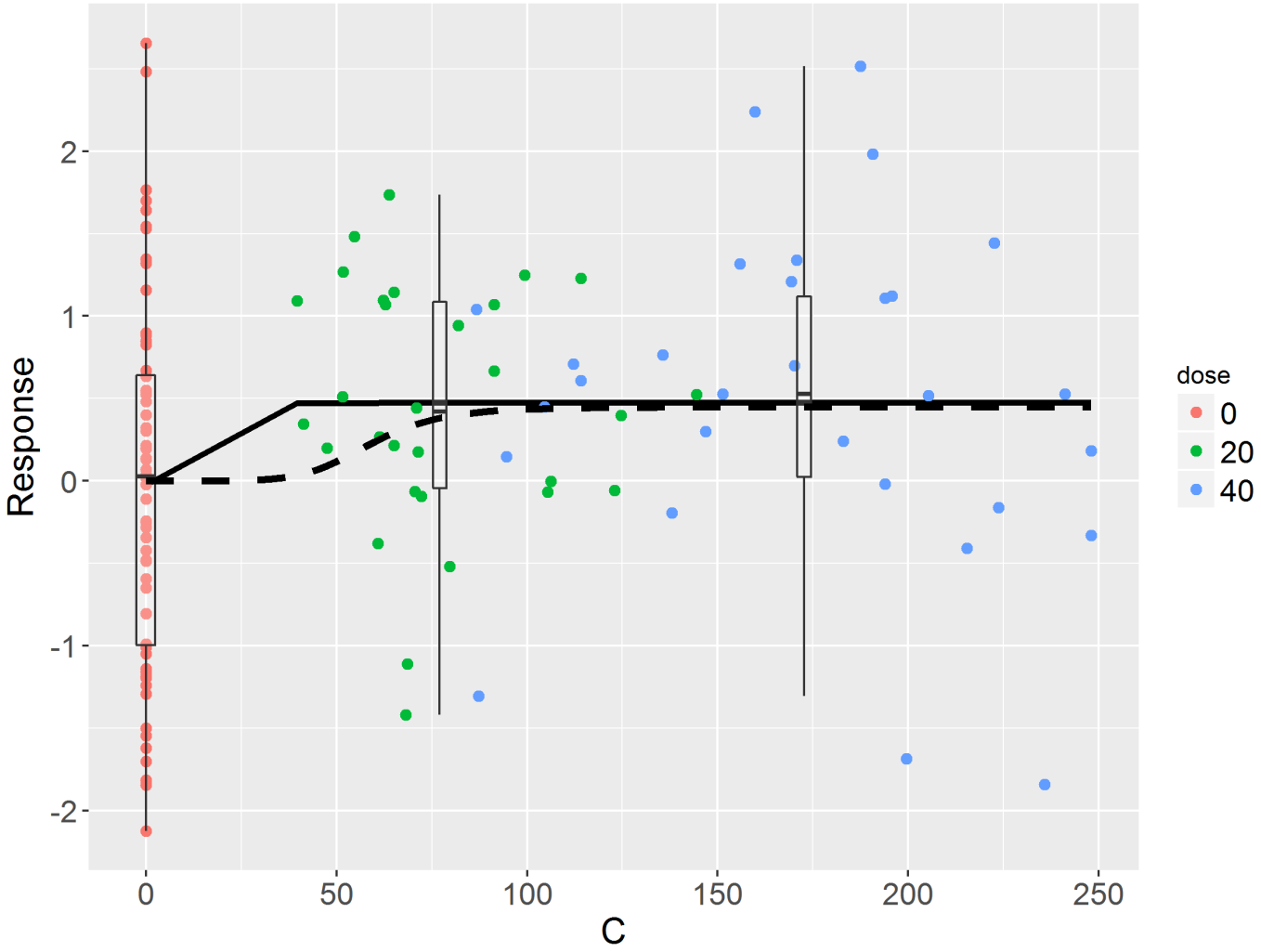
Response Estimation Errors for different σ_{ER} and CV



MCPMod ER fit (low σ_{ER} variability scenario)



MCPMod ER fit (realistic σ_{ER} variability scenario)



Conclusions and further thoughts

- Dose selection for Phase 3 is an estimation problem and should not be addressed via hypothesis testing
- Model-based dose finding methods are more informative and efficient than pairwise comparisons approaches; should be preferred for dose finding studies
- MCP-Mod combines features of traditional hypothesis testing with model-based methods – useful for dealing with potential model uncertainty
- ER extension of MCPMod opens possibilities for PK/PD modeling under model uncertainty, but considerable further research needed to characterize its pros and cons, make it more flexible, and allow its application to more complex models (e.g., indirect response, vaccines, etc.)

References

- Bretz, Pinheiro, Branson (2005) Combining multiple comparisons and modelling techniques in dose-response studies, Biometrics, vol. 61, p. 738-748.
- Bornkamp, Bretz, Pinheiro (2006) Design and analysis of dose finding studies combining multiple comparisons and modeling procedures. Journal of Biopharmaceutical Statistics, 16(5), 639-656.
- Cross et al. (2002) Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980 – 1999. Pharmacoepidemiology and Drug Safety. 11: 439-446
- Koenig et al. (2014) Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod. Presentation at the KOL Lecture Series on "Adaptive Designs"
- Pinheiro, Bornkamp, Glimm, Bretz (2014) Model-based dose finding under model uncertainty using general parametric models. Statistics in Medicine 33(10): 1646-661
- Sacks et al. (2014) Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs 2000 – 2012. JAMA 311: 378-384

BACK-UP

CHMP/EMA (2014) Qualification Opinion

- Qualification Opinion emphasizes importance of proper dose-finding studies before going to Phase 3
  - MCP-Mod will encourage better study designs (with more dose levels and broader dose-range)
  - MCP-Mod is only one (model-based) method among others
- Acceptance of model-based techniques often subject to discussion: EMA/CHMP positive on MCP-Mod
- How MCP-Mod differs from other model-based approaches
  - Modelling plan pre-specified at design stage (less „cherry-picking")
  - Acknowledges model uncertainty

FDA Fit-for-Purpose Determination of MCP-Mod

Fit-For-Purpose Tools and Supporting Information:

Disease Area	Submitter	Tool	Trial Component	Issuance Date and Supporting Information
Alzheimer's disease	The Coalition Against Major Diseases (CAMD)	Disease Model: Placebo/Disease Progression	Demographics, Drop-out	Issued June 12, 2013 • Determination Letter The tool is freely available at: https://bitbucket.org/metrumrg/alzheimers-disease-progression-model-adascog/wiki/Home
Multiple	Janssen Pharmaceuticals and Novartis Pharmaceuticals	Statistical Method: MCP-Mod	Dose-Finding	Issued May 26, 2016 • Determination Letter • Statistical Review • Pharmacometric Review

MCPMod (cont.)

- Combines MCP and modeling for model-based dose selection (and DR estimation) under model uncertainty
- Can test DR signal (MCP step) and estimated DR (Mod step): model selection or model averaging
- Can handle most common types of responses: continuous, binary, count, time-to-event, etc.
- Number of doses/dose range:
  - Minimum: 2 active doses (for the MCP-step), 3 active doses (Mod step)
  - Recommendation: 4-7 active doses, >10-fold dose range
- Software implementations: DoseFinding R package, ADDPLAN DF, PROC MCPMOD (Cytel) and SAS Macro

Comparing DR and ER MCPMod via simulations

- Exposure (C_{avg}) simulated as function of clearance (CL)
- Response simulated as function of exposure
- MCPMod applied to both DR and ER (need to relate target exposure back to dose)
- Simulation study evaluating different scenarios and comparing relative performance of MCP-Mod for DR and ER

Elements Evaluated in Simulations

- Standard deviation of response error term, σ_{ER} :
  - Actual expected study variability corresponds to $\sigma_{ER} = 1$
  - Values less than 1 were examined for sensitivity
- Exposure (PK) variability, CV = { 20, 30, 40 %}
- Type I error rates for MCPMod test: 2.5%, 30%

Response Estimation Errors under ER and DR