EMA EFPIA workshop
Break-out session no. 2

Case Study Title: Dose Finding under Model Uncertainty – A case study based on a multi-regional clinical trial

BOS2: Position statement

M&S analysis results should be the primary analysis to establish the dose(s) for phase II/III

Background & Rationale

- Case study
  - COPD, Phase II, global development
  - Endpoint: trough FEV_1 at week 2 (change from baseline)
  - No prior PK/PD model
  - Goal – Select dose to bring forward into Phase III

- Finding the right dose is not that simple
  - True shape of dose-response model is typically unknown
  - Choice of a working model may have a substantial impact on dose selection
  - Model selection using observed data needs to account for model uncertainty and associated multiplicity issues

Objectives of the M&S work

- Primary objectives
  - Proof of concept (PoC): any evidence of treatment effect
  - Dose selection – which dose to take into phase III
- Incorporating uncertainty
  - Design
    - ✓Dose levels investigated
    - ✓Sample size
  - Analysis
    - ✓Adjusting for multiplicity
    - ✓Incorporating model uncertainty
    - ✓Exploring ethnicity effect (particularly Japanese)

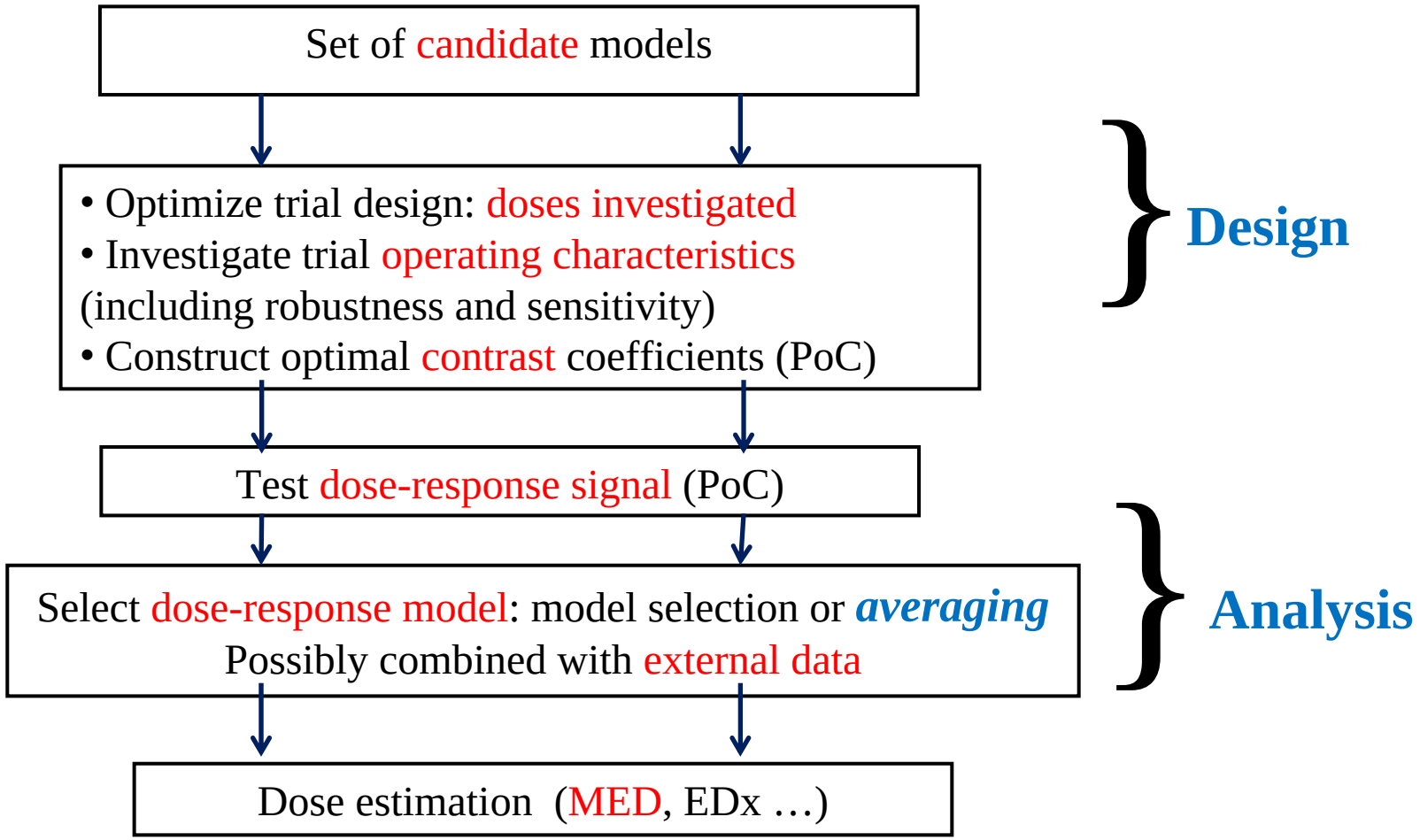
Available Data / Prior Models

After discussion with clinical team

- Placebo + 4 doses + active control
- Max treatment effect: 150 mL (improvement over placebo)
- Absolute clinically relevant differences (= 120 mL)
- Five candidate models

Model	Standardized form	Dose(s) (mg)	% of max effect
Emax_1	$d/(ED_{50}+d)$	1	80
Emax_2	$d/(ED_{50}+d)$	1	95
Quadratic	$d+\delta d^2$	1	95
Logistic	$\{1+\exp[(ED_{50}-d)/\delta]\}^{-1}$	(0.25, 1)	(15, 90)
Linear	d	No guesstimates needed	

Methods – MCP-Mod



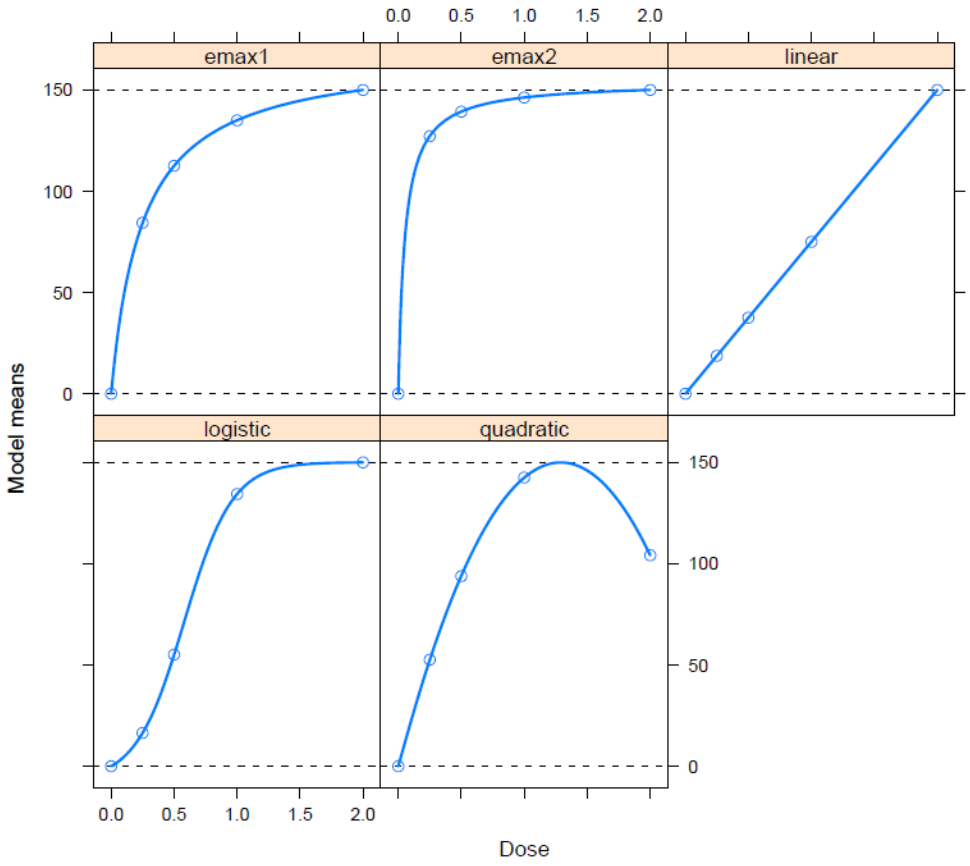
M&S Assumptions

- True underlying DR is equally likely to be any of the five candidate models

- Japanese and non-Japanese share the same dose-response form

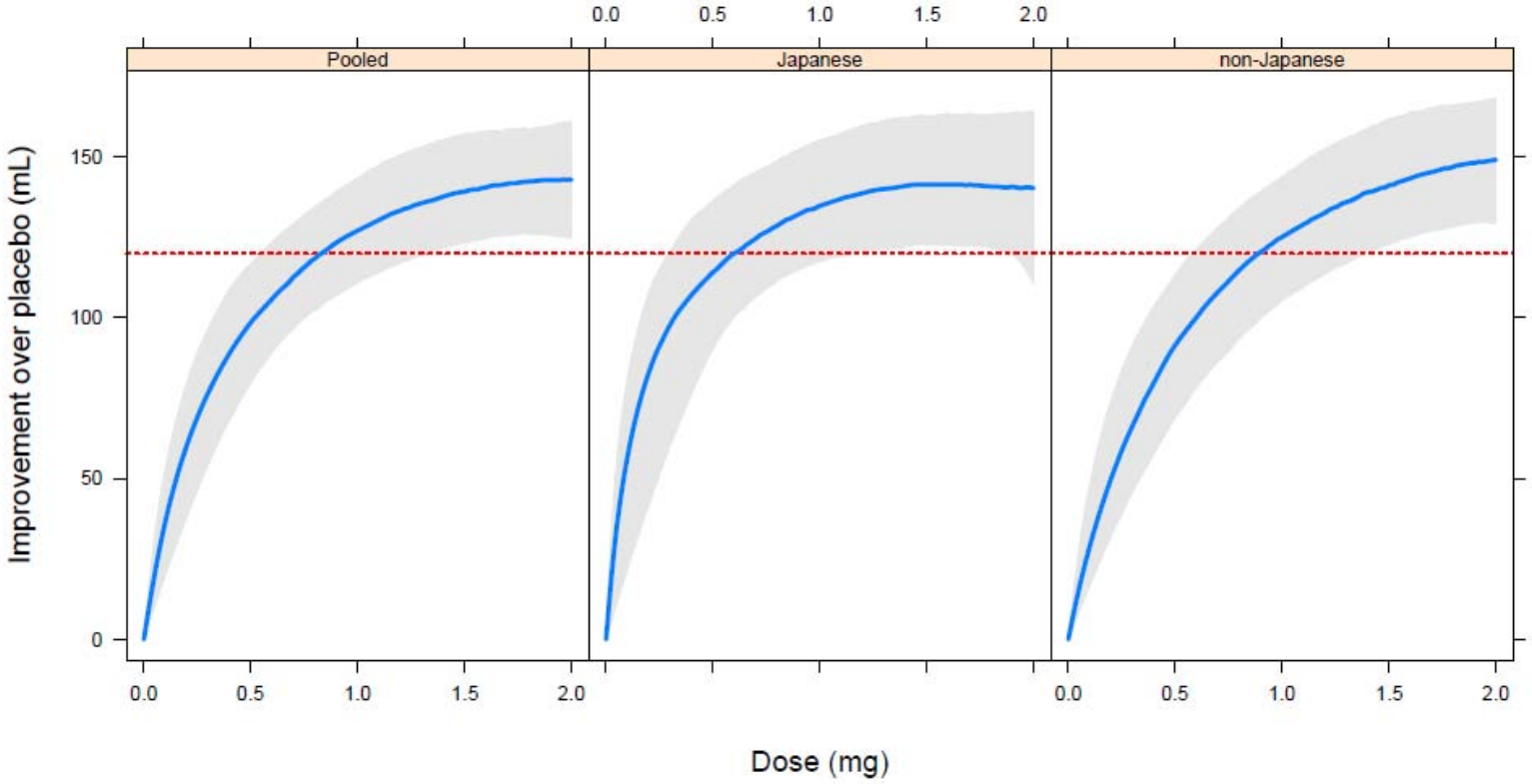
M&S Results – design

- 4 active doses were chosen among 7 available
- operating characteristics were investigated

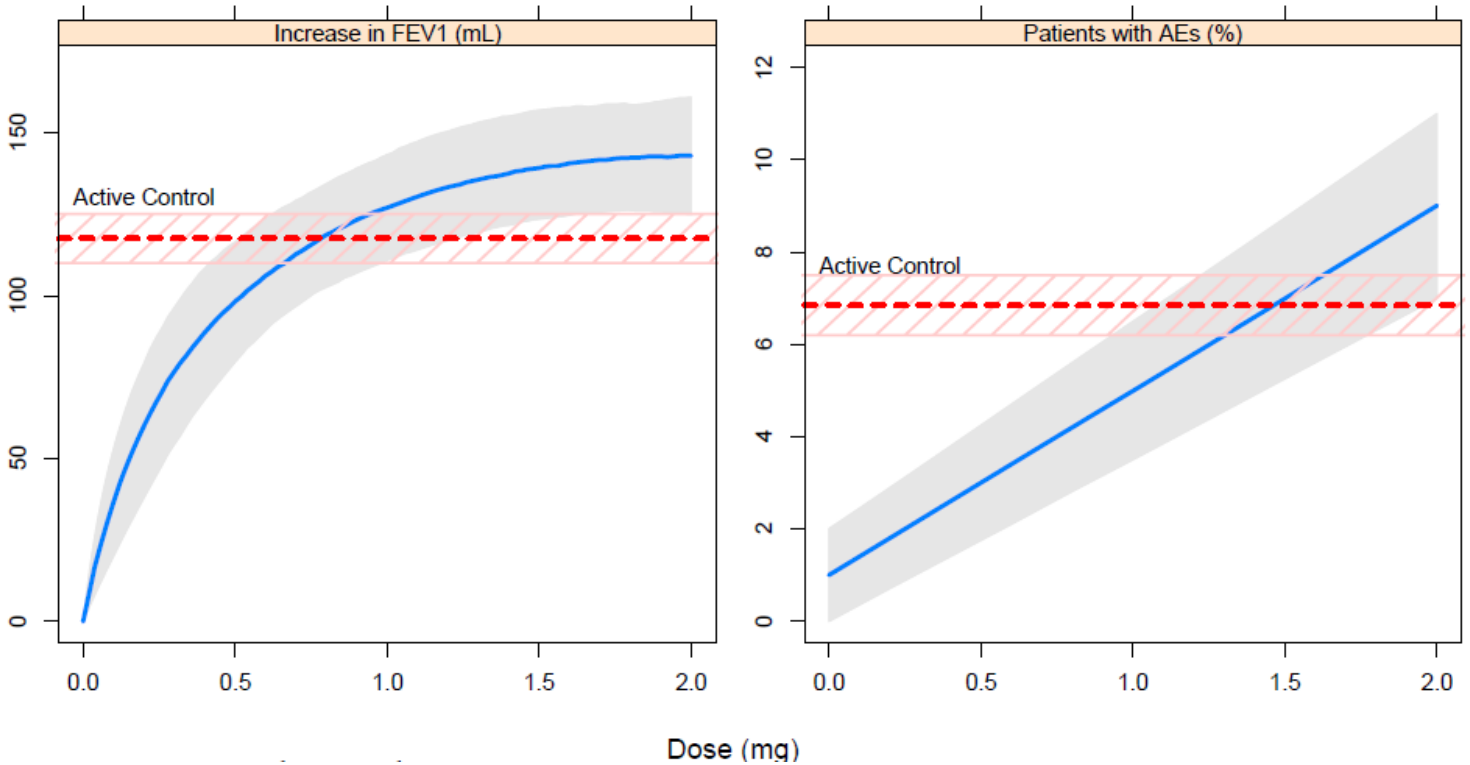


M&S Results – DR profiles

- Weighted dose-response curves – based on the goodness-of-fit of 4 fitted models (linear, quadratic, emax and logistic)



M&S Results – dose selection



Dose selected: 1 mg

Conclusions

- Our approach emphasizes modeling/estimation (learning) as opposed to hypothesis testing (confirming) of the conventional approach
- Uncertainty was incorporated at both trial design and data analysis phases
- Evaluate operational characteristics of alternative designs and methods via simulation study to make recommendations on their use in practice

Generalisation

- To ensure robust and sensible designs and analysis methods, modeling and simulations should be employed routinely
- Uncertainty should be accounted for decision making

Back-up