

Is Confirmatory PK/PD Modeling Possible?

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Outline

- PK/PD modeling – why, how
- Exploratory vs. confirmatory: when to use which?
- Difficulties of confirmatory PK-PD modeling
- A confirmatory approach in phase III population PK
 - Objective
 - Available information
 - Method
- Possible extensions

Model-based Drug Development (MBDD)

- Builds a model to predict probability distribution of trial outcome, given trial design
- Based on knowledge of the drug, patient and disease characteristics
- Integrates literature, pre-clinical and clinical information of NCE and related compounds
- Quantifies uncertainty in trial outcome due to model uncertainty and patient variability
- Provides quantitative rationale for selecting trial strategies

Demand of MBDD is Rising

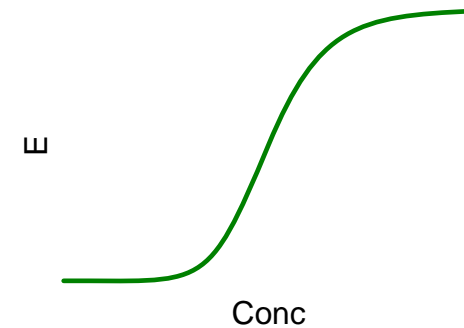
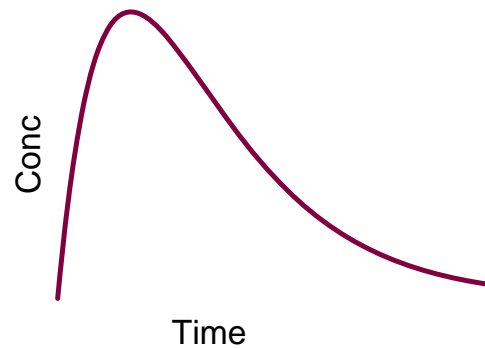
- FDA critical path list for drug development
- As drug development becomes more challenging, more information is demanded from data
- Learn – confirm paradigm:
 - Generate hypotheses at early stage
 - MBDD crucial
 - Confirm at late stage

PK/PD

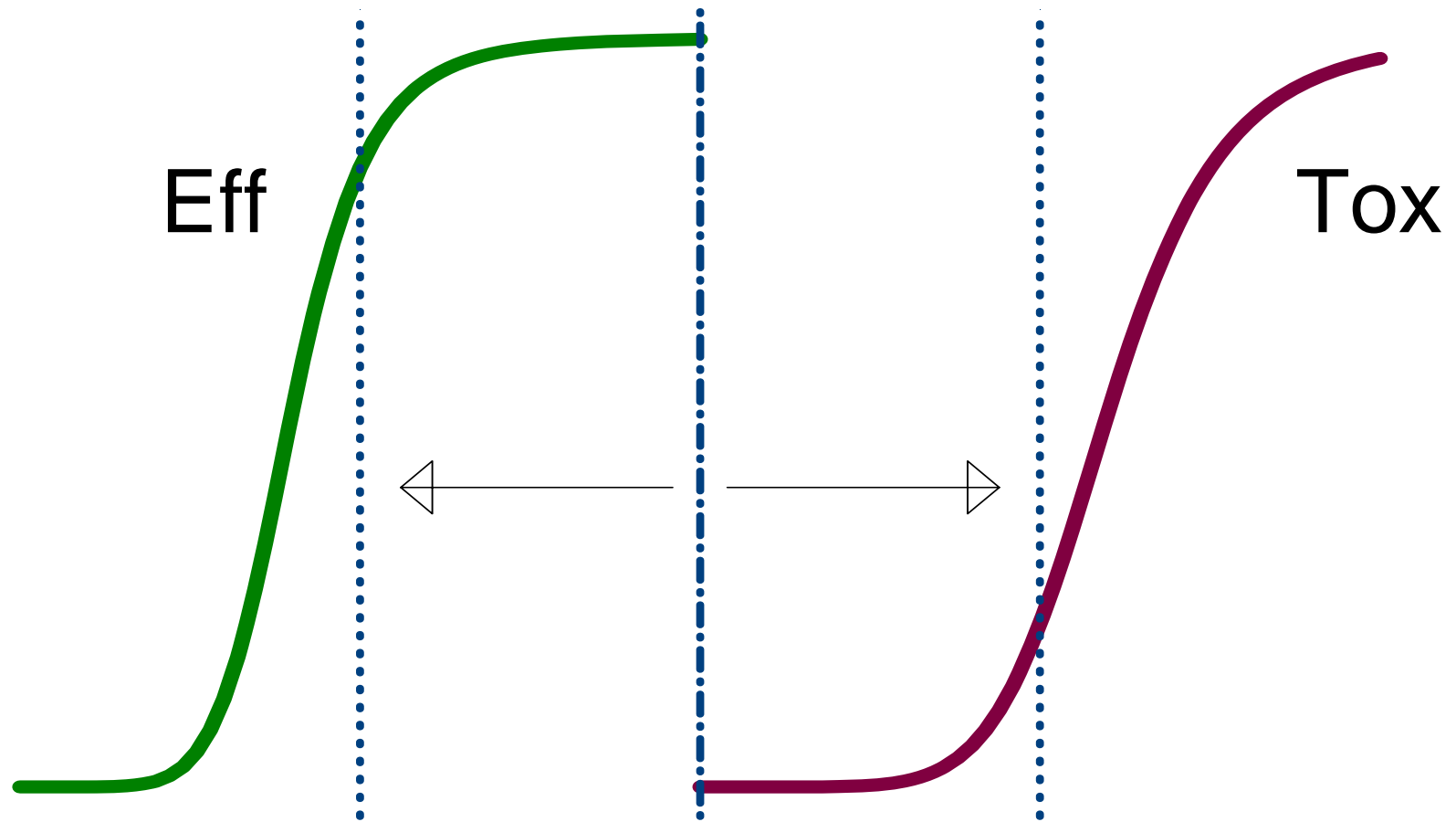
- Usually serves as a critical component of Model-based Drug Development
- Using scientific knowledge of drug
- PK: exposure – time profile
 - Dose - Exposure
- PD: using mechanistic knowledge of drug action
 - Exposure – Response
- PK/PD:
 - Dose (Regimen) – Response (Time Course)

How Drugs Work

- **PK:** What the body does to the drug
- **PD:** What the drug does to the body



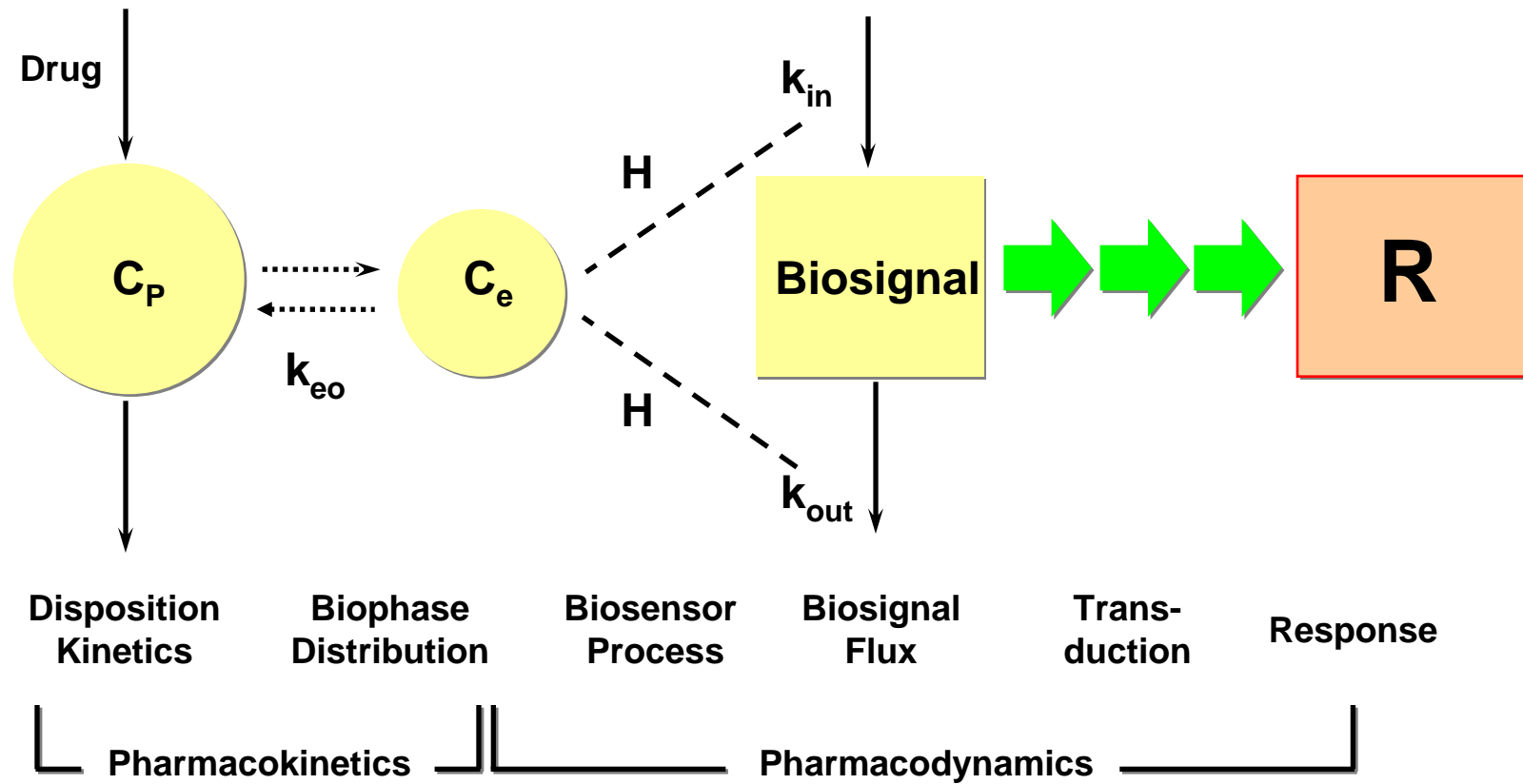
Therapeutic Window and Variability



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Exposure

A mechanistic view of PK and PD



Jusko et. al., JPB 23: 5, 1995

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PK/PD Data and Model Estimation

- Differential equation based structural models
- Typically multiple exposure/response measurements per subject
 - Nonlinear mixed effect models
- Model choices ideally mechanistically based, however information is uncertain
- Dominant analysis approach: extensive exploratory, searching for best fit among
 - Structural model (# of compartments in diff. eqn.)
 - Random effect forms
 - Covariate effects on parameters (fixed effects)

Some Quotes on Exploratory Analysis

- “Torture the data long enough and they will confess to anything.”
 - (Is water boarding torture?)
- “Treasure your result of exploratory data analysis, for you will not see it again.”
- “The journey of a thousand miles begins with a single step but you will not get far with stepwise regression.”
- “Stepwise regression: regression certainly, and many steps but wise?”

Exploratory vs. Confirmatory

Approach	Is model “likely?”	Unbiased parameter estimates? Interpretable p-value?
Exploratory	Yes	No
Confirmatory	No	Yes

In Practice

- PK and PD data contain useful information – how best to analyze in light of existing uncertainties?
- An Illustration in POP PK:
 - C. Hu and H. Zhou, An improved approach for confirmatory phase III population pharmacokinetic analysis, Journal of Clinical Pharmacology, 48: 812-822, 2008.

POP PK at phase III

- Powerful, well recognized
 - FDA, EMEA guidance in place
- Main objective: assessing covariate influence on exposure
 - Labeling and potential covariate-based dosing adjustment decisions
- (Typical exposure measures: AUC and C_{max})
- Phase III study PK: sparse sampling
 - Few samples per subject, large # subjects

What Can Phase III Sampling Estimate?

- Not good:
 - Complex structural model
 - C_{max}
- Good:
 - average exposure (AUC, or CL)
 - Simple structure models, e.g., 1-compartment
 - Average main PK parameter estimates (CL, V)
 - Kowalski & Hutmacher, Stat. Med. 2001
 - Covariate influence on CL

Known Problems that May Affect Exploratory POP PK

- Selection bias
 - Theory: linear regression model selection leads to over-estimated covariate effects (Harrell, Regression Model Strategies, 2000)
 - Potentially over-adjustment on dose
 - Simulations
 - Ribbing & Jonsson, J/PK/PD 2004: POP PK covariate model selection
 - Hu & Dong, Stat. Med. 2007: nonlinear regression (POP PK structural model)

Contrast: Statistical Analysis Plan

- Use only 1 pre-specified model
 - Even though best model is unknown, e.g., whether to adjust for sex, weight, etc.
- Alternative “what if” scenarios addressed by sensitivity analyses
 - Few cases, results treated accordingly (perhaps with lighter weights)

Idea for Confirmatory Phase III POP PK

- Main objective: covariate-based dose adjustment for labeling
 - Covariate effect on CL is main focus
- Usually not enough power to support exploratory schemes anyway (GDF concept: Ye JASA 1999)
- Use full model assessment for CL only, not any other parameters
- How to specify base model (1 or 2 compartment, What random effects)?

Pre-specify Base Model

- Prior POP PK model usually available, built from phase I/II data
 - Usually more extensively sampled, thus more complex than phase III data can support
- Combine this with phase III study design (i.e., dose/sampling scheme)
 - Use simulated study data to select identifiable base model
- Unlikely to influence covariate model estimates; however needed to maintain confirmatory nature

Confirmatory Phase III POP PK Proposal

- Pre-specify analysis of phase III POP PK
- Structural model
 - Use phase I/II model to simulate under phase III design, to find the best identifiable model
 - 1 simulation usually enough
 - Pre-specify
- Covariate model: use full model (with all covariates) on CL
- 2 – 3 additional sensitivity analyses, to guard against alternative scenarios, e.g., influence of inaccuracies in time recording, and assess robustness
 - Exploratory analysis could be a sensitivity analysis

Sensitivity Analysis (a)

- Mechanistic Rationale in literature to suggest
 - $CL \sim \text{weight}^{0.75}$, $V \sim \text{weight}$
- Fix this relationship in base model
- Use full covariate model for rest of the covariates
- Gives a sense of robustness on
 - Covariate effect on V
 - Influence of other covariates

Sensitivity Analysis (b)

- Linear mixed effect (LME) model:

$$\text{Log(conc)}_{ij} = \text{Dose TI Cov1 Cov2 ... CovN} + \eta_i + \varepsilon_{ij}$$

- TI: time indicator (adjusting for time, 0 – 4 categories)
- Assesses covariate effect on average exposure (closely related to CL)
- Use full covariate model
- Examine robustness to
 - Structural model
 - Dosing/sampling time inaccuracies

Analysis Characteristics

- LME model analysis:
 - A step function approximation to structural model
 - Less efficient \Leftrightarrow more robust
 - May be expected to produce a lower bound on covariate effects
 - Easy (!) to implement
 - Results may be down weighted, if losing too much efficiency (wide CI)
- Confirmatory analyses need planning!

Preplanning: Confirmatory Analyses

- Base model assumptions
 - A “feel good” factor? Simple choice may be fine
 - Likely not crucial for covariate effect assessment
- Covariate list may need trimming to ensure enough power
- Trimming criteria are situation specific, but for a nominal proposal:
 - At least 20 subjects per covariate category
 - Remove covariates having correlations > 0.5 – 0.75 , based on pharmacological rationale

Preplanning: Exploratory Analyses

- Should be done, however
 - Easy (incentive) to ignore, as most evaluations focus only on “final” model
- “Validations” used in practice instead, however
 - No practical way to account for model exploration, therefore interpretation dubious
 - Use of mixed effect models vary, “overall” criteria may not be useful for the specific assessment
- Helpful to have a confirmatory mindset – refrain from explore options with no power

Deciding on Covariate-based Dosing Adjustment

- In principle, no different than exploratory approach
- Assess covariate effect using model estimate (and CIs)
- Deciding a threshold beyond which dosing adjustment would be needed
 - Knowledge on therapeutic window needed – however this is usually not explicit
- The BE 80-125% criterion can be considered as a lower bound
 - Used here for illustration purpose only

Application Example – A Phase III study

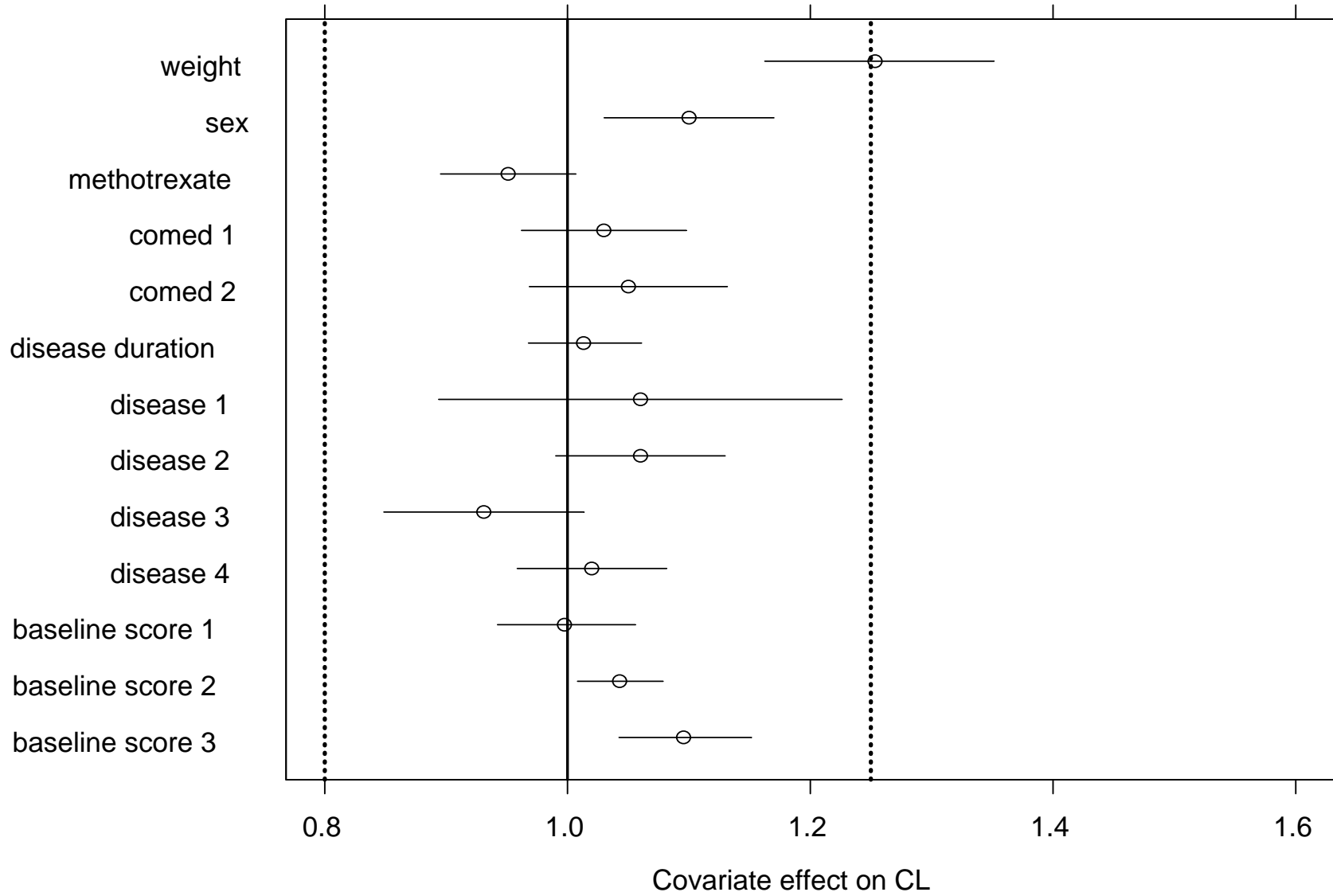
- Subcutaneous dosing
- ~ 600 patients, 3400+ concentration observations
- 16 covariates in the dataset: weight, age, concurrent disease, comed, etc.

- Considerations before analysis begins
 - Established a priori covariate order
 - Covariates with <20 patients dropped from consideration
 - For LME model: 4 time indicator categories
 - Week 4 trough, Week > 4 trough, early non-trough, late non-trough

Base model

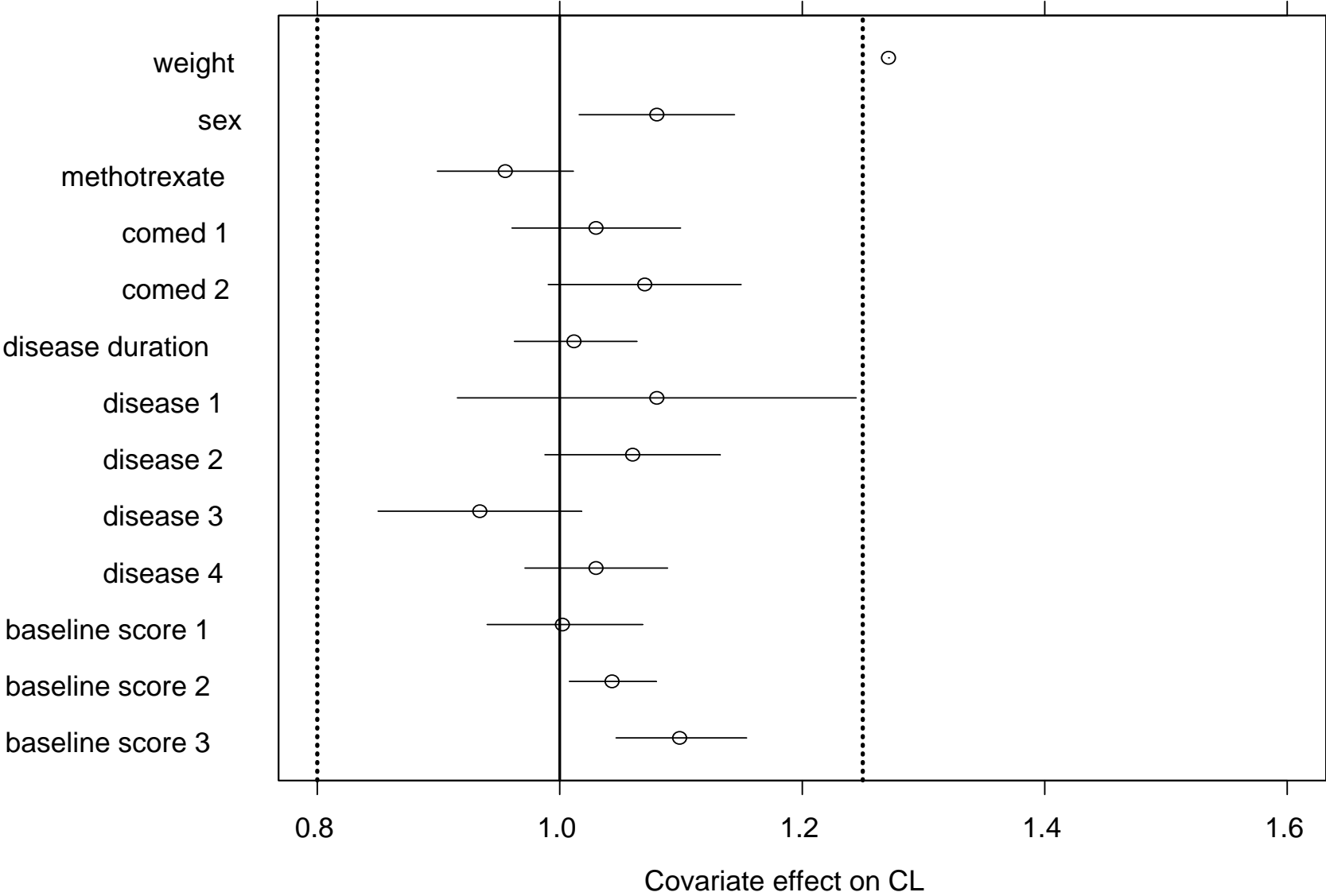
- Previous POPPK model developed from phase I/II data
 - 2-compartment model with 1st order absorption
 - Full var-cov matrix for between-subject variability on all 5 structural model parameters
 - Additive + proportional within-subject variability
- 1 simulated dataset using previous POPPK model with current study design considered for base model
 - Simple exploration shows only 1-compartment model with 1st order absorption could be identified
 - var-cov matrix for between-subject variability on (CL, V)
 - Weight effect on (CL, V)

Primary analysis estimate and 90% CI



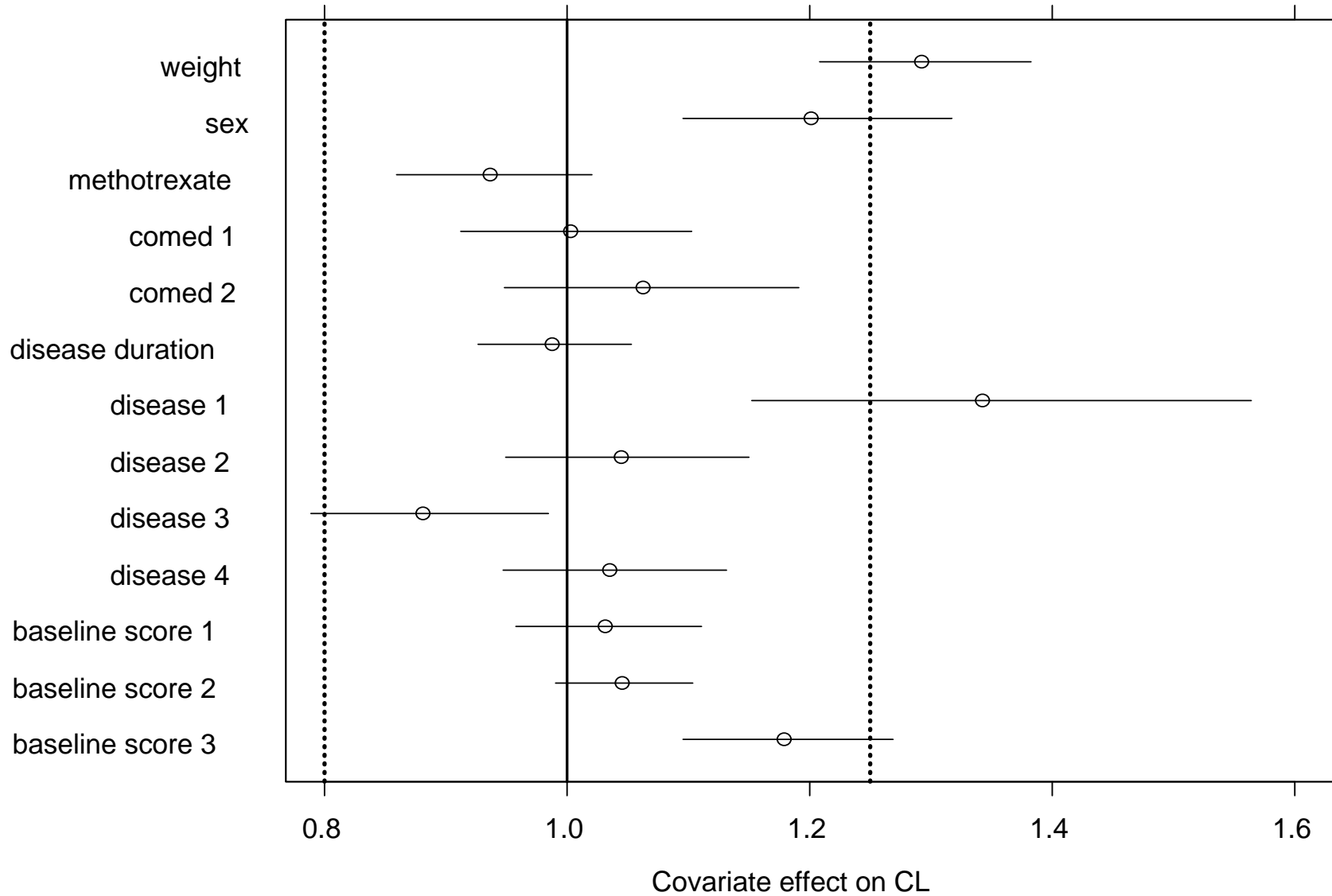
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Allometric model estimate and 90% CI



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Regression model estimate and 90% CI

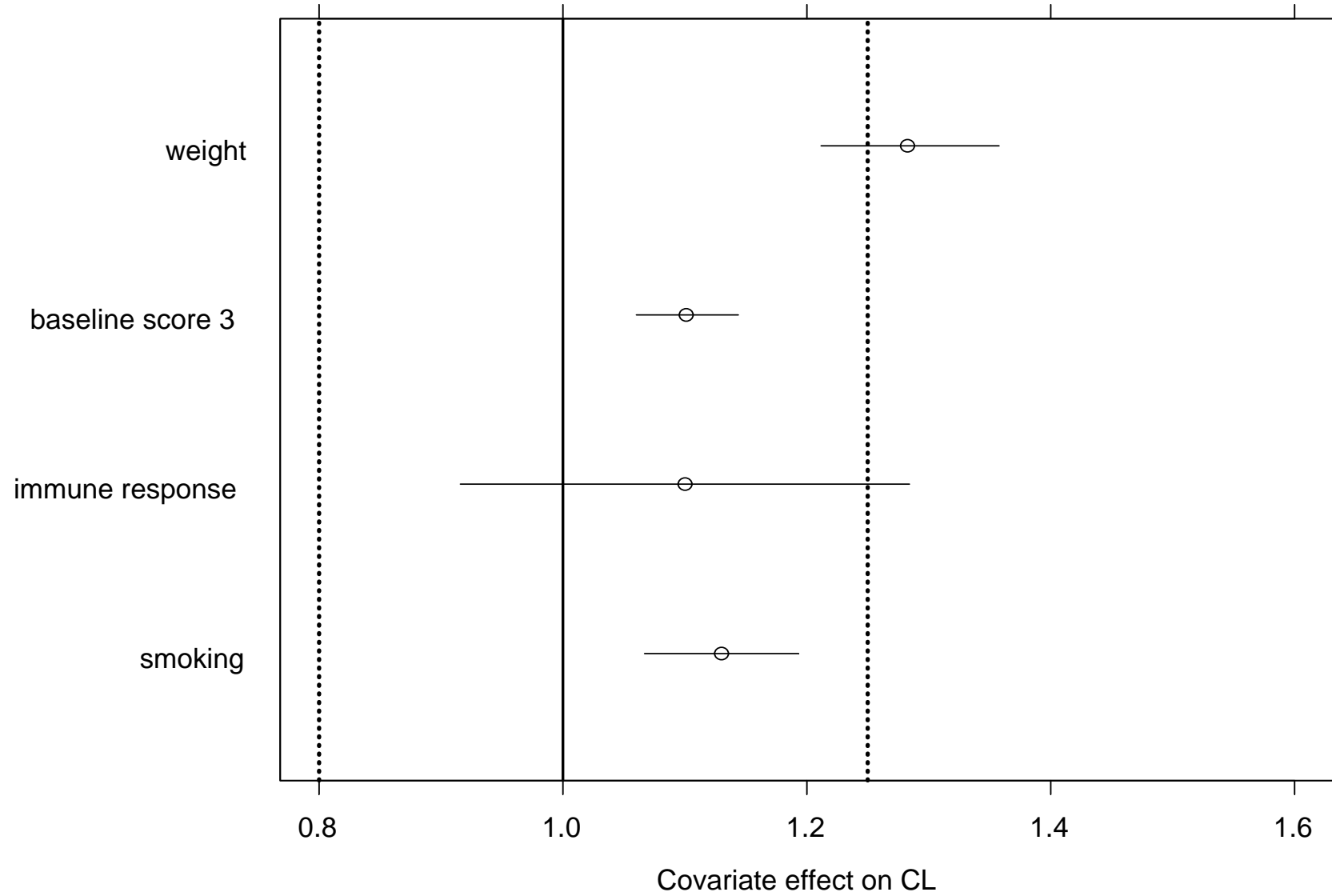


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Confirmatory Analysis Conclusions

- Weight may be considered relevant (25~30% effect on CL)
- Sensitivity analysis also might suggest sex, concurrent disease 1, 3, and baseline disease score 3
 - Borderline average effects, wide CI
- Conclusion:
 - Weight may be the only potentially relevant covariate, with 25% effect on CL

Exploratory model estimate and 90% CI



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Application Example Result Summary

- Main results quite similar between confirmatory and exploratory analyses
 - More generally, likely sufficient power with common phase III analyses
- Each traditional analysis documented explicitly 50+ models
 - Other analyses go into hundreds
 - Many undocumented ones, required much deliberation time over which models to adopt at different stages
- New proposal: <10 models used
- Advantage of confirmatory analysis: much **less work**, theoretically **more accurate result**

How Convincing Is 1 Example?

- Simulation study may be natural to ask, however
 - Existing simulations already showed potential biases of exploratory approach
 - Confirmatory analyses are unbiased, as long as assumptions are met
 - Practical situations vary, many mechanism not easy to postulate
 - e.g., how dosing/sampling error occur
- Example result consistent with expectations and serves as illustrations

Confirmatory POP PK: Current Experience

- Applied to several phase III examples – 6 and ongoing
 - # subjects ranging from 500 to 3,000
 - Consistent results observed - more so with larger sample cases
- Reasonable for phase III
- Should be usable for phase II

Future Extension to PK/PD

- Certain exposure-response models are commonly used, e.g., Indirect Model
- Same approach applicable to phase 3 analysis
 - Need prior PK/PD model from phase 2
- Benefits of confirmatory PK/PD analysis
 - Results more interpretable, unbiased
 - Reduced analysis time

Extension to PK/PD – Current Difficulty

- PD endpoints vary – less standard
- PK/PD modeling less frequently conducted than (POP) PK
- Less experienced analysts
- Nevertheless, could aim to conduct whenever possible

Future

- FDA encourages innovation
- Resistance: “modeling is an art”
- Transform M&S from ad hoc processes to a rigorous, standardized paradigm helps to facilitate MBDD
- A formal paradigm could enable
 - Easier acceptance across different disciplines
 - Better planning
 - Eventually, fully integrating MBDD into drug development
- In 5 years (?)
 - Confirmatory POP PK for phase II-III
 - Confirmatory PK/PD for phase III

Future - Ideal (?)

- Standard (confirmatory) analysis plan for POP PK and PK/PD in all phases
 - Using all information from earlier studies, same class of compounds, etc.
- Exploratory analysis specified as sensitivity analysis
 - More frequent, and carry more weight in earlier phases

Summary Thoughts

- Learn – confirm paradigm
 - Exploratory analysis has its benefits, especially at early stage
- All stages can benefit from confirmatory analyses
 - Even when exploratory, having a confirmatory mindset can help to keep exploration within reason (power of data)

When a new idea comes ...



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