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Confirmatory Phase III Population Pharmacokinetic Analysis

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Outline

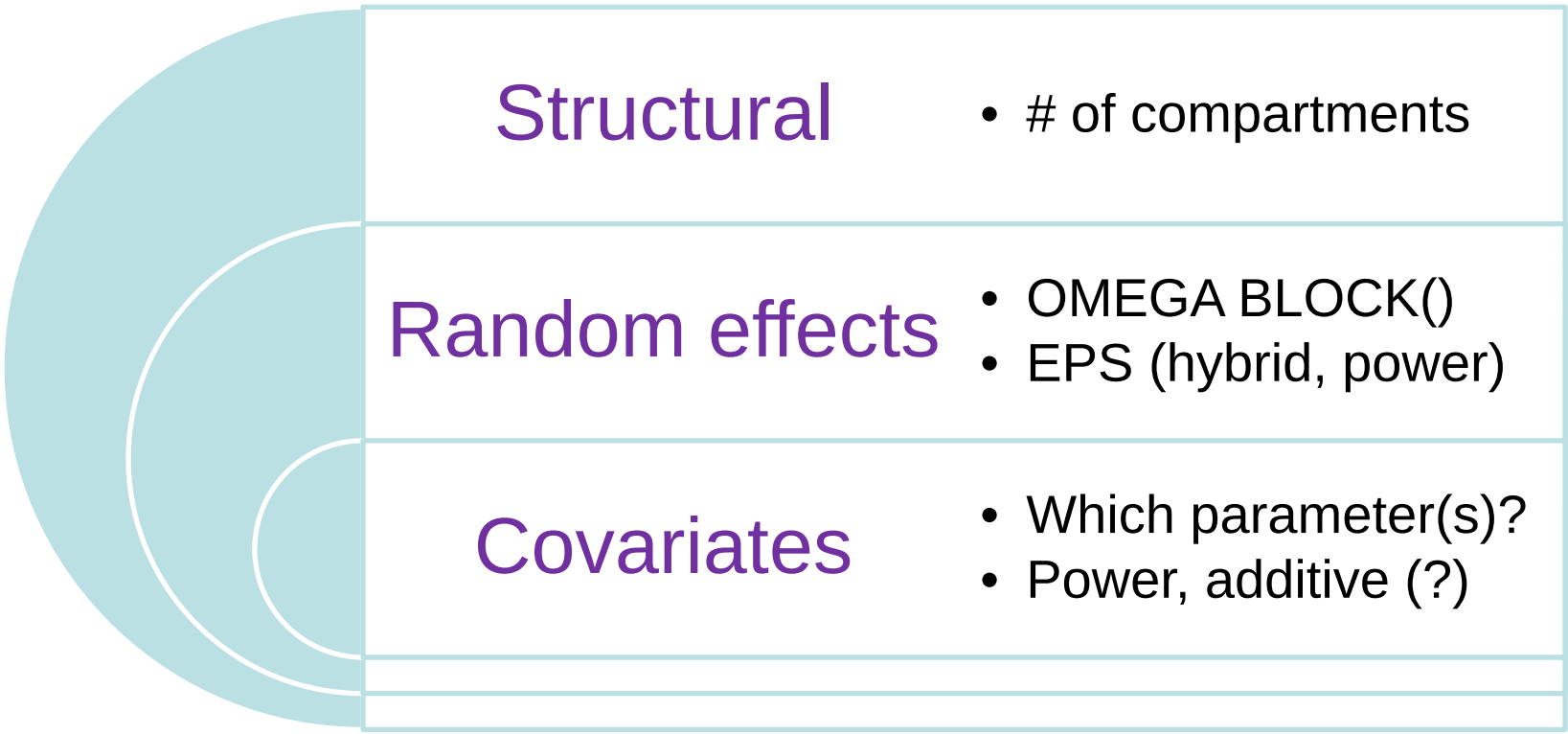
Why use confirmatory POP PK?

- More appropriate than exploratory, at least for a primary objective in Phase III

Implement confirmatory POP PK in phase III

- Methodology: Hu & Zhou, JCP 2008
- (Minor modification, new example)
- Necessary, potentially even in earlier phases

Choosing POP PK Model Components



Exploratory analysis: searching for best fits (FDA, EMEA guidance)

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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?"

Contrast: Standard (Confirmatory) 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)

Exploratory vs. Confirmatory

	Is model "likely?" Generate new hypothesis?	Unbiased parameter estimates? Interpretable p-value?
Exploratory	Yes	No (selection bias)
Confirmatory	No	Yes

POP PK at phase III: What is Important?

Is model likely?
 	
Generate new hypothesis?
	• No
	  • Sparse sampling design cannot support complex model
	  • No future plan to confirm new hypotheses

Unbiased parameter estimates?
Interpretable p-value?
	• Yes
	  • Important for labeling, covariate-based dosing adjustment
	  • Main focus: covariate effect on CL

Confirmatory approach is more suitable!

Confirmatory Approach: Primary analysis

Base model (structural + random effects)

- Use phase I/II model to simulate under phase III design, to find the best identifiable model
  - 1 simulation usually enough

Covariate model

- Use full model (with all covariates) on CL
  - Unless mechanistic knowledge indicate otherwise

Confirmatory Sensitivity analyses

(1) Allometric

- CL ~ weight$^{0.75}$, V ~ weight

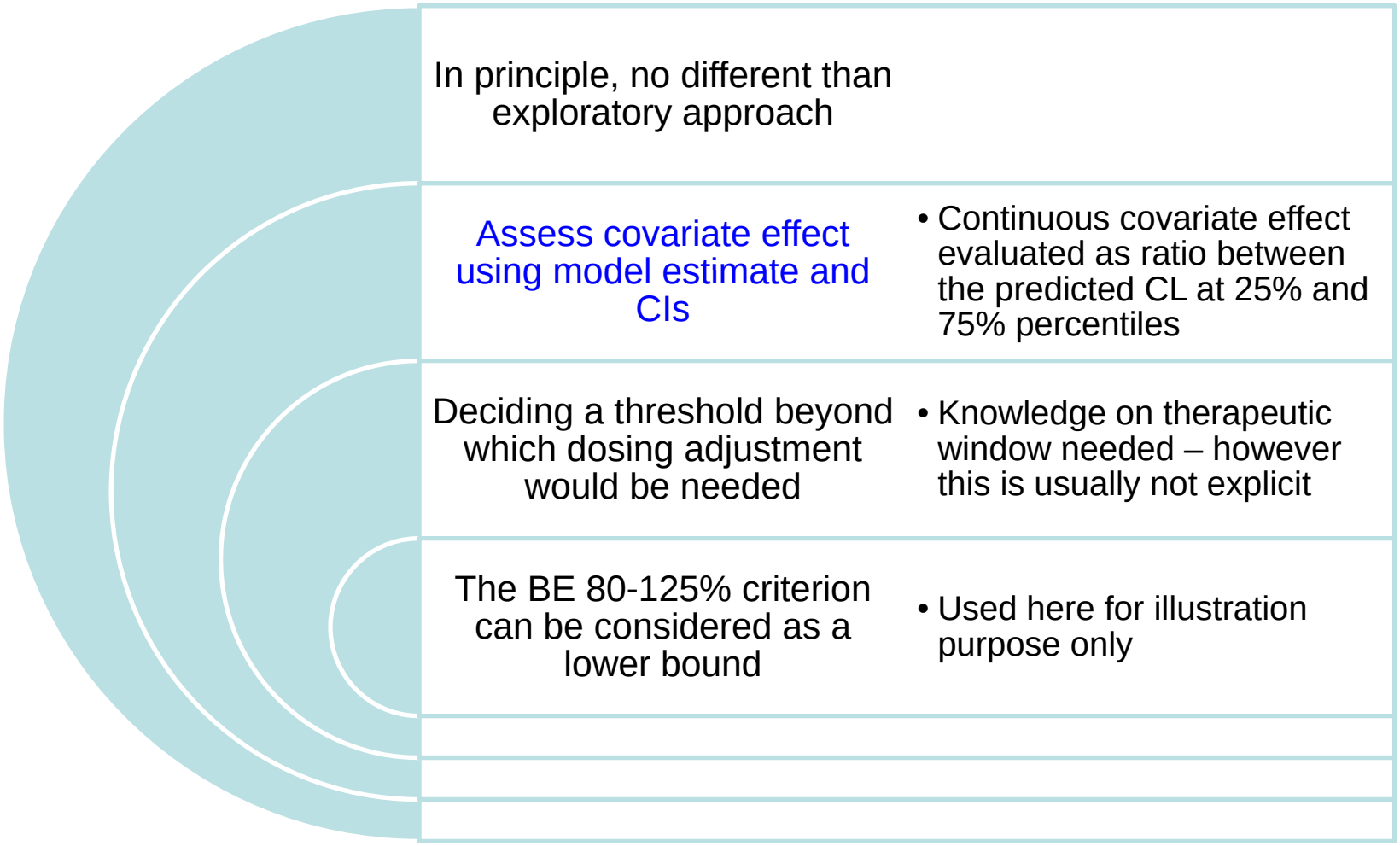
(2) Linear mixed effect model

- Log(conc)$_{ij}$ = Dose TI Cov1 Cov2 … CovN + η_i + ε_{ij}
- TI: time indicator (adjusting for time, 0 – 4 categories)
- Analyzing covariate effects on average observed exposure

Exploratory analysis could be a sensitivity analysis

Guard against alternative scenarios, e.g., influence of inaccuracies in time recording

Deciding on Covariate-based Dosing Adjustment



Preplanning: Confirmatory Approach

Base model: simple may be fine

- Only a “feel good” factor when fitting is good (?)
- 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 Approach

Should be done, however easy (incentive!) to ignore, as most evaluations focus only on “final” model

“Validated” models may not be good enough

- 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 use

Helpful to have a confirmatory mindset – refrain from exploration with no power

Application Example – A Phase III study

Study characteristics

- 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

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Base model (pre-specification)

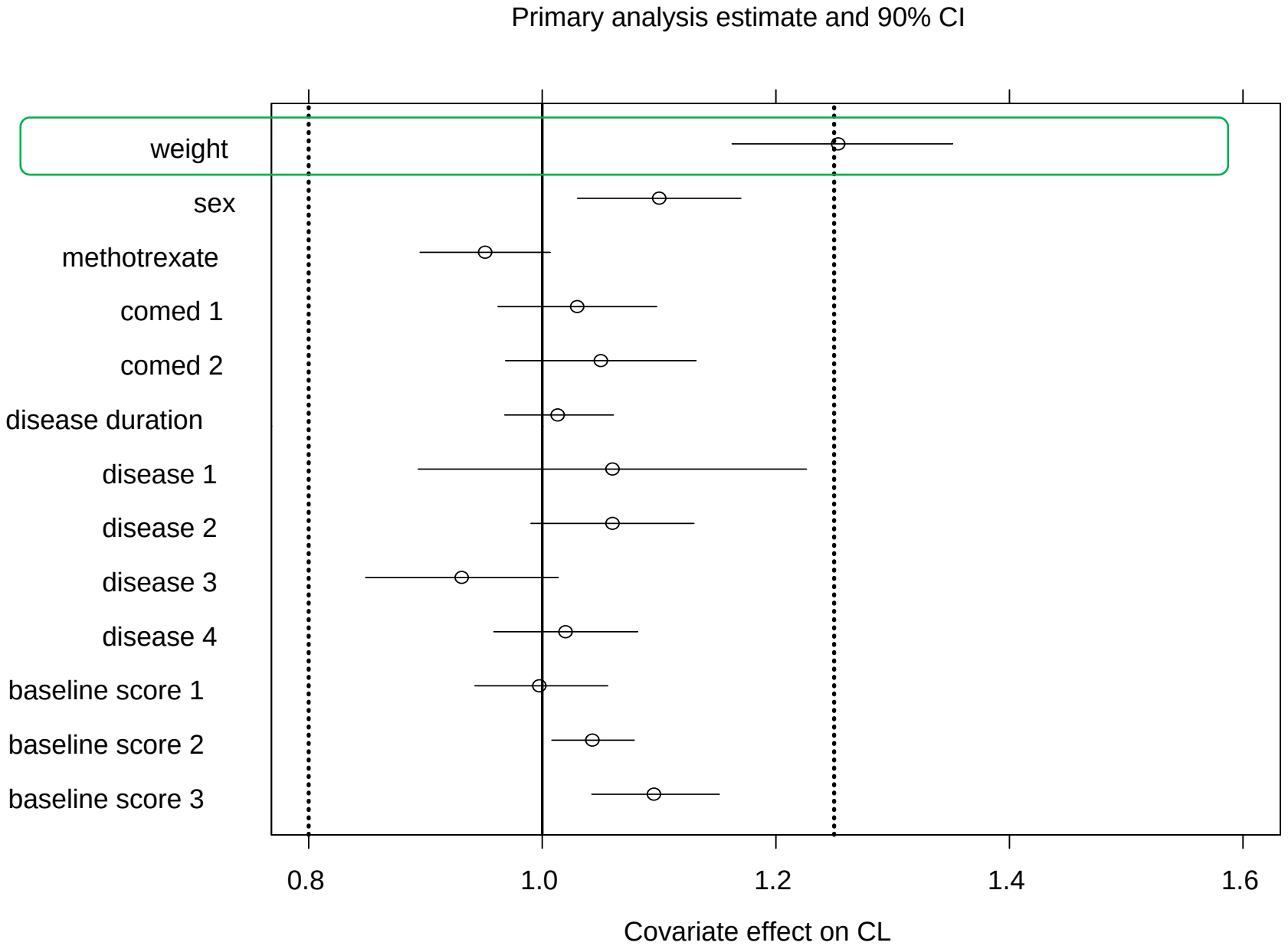
Previous POPPK model developed from phase I/II data

- 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)



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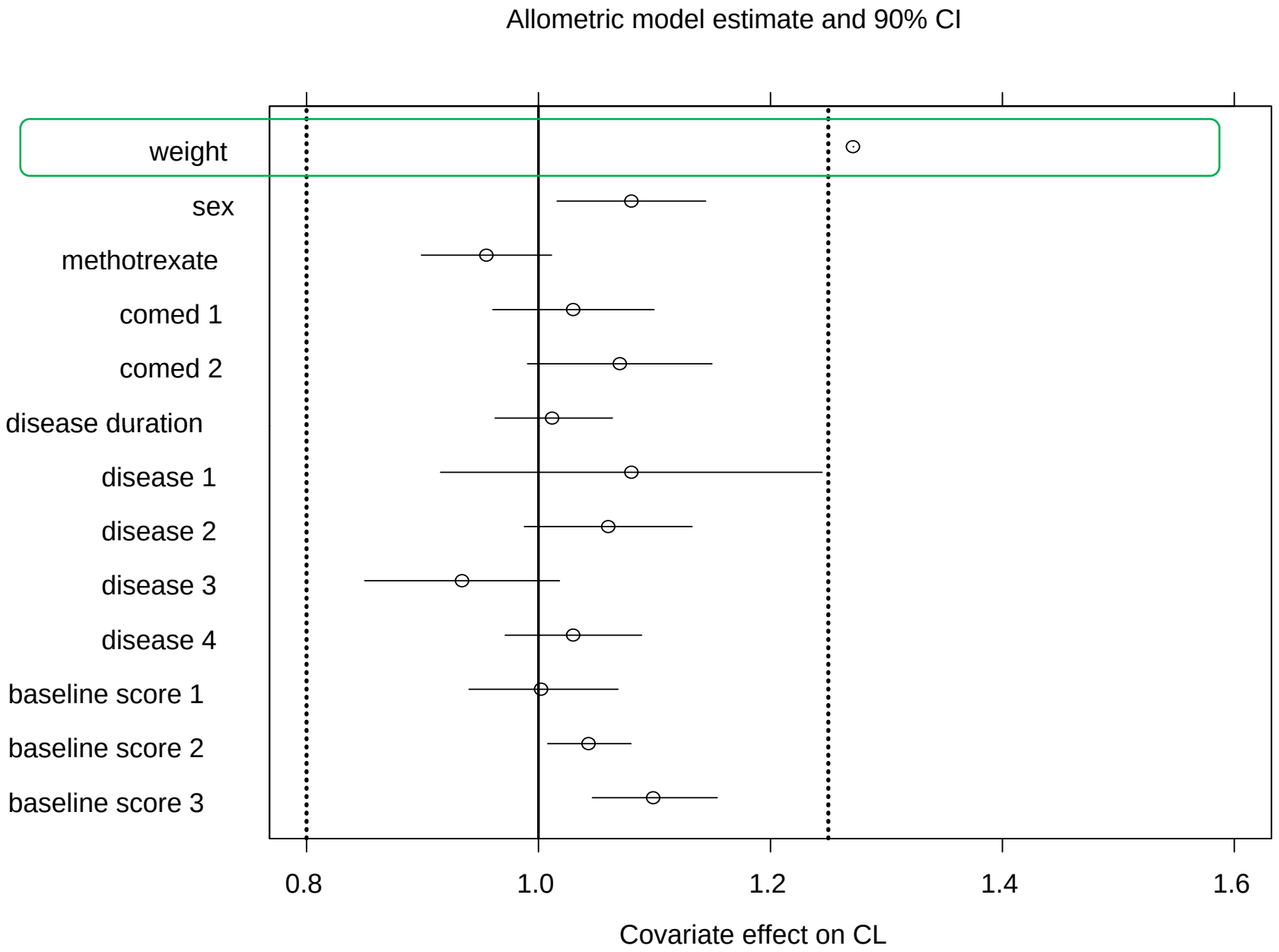

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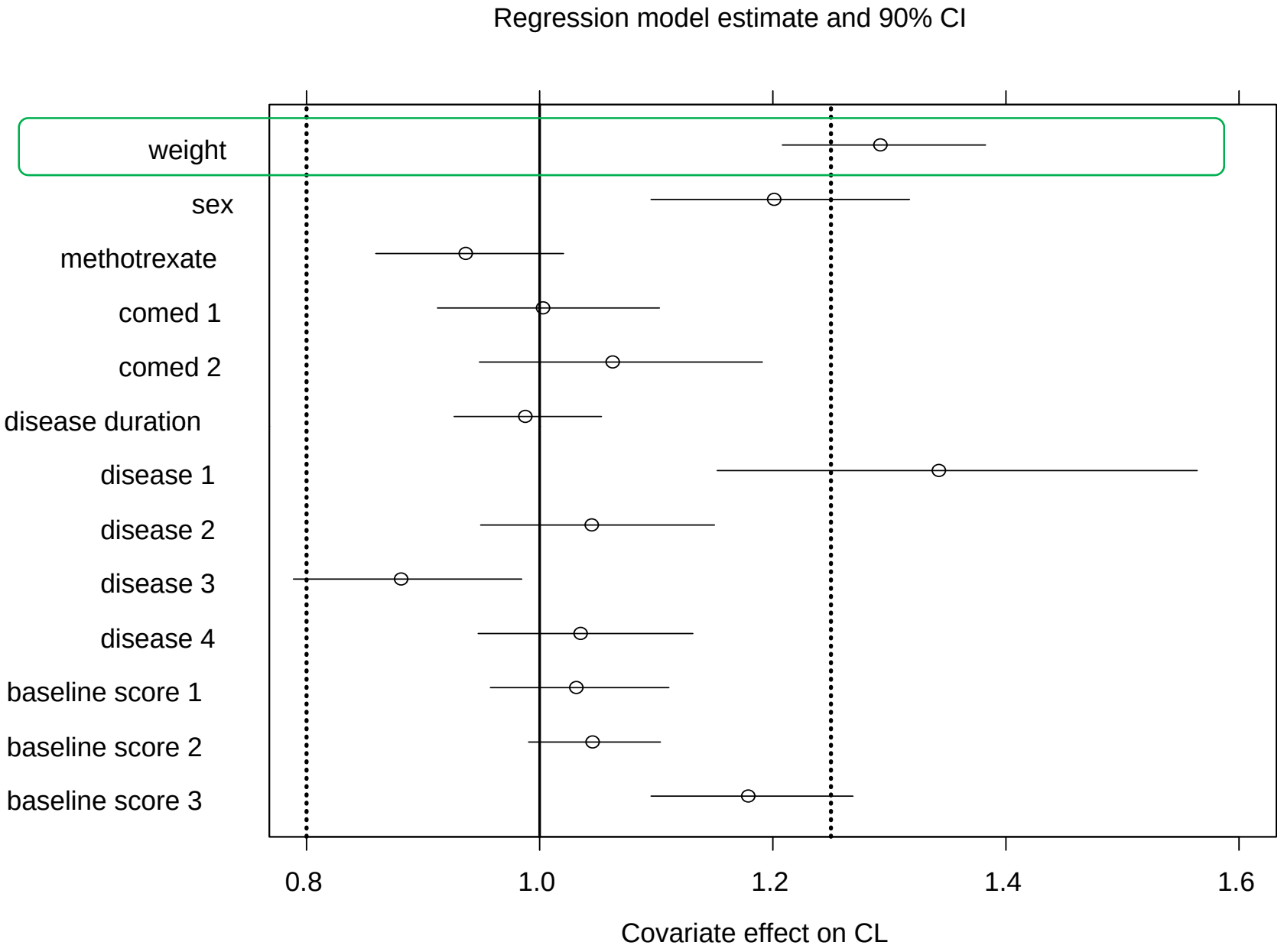

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Confirmatory Analysis Conclusions

Primary analysis

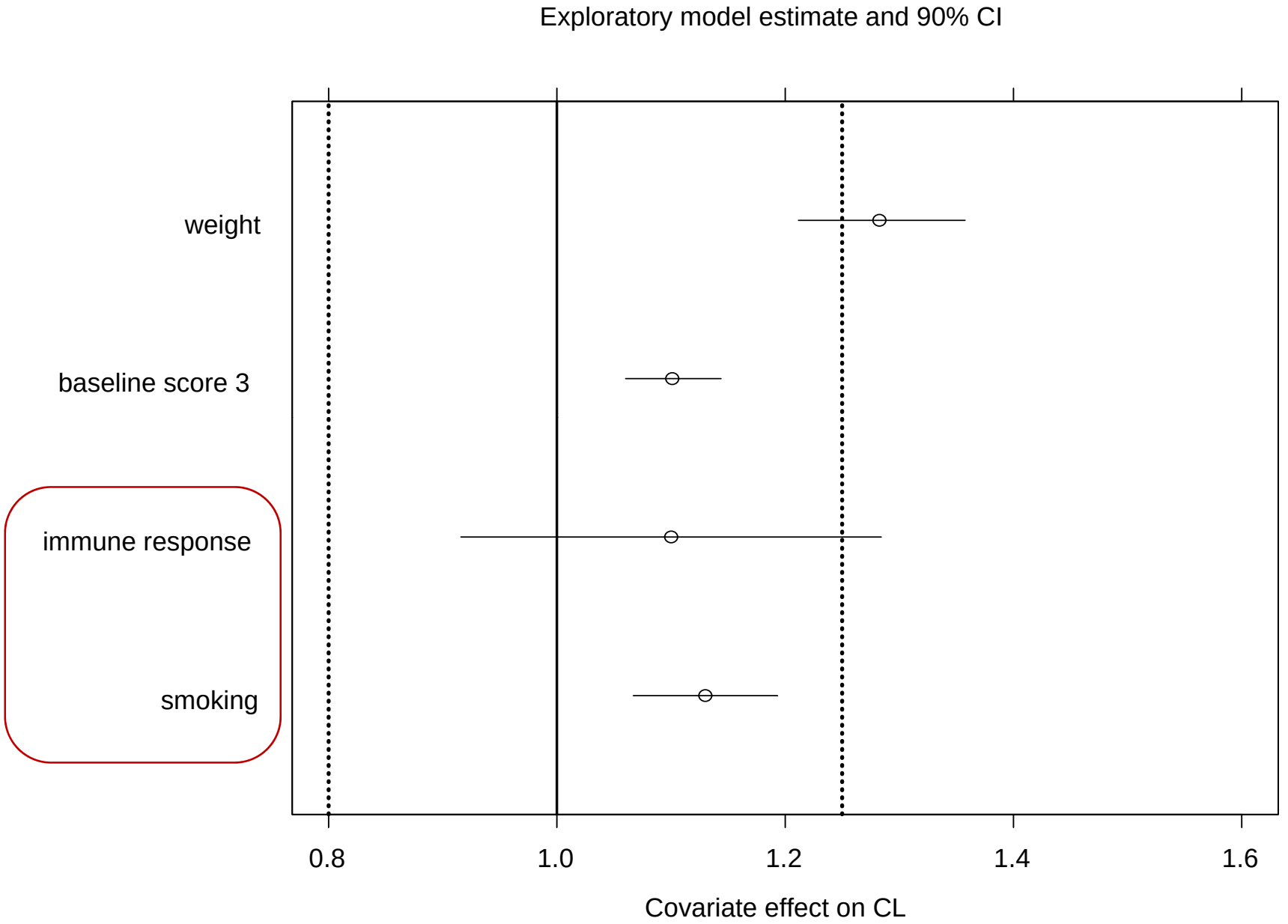
- Weight may be considered relevant (25% effect on CL)

Sensitivity analysis

- Might suggest sex, concurrent disease 1, 3, and baseline disease score 3
- However Borderline average effects, wide CI

Conclusion:

- Weight may be considered relevant (25% effect on CL)



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Application Example Result Summary

Main results quite similar between confirmatory and exploratory analysis

- More generally, likely sufficient power with common phase III analyses

Exploratory had explicitly >50 NONMEM runs documented

- Many undocumented ones, required much deliberation time over which models to adopt at different stages

Confirmatory used <10 NONMEM runs

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 approach 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

Summary on Confirmatory Analysis

Many benefits

- Forces careful analysis planning
- Many fewer model runs
- Conceptually more accurate and interpretable results
- Fits phase III main objective

Should be conducted routinely, at least in phase III

- Keep selection bias in check, even if exploration wanted