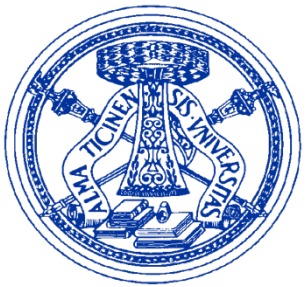
Bayesian population approaches to pharmacometrics and clinical trials



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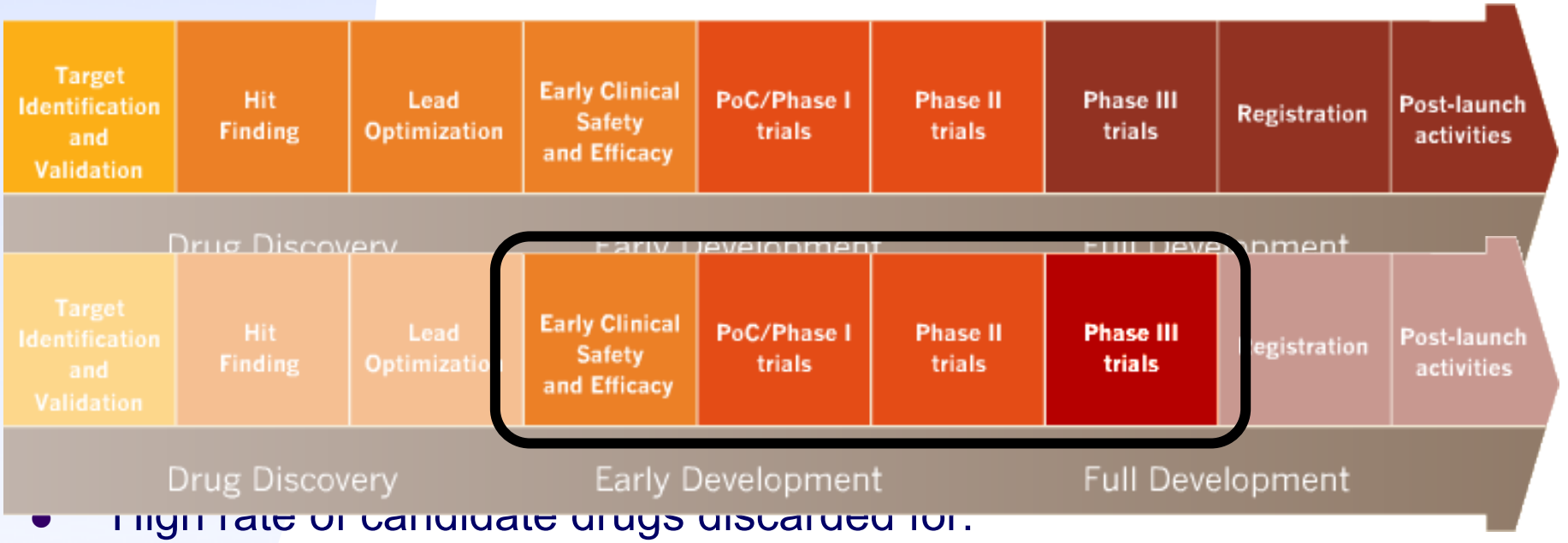
Drug discovery & development

Facts & figures



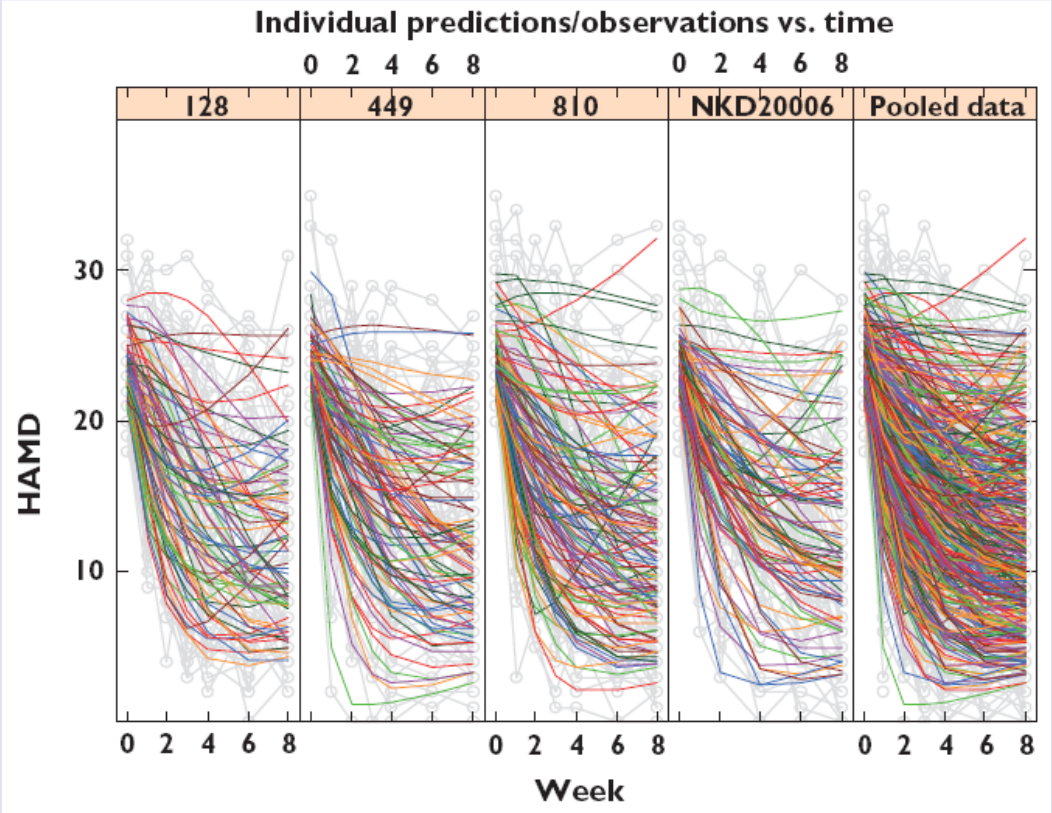
- High rate of candidate drugs discarded for:
  - Lack of efficacy
  - Excessive toxicity
- Application of mathematical models:

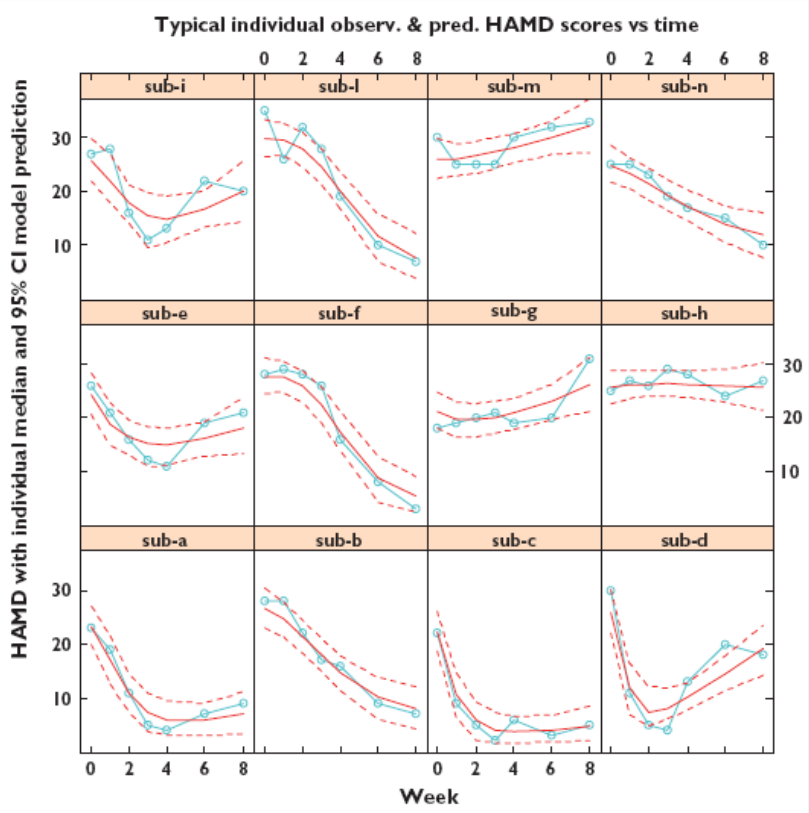
  Model Based Drug Discovery (MBDD)

Source: J. Orloff *et al*. The future of drug development: advancing clinical trial design. *Nature Reviews Drug Discovery* 8, 949–957, 2009

Population modelling

Example: longitudinal depression studies





Problem: estimating the characteristics of a population

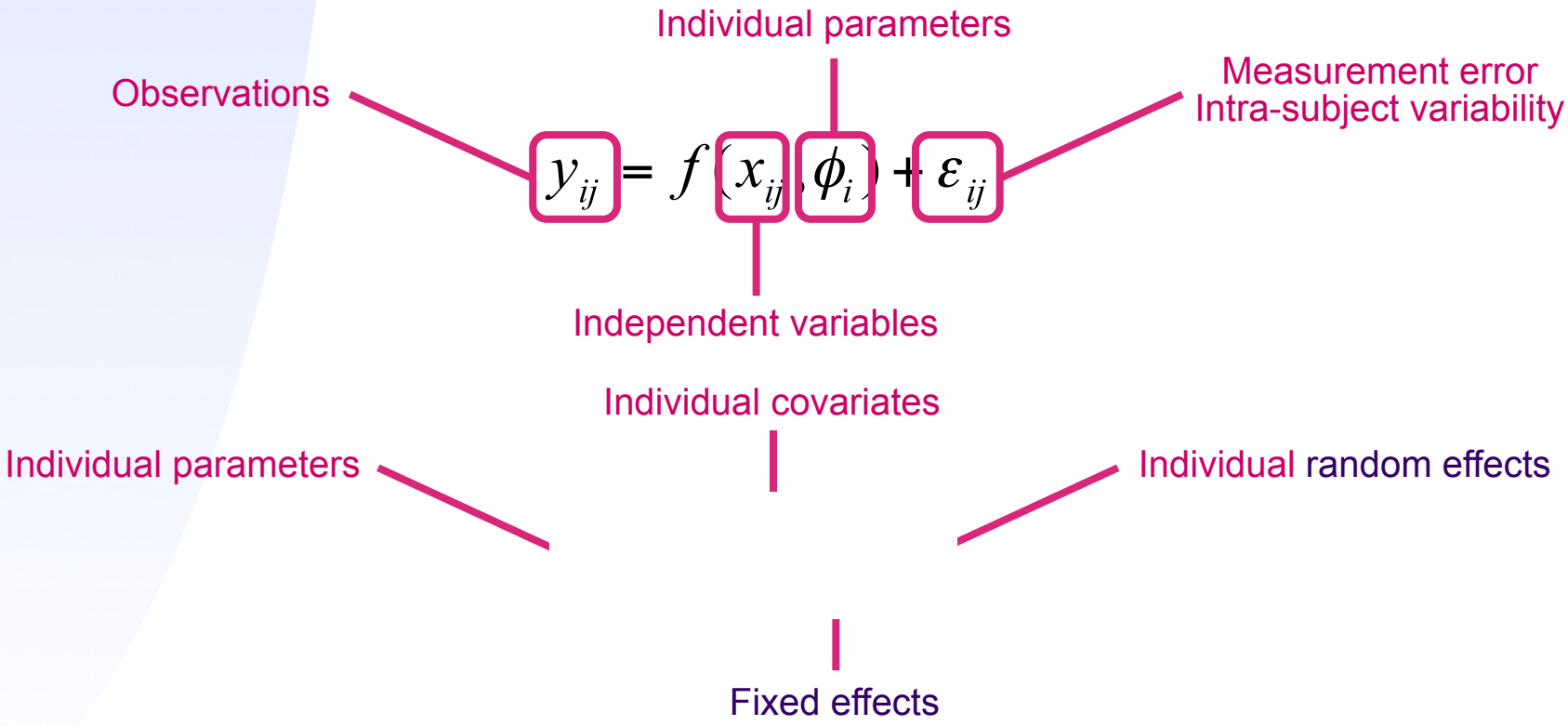
Source: R. Gomeni and E. Merlo-Pich. Bayesian modelling and ROC analysis to predict placebo responders using clinical score measured in the initial weeks of treatment in depression trials. *British Journal of Clinical Pharmacology* 63, 595–613, 2006

Population modelling

Modelling framework

Subject index: i

Measurement index: j



Drug discovery & development

Population modelling

- Characterization of:
  - A particular subject (e.g. a patient enrolled in a clinical study)
  - The “typical” subject
  - The population distribution: typical subject + inter-individual variability
- Full utilization of the (usually scarce) available data
- Robust extrapolation for poorly sampled subjects
- Reduction of the required *sample size* of a study ⇒ costs reduction

...and Bayesian approach

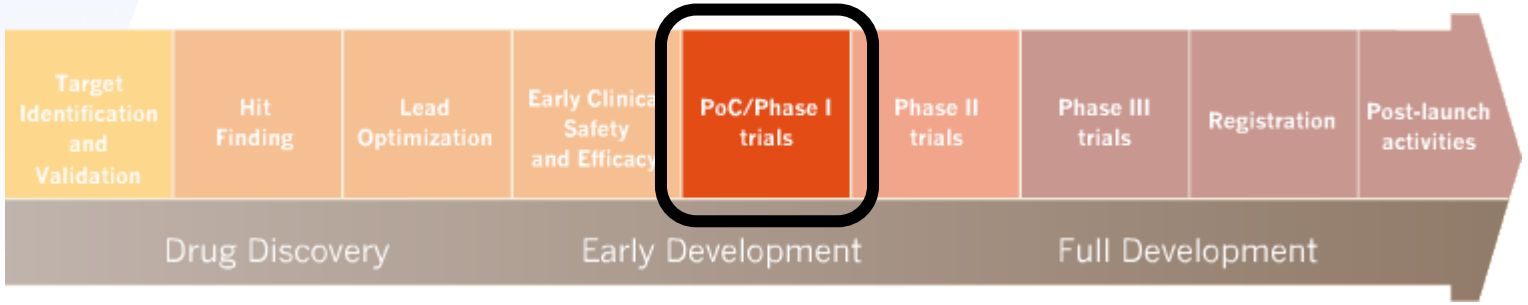
- Full characterization of uncertainty and variability
- Possibility to incorporate prior information
- Availability of Markov Chain MonteCarlo algorithms for fast computation

Phase I clinical trials

Parametric modelling of dose escalation data

In collaboration with

GlaxoSmithKline



Phase I – Parametric dose escalation

Problem statement

Fact

Excessive doses may induce toxicity

Goal

Identify the *Maximum Tolerated Dose*

for subjects enrolled in the trial and for the population

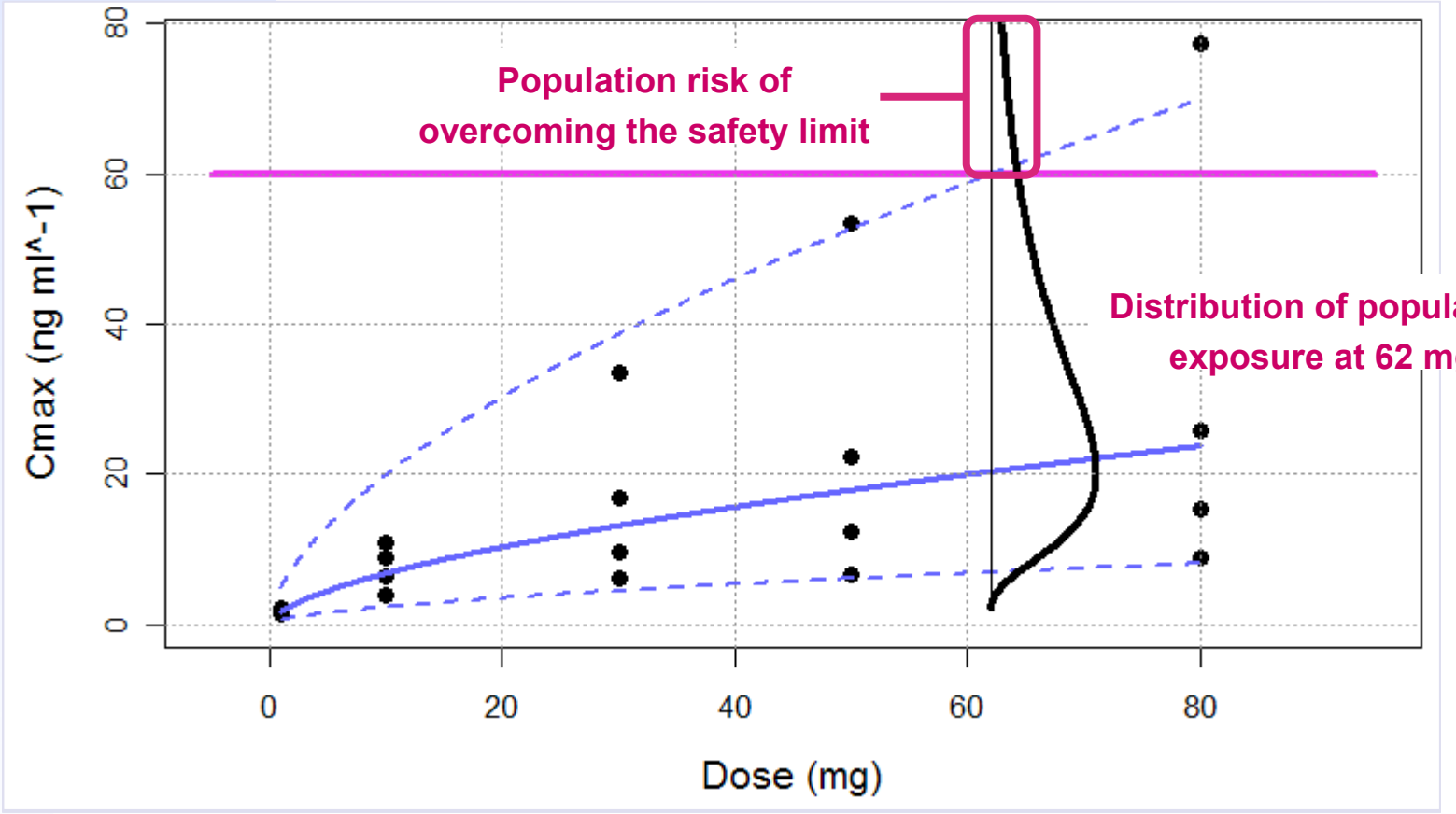
Standard approach

Measure the subjects' exposure (C_{max}, AUC) to increasing dose levels.

Stop escalating when a predefined *stopping limit* is reached

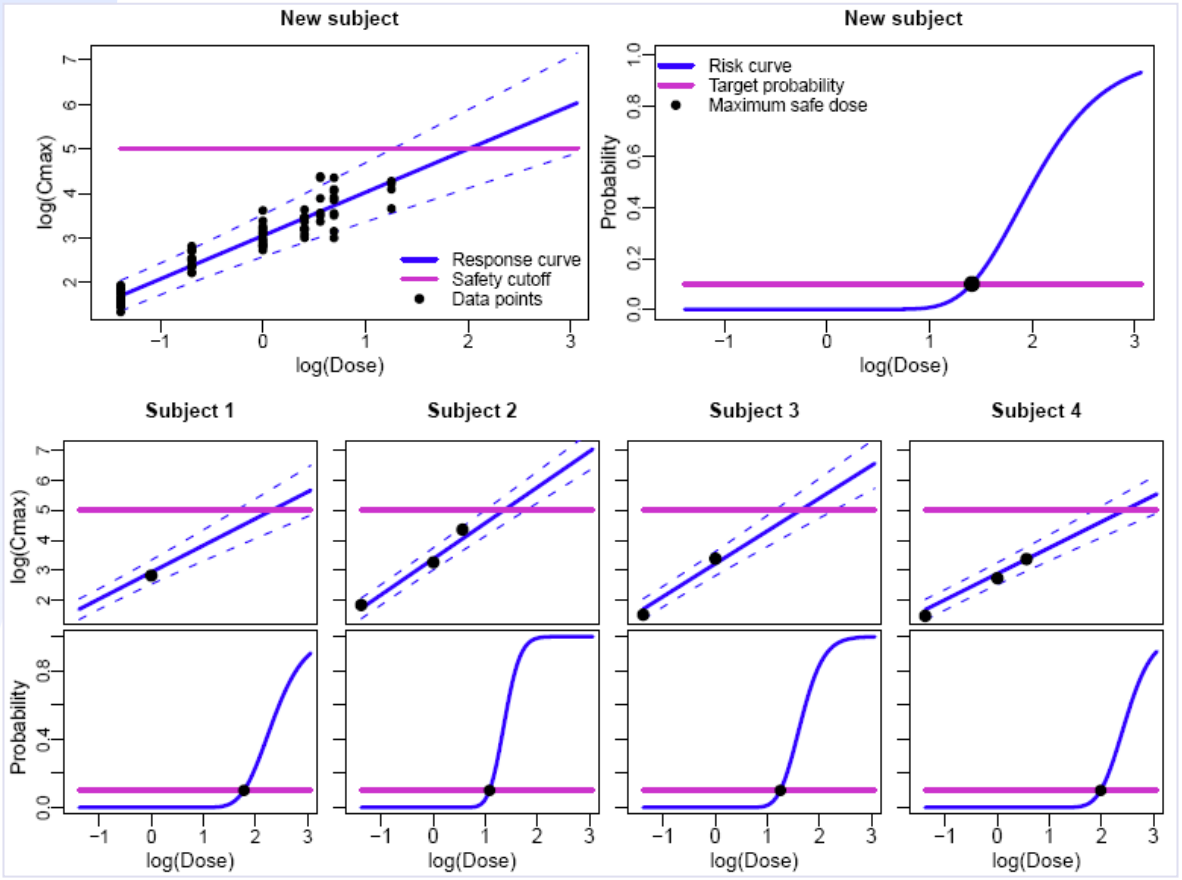
Phase I – Parametric dose escalation

Example scenario



Phase I – Parametric dose escalation

Example: dose escalation study of an antidepressant drug



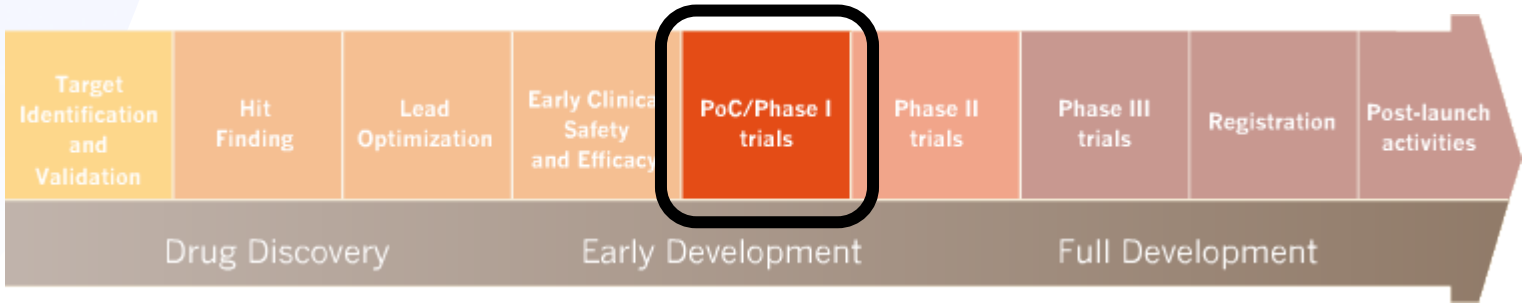
A. Russu *et al*. Bayesian population approaches to the analysis of dose escalation studies. Submitted to *Computer Methods and Programs in Biomedicine*

Phase I clinical trials

Nonparametric modelling of dose escalation data: Population Smoothing Splines

In collaboration with

GlaxoSmithKline



Phase I – Population Smoothing Splines

Fact

Parametric models (power, E_{max}, ...) are widely used in pharmacometrics: simple, but not flexible enough

Few available data $\Rightarrow$ high chance of *model misspecification*

Idea from Machine Learning: Gaussian Processes

Model-free and *smooth* alternative to parametric approaches

Can be adapted to population analyses: *Population Smoothing Splines*