

Industry Experience in Establishing a Population Pharmacokinetic Analysis Guidance

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Introduction

Population pharmacokinetic (POPPK) analyses are an integral part of model-based drug development [1] and have become a standard component of regulatory submission in support of drug labelling [2,3].

Model development is an iterative process through “learning” and “confirming” phases of clinical drug development involving years of time [4]. Assumptions and choices made by analysts during model building can appear subjective and are often influenced by the analyst’s experience, expertise, and tools used.

Within a large pharmaceutical organization, the development and implementation of standard procedures for conducting and reporting POPPK analyses would facilitate consistently high quality output. The importance of improved efficiency through streamlined and standardized approaches should not be underestimated.

A recent joint workshop between EMA and EFPIA [5] called for standardisation of approaches and workflow, and sharing of good practice documents in modelling and simulation.

An industry experience is shared which strives for improved consistency, efficiency and a more systematic approach to model building through the development of a guidance for POPPK analyses.

Objective: To present the process by which the guidance was developed and some examples from the guidance document.

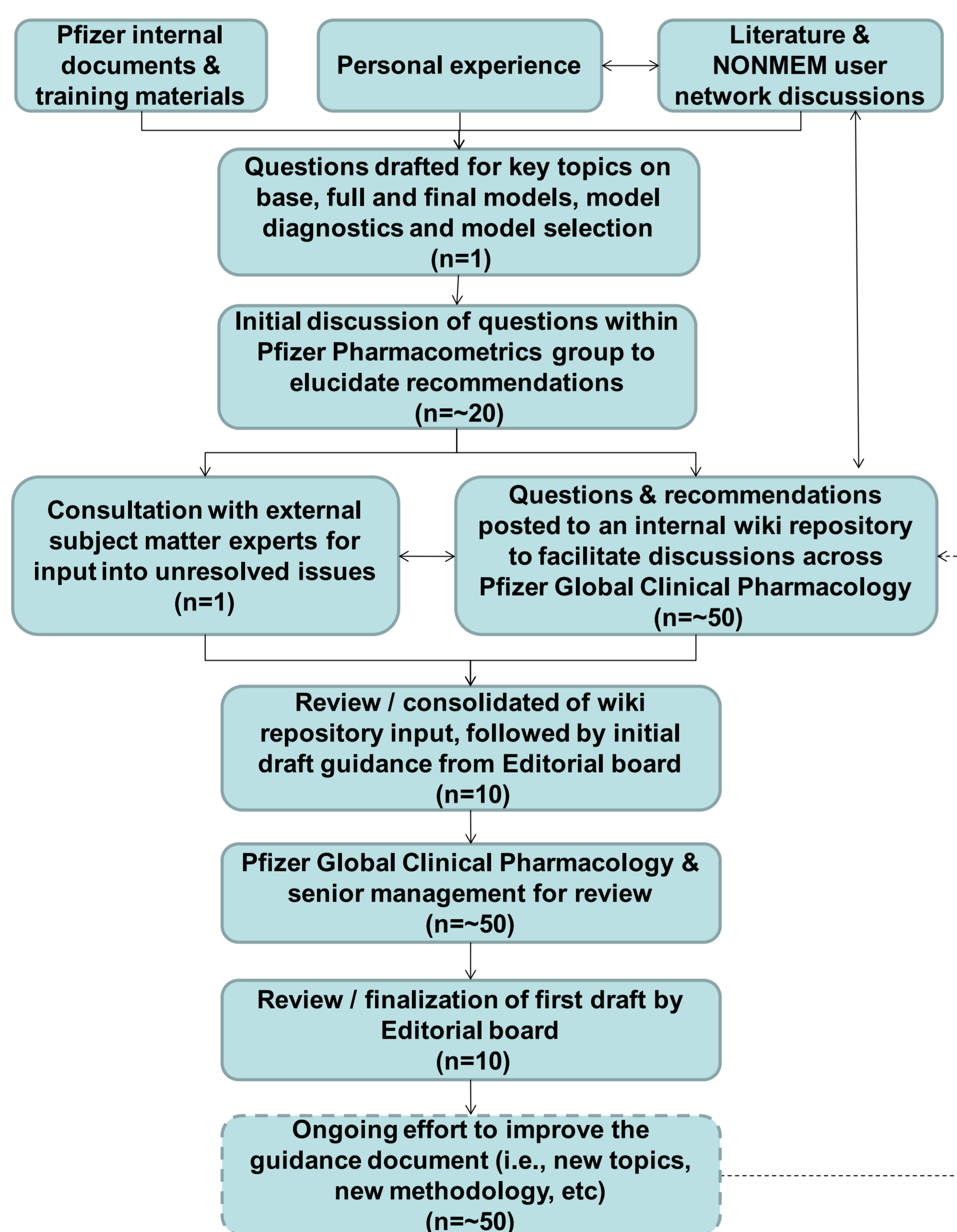
Methods

Questions for key topics on base, full and final models, model selection and diagnostics were drafted and preliminarily discussed within the Pfizer Pharmacometrics group to elucidate recommendations.

An internal wiki repository was then created to function as a hub for collating viewpoints across the Pfizer Global Clinical Pharmacology (PGCP) organization.

An editorial board was formed to consolidate recommendations, capture pertinent examples, draft and revise the guidance. The draft guidance was circulated to PGCP and senior management for review and endorsement.

Figure 1 Process Workflow for Development of the POPPK Guidance.



* n represents the number of individuals involved in each step.

Conclusions

A POPPK guidance was developed to implement a systematic, streamlined, and standardized approach to optimize and harmonize the processes which contribute to the POPPK analysis.

As population modeling is an area of continually evolving science and technology, the guidance needs to be updated and revised periodically.

References

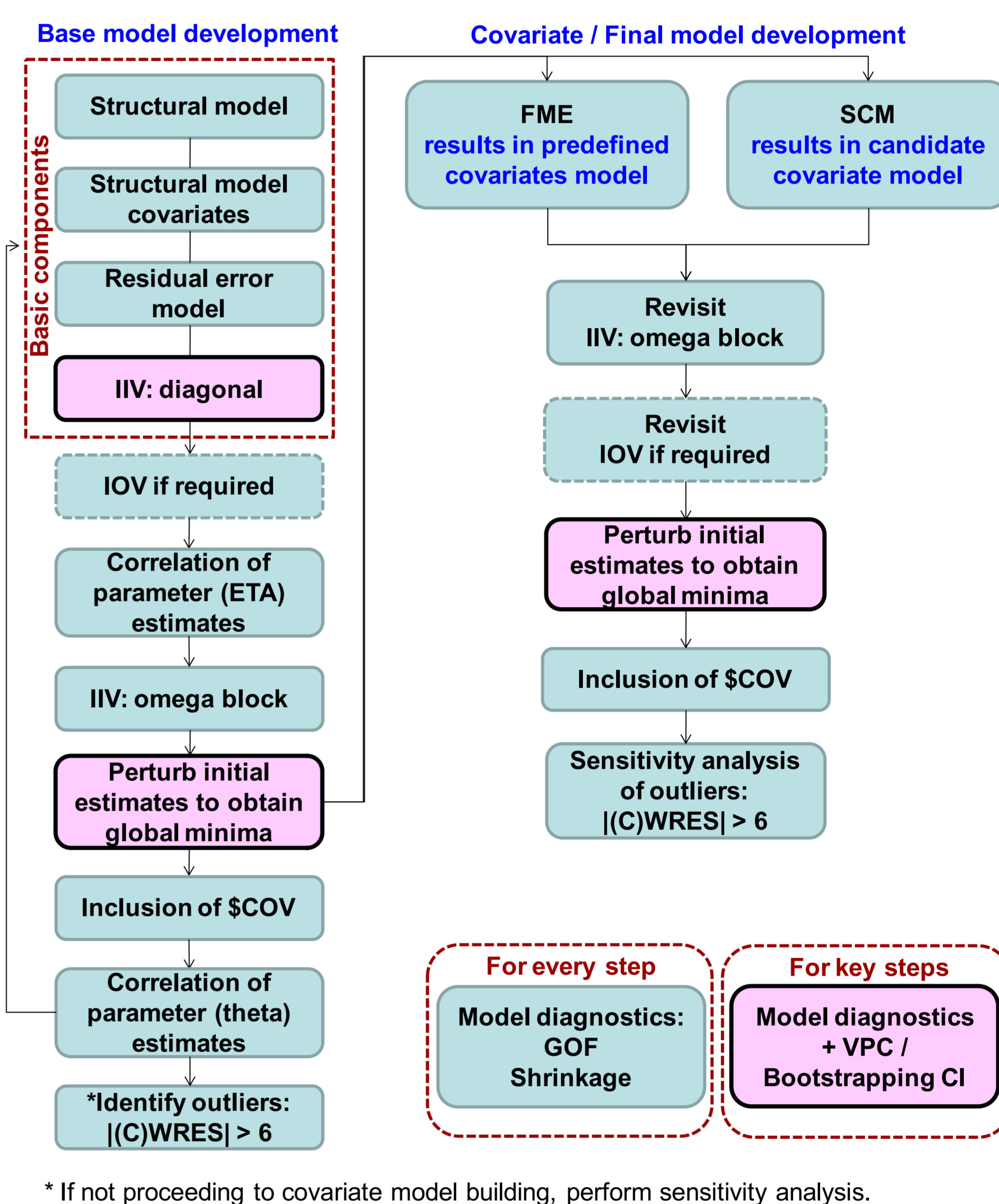
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Results

Figure 2 Table of Content for the POPPK Guidance

1. Purpose	6.7 Random Effects
2. Scope	6.8 Additional Topics
3. Background	6.8.1 Outliers
4. Points to Consider before Conducting a Population Pharmacokinetic Analysis	6.8.2 Over-parameterization
	6.8.3 Fixing Parameters Based on Prior Information
5. Population Pharmacokinetic Base Model	7. Graphical and Numerical Diagnostics
5.1 Definition	7.1 Types of Diagnostics
5.2 Inferences from Population Pharmacokinetic Base Models	7.2 Inferences from Diagnostic Plots
5.3 Data	7.3 Recommended Diagnostics
5.3.1 Full versus Validation Datasets	7.4 Training and Examples Available For Diagnostic Plots
5.3.2 Below Limit of Quantification Concentration Data	7.5 Prediction-Based Diagnostics
5.3.3 Missing Concentration, Sample, and Dosing Time Data	7.5.1 DV (or OBS) versus PRED
5.3.4 Ordinary versus Log Domain	7.5.2 DV (or OBS) versus IPRED
5.4 Assessment of Model Adequacy	7.5.3 Individual Concentration-Time
5.5 Structural Model Development	7.6 Residual-Based Diagnostics
5.5.1 Structural versus Error Model	7.6.1 Weighted Residual versus TIME
5.5.2 Parameterization	7.6.2 Weighted Residual versus Predicted Values
5.5.3 Structural Model Covariates	7.6.3 Histogram and/or Quantile-Quantile Plot of Weighted Residuals
5.6 Random Effects Model Development	7.7 Empirical Bayes Estimates-Based Diagnostics
5.6.1 General Principles	7.7.1 Shrinkage of ETA and EPSILON
5.6.2 Interindividual Variability	7.7.2 Scatter Matrix Plot of Parameters and ETAs
5.6.3 Off-Diagonal Elements of OMEGA Matrix	7.7.3 Histogram of Parameters and ETAs
5.6.4 Residual Error Model	7.7.4 ETAs versus Covariates
5.6.5 Interoccasion Variability	7.7.5 Other Parameter Based Diagnostics
5.6.6 Covariance Step	7.8 Simulation-Based Diagnostics
5.6.7 Eigenvalues of the Correlation Matrix	7.8.1 Mirror Plots
6. Population Pharmacokinetic Final Model	7.8.2 Using Statistics to Assess Model Fit
6.1 Definition	7.8.3 Visual Predictive Checks
6.2 Inferences from the Population Pharmacokinetic Final Model	7.8.3.1 Principles
6.3 General Principles	7.8.3.2 How to Conduct a Visual Predictive Check
6.3.1 Covariate Model Building Procedures	7.8.3.3 Points to Consider when Performing a Visual Predictive Check
6.4 Covariates	7.8.3.4 Information Provided by the Visual Predictive Check
6.4.1 Types of Covariates	7.8.3.5 Features of Visual Predictive Check Plots
6.4.2 Missing Covariates	7.8.3.6 Recommended Visual Predictive Check Plot Styles
6.4.3 Implementation of Covariate Models	7.8.4 Other Simulation-Based Diagnostics
6.4.4 Boundary for Covariate Parameters	8. Conclusions
6.5 Full Covariate and Final Model Interpretation	
6.6 Assessment of Model Adequacy	

Figure 3 General POPPK Workflow



* If not proceeding to covariate model building, perform sensitivity analysis.

IIV : interindividual variance; IOV: Interoccasion Variance ; FME: Full Model Estimation;;SCM Stepwise Covariate Modeling; GOF: Goodness of Fit; CWRES: Conditional Weighted Residuals; \$COV: covariance step; VPC: Visual Predictive Check

Some recommendations

Developing a population modeling analysis plan (PMAP) to prospectively outline the modeling approach prior to conducting a POPPK analysis. A well-prepared PMAP should provide an overview of the purpose of the modeling exercise, prior information used, the choice of studies/data to be included for analysis, the proposed modeling approach, and assumptions made.

When draft data become available, it is recommended that thorough data checks and exploratory data analyses (graphical and/or statistical summary) be conducted in advance of analyses.

When substantial proportion of BLQ data ($\geq 10\%$) is present, the recommended approach is based on simultaneous modeling of continuous and categorical data, in which the BLQ observations are treated as categorical data [6] (often referred to as the M3 approach).

Inclusion of scientifically or biologically plausible structural covariate parameters in the base model to ensure model stability when highly influential covariates are known.

Two main approaches are recommended for inclusion and evaluation of covariates in order to arrive at the final model - the most parsimonious model for which all relevant covariates of interest have been evaluated and retained.

- Full model estimation procedure (FME) [7] approach emphasizes parameter estimation (as opposed to stepwise hypothesis testing) and measures of estimation precision, allowing for the direct assessment of the clinical relevance of covariate effects. The FME procedure enables a direct assessment of all covariate relations of interest without the need to rely on data-driven model selection criteria.
- Stepwise covariate modeling (SCM) includes a forward selection (resulting in a full covariate model) followed by a backward elimination process (resulting in a final model). The forward selection process within SCM is particularly prone to the effects of collinearity when two or more covariates (or covariate parameters) are highly influential.

Once the planned, definitive analysis is completed, the results should be summarized in a population modeling analysis report (PMAR). It is important to stress that any assumptions and decisions made during model development be clearly documented in the PMAR.