

Recommended Approaches for Integration of Population Pharmacokinetic Modelling with Precision Dosing in Clinical Practice

Vesynta

Newcastle University

Monika Berezowska¹, Isaac S Hayden¹, Andrew M Brandon², Arsenii Zats¹, Mehzabin Patel¹, Shelby Barnett², Kayode Ogungbenro³, Gareth J Veal², Alaric Taylor¹, Jugal Suthar¹

¹Vesynta Ltd, Innovation Gateway, The London Cancer Hub, Cotswold Road, Sutton, London, UK
²Translational and Clinical Research Institute, Newcastle University Centre for Cancer, Newcastle upon Tyne, UK
³Division of Pharmacy & Optometry, School of Health Sciences, University of Manchester, Manchester, UK



http://doi.org/10.1111/bcp.16335

Background

Clinicians often lack patient-specific insights when making dosing decisions. Overreliance on imprecise dosing methods fails to consider interpatient variability, leading to suboptimal outcomes.

MIPD, supported by popPK can personalise dose selection by accounting for patient demographics, organ function, and response. Despite its potential, PK-informed precision dosing remains underutilised due to a lack of standardisation, robustness and clinical integration.

Aims and Methods

This systematic review aims to provide:

- 1. A summation of industry and regulatory recommendations for best practice popPK modelling and validation.
- 2. Recommendations for integrating popPK models into software to facilitate dose individualisation at the point of care.
- 3. An assessment of the potential of machine learning to improve model accuracy and dosing recommendations.

Results

Best practice recommendations were provided for each stage of popPK modelling and MIPD integration:

- **Data considerations:** importance of standardised data collection, formatting, exploration, and cleaning to ensure compliance, reproducibility, and accuracy.

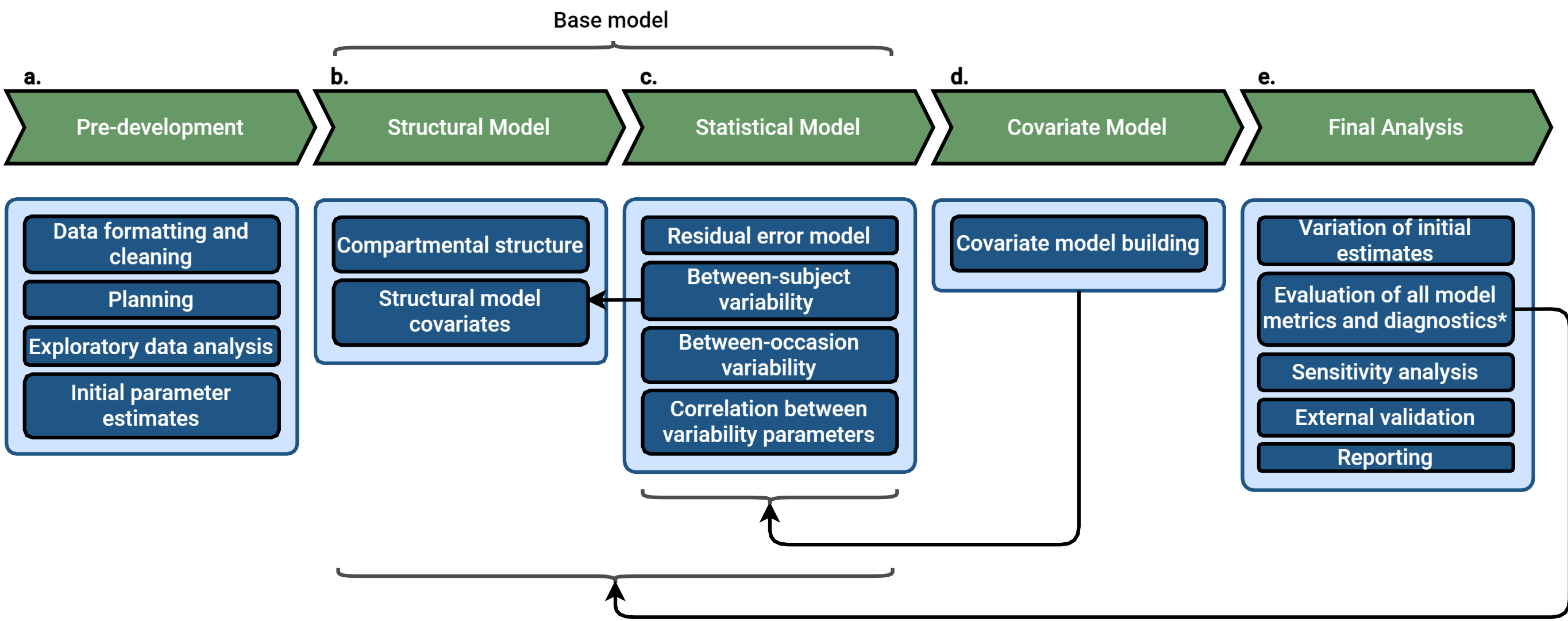


FIGURE 1 A workflow diagram of the recommended steps in the pharmacokinetic model development process: a. Pre-development, b. Structural model, c. Statistical model, d. Covariate model, e. Final analysis. * Appropriate metrics and diagnostics should be considered throughout the building process, but all should be considered collectively at this step. Adapted from Byon *et al.* [1]

- **Model building:** planning, software selection, and developing nonlinear mixed-effects models, including structural, statistical, and covariate models.
- **Adaptation of literature models:** guidelines for sourcing, transcribing, verifying, and evaluating published models.

- **Application in healthcare:** strategies for model selection, *a priori* and *a posteriori* predictions, uncertainty quantification, treatment regimen optimisation, and continuous integration of patient data.

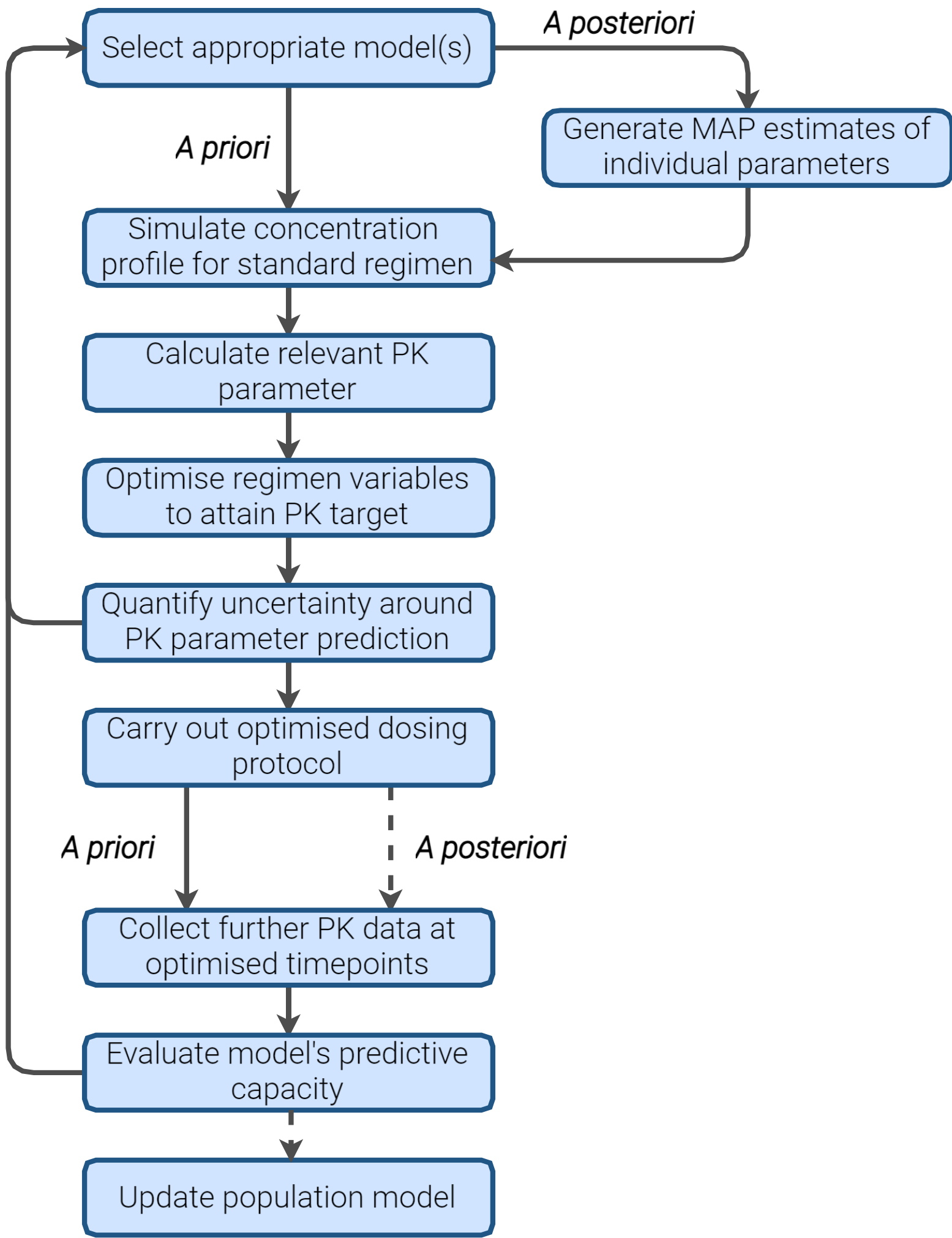


FIGURE 3 Workflow diagram illustrating the application of popPK models to optimise treatment. Dashed arrows indicate steps to be performed after several iterations of the preceding workflow have been carried out. PK: Pharmacokinetic, MAP: Maximum *a posteriori*.

- **Software integration:** requirements for interoperability with electronic health records, adherence to regulatory standards, and quality control measures for clinical deployment.

Conclusion

- The consolidation of recommended approaches into standardised guidelines covering the entire workflow from data handling to clinical application.
- The adoption of suggested measures to integrate with software and healthcare records can transition academic effort into direct patient impact.

Acknowledgements and References

The authors thank UK Research and Innovation for their financial support (Project ID 10111236).
[1] Byon W, Smith MK, Chan P, Tortorici MA, Riley S, Dai H, Dong J, Ruiz-Garcia A, Sweeney K, Cronenberger C. Establishing best practices and guidance in population modeling: an experience with an internal population pharmacokinetic analysis guidance. CPT: Pharmacometrics & systems pharmacology, 2013;2:51.

Abbreviations used: MIPD: model-informed precision dosing, popPK: population pharmacokinetics
Correspondence: jugal.suthar@vesynta.com

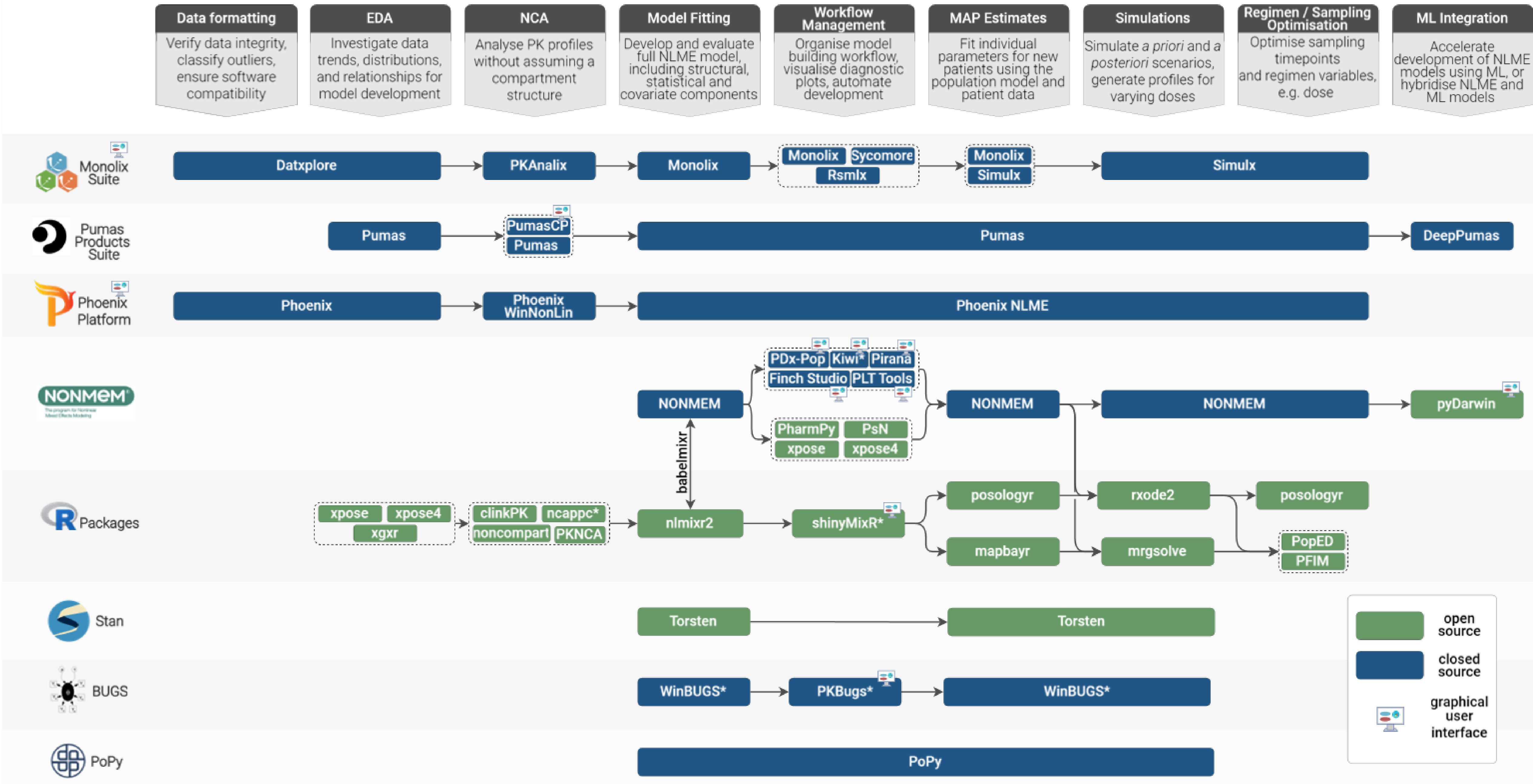


FIGURE 2 An illustrative map of population pharmacokinetics (popPK) modelling software packages across stages of the model building workflow. Tools marked with an asterisk (*) were last updated before 2020. EDA: Exploratory data analysis, NCA: Non-compartmental analysis, NLME: Nonlinear mixed-effects, MAP: Maximum *a posteriori*, ML: Machine learning.