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Pharmacometrics Workflow: Points to Consider for Efficient, Reproducible, and High-Quality Analyses

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ABSTRACT

Pharmacometrics and model-informed drug development (MIDD) support critical decisions across the drug lifecycle. Standardized workflows for pharmacometrics analyses are essential to ensure efficiency, reproducibility, and quality in this constantly evolving and fast paced environment. This white paper outlines key principles and recommendations for evaluating, developing, and maintaining pharmacometrics workflows. Core workflow components include analysis planning, data management, model building and simulation, reporting, quality control, and the analysis environment. Points for consideration emphasize documentation, automation, reproducible practices, use of data standards, and structured quality control processes. While no universal workflow exists, the guidance presented provides a foundation for optimized processes in both individual and institutional settings, enabling pharmacometricians to deliver consistent and traceable analyses that meet scientific and regulatory requirements.

KEYWORDS

Pharmacometrics, Model-informed drug Development, Workflow, Standardization

BACKGROUND

The discipline of pharmacometrics and model-informed drug development (MIDD) has seen significant adoption and advancement over the past 20 years [1-3]. Drug development teams now routinely rely on pharmacometric analyses to address a wide range of questions spanning the spectrum of drug development, from pre-clinical to post-marketing activities. As a result, the pressure on modeling and simulation scientists to help inform decisions from both internal and external stakeholders continues to increase. Individual pharmacometricians and the broader pharmacometrics community must, therefore, determine how to perform complex analyses in a constantly changing and highly regulated environment in the most efficient manner possible, while maintaining a high standard of quality. To accomplish this, a standardized pharmacometrics workflow is needed.

The goals of this white paper are to describe how a well-defined and standardized workflow can lead to more efficient and consistent deliverables, and to provide recommendations on key principles within the core elements of analyses that pharmacometricians may consider implementing. These recommendations may be adopted by individuals conducting pharmacometric analyses or incorporated by organizations with customization to align with their internal processes and operational needs. Indeed, a singular default workflow is unlikely to be suitable for all institutions due to differences in philosophy, head count, technical experience, and available tools and resources. The components of pharmacometric analyses covered in this document include analysis planning, data management, model building and simulation, reporting and archiving, quality control, and the underlying environment in which analyses are conducted (Fig. 1). While these components and the key concepts discussed in this manuscript reflect

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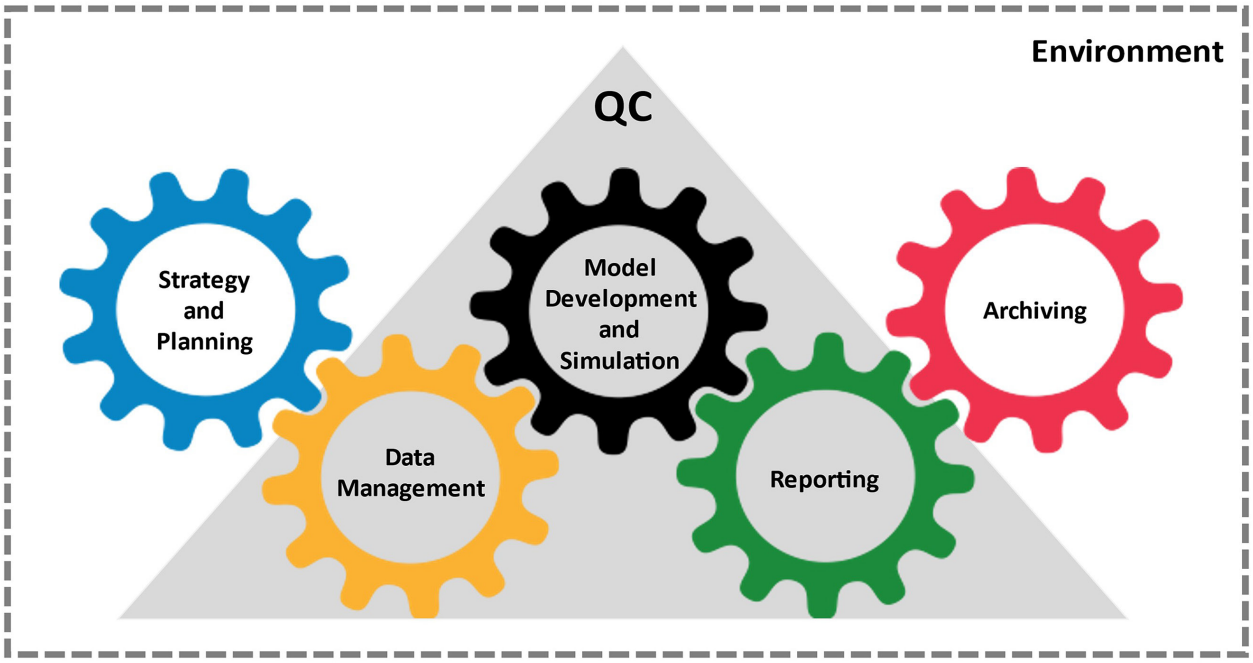


Figure 1: Core components of a pharmacometric analysis. QC: Quality control.

a traditional population pharmacokinetic (PK) or pharmacokinetic-pharmacodynamic (PK-PD) analysis, the proposed recommendations are generally applicable to other types of pharmacometric modeling including physiologically-based PK (PBPK), quantitative systems pharmacology (QSP), and machine learning (ML)- and artificial intelligence (AI)-based approaches. It is important to note that this white paper focuses on the concepts and principles to support a *general* framework for efficient, reproducible, and high-quality workflows; therefore, it does not provide specific recommendations for model development practices or specific software or hardware considerations. Examples of commonly used tools and approaches, however, may be discussed to illustrate workflow concepts, but these should not be interpreted as preferred or mandatory solutions.

STANDARDIZING PHARMACOMETRICS WORKFLOWS

The concept of a pharmacometrics workflow is not new and is simply how pharmacometrics work gets done. Pharmacometrics work includes, but is not limited to, the planning, execution, and quality control of analyses, and generating detailed technical documents intended for a wide range of stakeholders. A standardized workflow should leverage tools, templates, and automation to reduce timelines and to ensure the quality of the various components of the analysis from start to finish. Good workflows need to support proper documentation such that the analyst, their colleagues, and external stakeholders can follow, and if needed, reproduce or expand upon, each of the steps taken in an analysis, both at the time the documentation was written and into the future. In addition, the analysis environment (e.g., analysis tools, software versions, and operating systems) must be accessible over time, so that work can be reproduced at a later date.

Pharmacometric analyses are iterative in nature; as more data become available, models continuously evolve through the learn-and-confirm paradigm over the lifecycle of a drug [4]. Because this lifecycle can span many years, multiple analysts may be involved with modeling and simulation deliverables for a given drug, and without clear documentation and reproducible practices, it becomes difficult to understand, reproduce, or extend work that has been performed previously by other colleagues. Even if good documentation practices are followed, reproducibility may be hampered by the environment in which the work is conducted; this environment must be reproducible in order to enable others to replicate it with minimal effort, sometimes many years later. Reproducibility was a major challenge identified by participants attending the American Conference on Pharmacometrics (ACoP12) Preconference in 2021: "Integrating Standardization and Innovation in Your Organization: Find A Workflow That Works For You!" In a survey prior to the preconference, the results indicated that while participants had great confidence in the traceability and reproducibility of their own work, they had far less confidence in their ability to reproduce work performed by colleagues (Fig. 2).

Individual pharmacometricians and institutions may face several risks without a standardized pharmacometrics workflow: missed timelines or compromised quality of deliverables due to inefficiencies, loss of work (or the need for

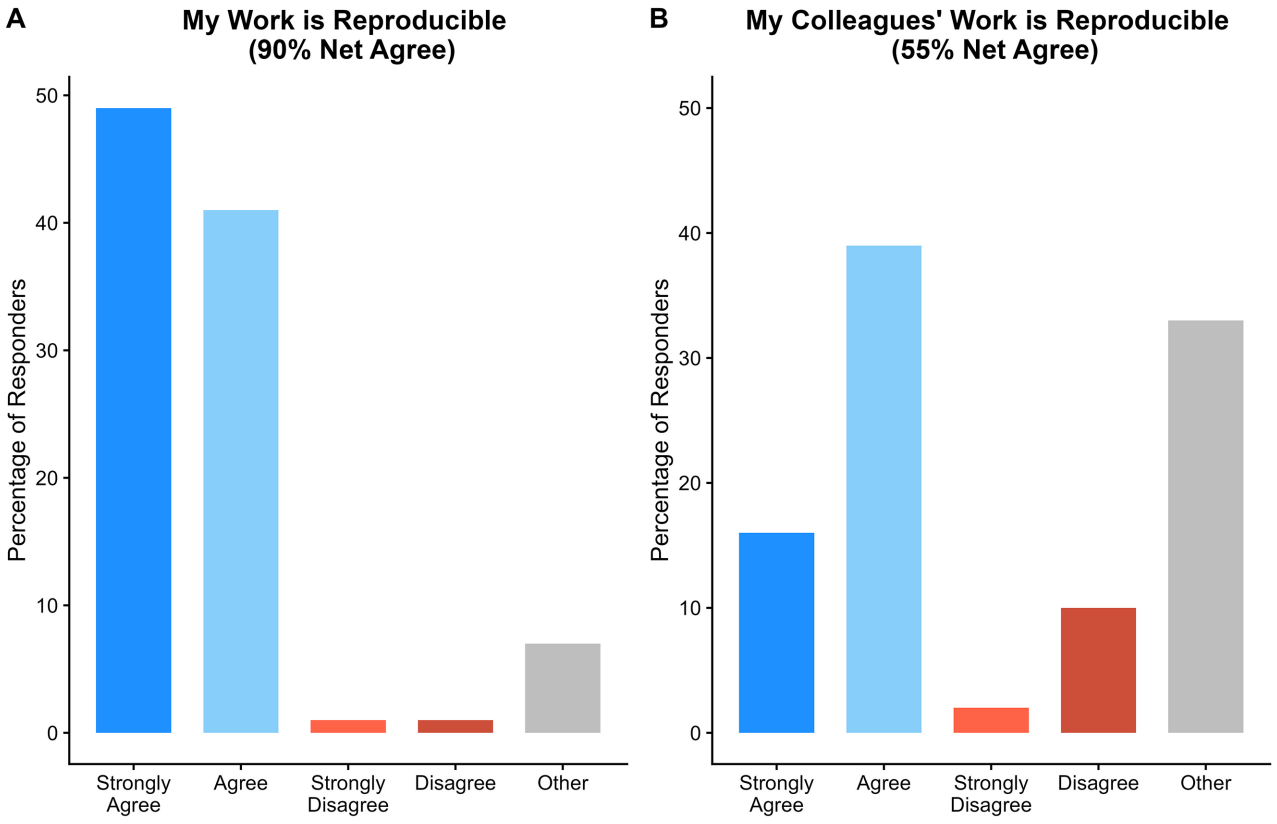


Figure 2: Reproducibility in pharmacometric workflows. Survey results from the American Conference on Pharmacometrics (ACoP12) Preconference (2021): "Integrating Standardization and Innovation in Your Organization: Find A Workflow That Works For You!" Participants were asked to agree or disagree with the following statements about their workflow and their colleagues' workflow. A) Self-Assessment: I consider my work to be reproducible (re-run my code on the same data in 6–12 months and get the same results and output). B) Peer-Assessment: If I inherit work (a project or results) from colleagues or co-workers, I am confident I could understand and build on their work without having to redo significant amounts of work.

re-work) due to poor documentation and archiving, challenges in collaboration and QC due to differences in working environments or incompatible software, and preventable mistakes due to individual preferences or misalignment in processes and tools across projects or between collaborators. The risks described above are real.

Pharmacometrics workflows will be constantly evolving to incorporate new software, internal processes, and tools. This is especially true now, as artificial intelligence (AI) capabilities have begun to be integrated within the pharmacometrician's toolbox. As such, workflows should regularly be evaluated for gaps and inconsistencies that coincide with these modifications; in other words, the "health" of the pharmacometrics workflow should be regularly checked, just like one has their yearly physical exam. A tool to facilitate this Health Check is provided in Table 1. It includes simple questions to assess each of the components of a pharmacometrics workflow. If you answer "yes" to all of these questions your workflow is likely in great shape. If you answer "no" to some of these questions, however, this may help you to identify shortcomings in your workflow and institute changes to improve the efficiency, reproducibility, and quality of your pharmacometrics analyses.

CHALLENGES & BARRIERS TO ADOPTION OF WORKFLOWS

Some pharmacometricians have voiced concerns that standardizing their practices will stifle creativity and innovation. However, having a workflow does *not* mean rigid uniformity, but instead is about adopting a process that ensures consistency and regularity in outcomes [5]; this can actually help to reduce, simplify, or eliminate mundane and repetitive tasks, allowing *more* time and freedom for interesting models and innovative MIDD approaches. In fact, though the idea of adhering to a workflow may initially cause discomfort, most pharmacometricians employ their own version of a workflow already. This may include the reuse of code snippets, adhering to naming conventions for scripts and documents, or employing standard text in report templates.

Despite this fact, practical barriers to the acceptance and implementation of a standardized workflow are not insignificant. In the survey sent out to attendees of the ACoP12 preconference (Supplement 1), the most commonly identified reasons for resisting implementation of a standardized workflow were concerns that: it might not be flexible enough to use for all project types, that it might not permit the use

Table 1: Workflow health check.

#	Question	Answer (Yes/No)
1	Do analyses that you conduct include feedback from stakeholders collected prior to initiating your planned analysis?	
2	Do pharmacometrics datasets you work with undergo a quality review (by you or someone else) before you begin modeling activities?	
3	Does your workflow have a process to capture and document model-building decisions in real-time?	
4	Could you reproduce a recently completed analysis tomorrow, next year, or 5 years from now?	
5	If you experienced a catastrophic hardware or system failure, is your work backed up such that, at most, you would only lose 1 day of work?	
6	Do analyses you complete undergo a documented peer review QC process at specific milestones to ensure key models are coded correctly and best practices within your institution are being followed?	
7	Could a colleague take over your analysis or perform QC review of your analysis without difficulty? Please consider file structure, naming conventions, environment, code annotation practices, and software availability.	
8	Do your pharmacometrics reports undergo a documented QC process to make sure that information in the document is consistent with the source information (study report, source code, model scripts)?	

of a particular software or tool, and that time requirements to familiarize, train, and maintain a workflow are too great in the context of other commitments. Instituting a new pharmacometrics workflow or initiating a change in an existing one indeed requires an unavoidable initial investment of both time and resources, which can be considerable. Another potential challenge is that it may be difficult to obtain agreement within an organization regarding specific features of the workflow, given that different individuals may interpret the workflow and its scope in varying ways. Each of these considerations must be balanced with the risks that may occur by not having a standardized workflow.

WORKFLOW CONSIDERATIONS FOR CORE COMPONENTS OF PHARMACOMETRICS ANALYSES

A pharmacometrics workflow must consider each of the interconnected components of pharmacometrics analysis (Fig. 1). The following sections outline key considerations and best practices for analysis planning, data management, model building, reporting, quality control, and the computational environment.

Analysis planning

Analysis planning is intended to outline strategic approaches to address pertinent clinical and regulatory questions of interest before initiating any modeling activities, and to establish the scope of work, analysis objectives and methods, and data to be included in the model. These should be documented in a dedicated Model Analysis Plan (MAP). A well-defined MAP facilitates alignment on the analysis strategy between the modeler, the development team, and other key stakeholders prior to conducting the analysis, and outlines how the results may support the answer to questions of interest, consistent with principles outlined in ICH M15 [6]. The MAP also establishes a clearly defined scope and roadmap for the analysis, which can manage expectations as the analysis proceeds and concludes.

The MAP typically includes the general drug information, objectives of the analysis, an overview of the studies and data to be analyzed, the covariates to be evaluated along with the rationale for their inclusion (e.g., mechanistic, biological or clinical), and the anticipated modeling and simulation methods and software. Key tables, figures, and listings to be included as the analysis outputs may be templated in the MAP or elaborated in a stand-alone data presentation plan.

The MAP can facilitate the acquisition of the necessary data and information for modeling by clearly documenting the access requirements to cross-functional partners. It also should describe the data handling procedures. Planning for data deliverables should also be considered; in particular, interim deliverables often require early unblinding of a subset of available data, which should be defined and documented based on pre-established timelines and criteria.

It is recommended to finalize the MAP prior to database lock of a key phase clinical trial(s) if possible, thereby meeting the pre-specification requirement and minimizing the need for amendments or updates. A comprehensive and well-written MAP, ideally in a report-ready format, also facilitates efficient reporting since sections like introduction, objectives, data plan, methods, and study summaries can be integrated directly into the final report.

The mechanics for producing a MAP have been presented previously [7] and are not the focus of this article. However, one may consider utilizing standardized templates and tools such as LaTeX or Markdown-based (Quarto or R Markdown) [8-10] to enable automation in this step as well as the reporting step.

Data management

A pharmacometrics analysis may involve several analysis datasets which include subject-level and disease-level data such as demographics, concomitant medications, covariates, dosing history, drug concentrations, and pharmacodynamic measures such as biomarkers and clinical endpoints for efficacy and safety, assembled from various sources. A data

specification document should be prepared for each analysis; this may be part of the MAP or a separate document. It is recommended to include all relevant formulas, derivations, units, groupings, algorithms, and imputation rules in this document.

Over the past two decades, a significant effort has been made to develop and advance quality data standards in clinical trials, including the formation of the Clinical Data Interchange Standards Consortium (CDISC) [11]. Data collected in a case report form from subjects in clinical trials can be converted into Study Data Tabulation Model datasets (SDTM) for tables, figures, and listings (TFLs) and Analysis Data Model (ADaM) datasets for analyses. PK concentration data are often available as separate files from bioanalytical labs and are mapped to the SDTM domain called PC.

For pharmacometrics analyses, data would be extracted from SDTM and ADaM datasets to create derived analysis datasets. The ADPPK Implementation Guide, developed through a collaboration between CDISC and the International Society of Pharmacometrics (ISoP), was recently introduced to present the basic data structure and required extensions for population PK analyses [12, 13]. This was an important step towards the consistency, reproducibility, and traceability of datasets used for population PK analyses conducted throughout the life cycle of a drug development program; the intention was to improve quality and efficiency by maintaining a standardized structure and data definitions across analyses, to facilitate interpretation, and to support both scientific and regulatory interactions.

As outlined in the ISoP initiative paper [13], the ADPPK data standard ensures that population PK datasets are prepared per a standard core specification using SDTM/ADaM with clear source data identification: derived and missing data are handled in a consistent manner, CDISC controlled terminology is used for character variables, and there is a code list and units defined for numeric variables. Standardized code or tools are suggested to facilitate the creation of an electronic Common Technical Document (eCTD)-compliant data definition file from the ADPPK for regulatory submission [14, 15]. While ADPPK standards are tailored for population PK data, the general principles, such as traceability, consistency, and structured documentation, could be applied to other types of analyses such as PK/PD or exposure-response analyses.

In addition to data standards, it is recommended to have a naming convention for datasets and a standard folder structure to organize and store datasets and files throughout the life cycle of a program, to facilitate use of qualified common code and automation efforts. Analysis-related files should be given unique, descriptive identifiers and should be easily located by any team member at any phase of analysis. For example, the use of ISO 8601-compliant date formatting (e.g., YYYY-MM-DD), provides several advantages, including chronological sorting time stamps, and represents a useful and widely accepted best practice. Each project should have a parent directory containing subfolders to clearly distinguish the types of files content such as analyses, datasets, documents, outputs, reports, scripts (etc.), for traceability and easy retrieval. Additional folders can be created within these to provide greater granularity, e.g. separate subfolders each containing data from different studies. Project names should be as specific as possible to reflect compound name, therapeutic area, type of analysis and version information (captured as version number or with version date).

Model building and simulation

Many guidance documents and journal articles have been published on best practices and points for consideration for exploratory data analysis (EDA) and modeling and simulation methodologies [16-19]. These publications are important for advancing our discipline. The purpose of this section, however, is not to focus on any specific area of EDA or the model building and simulation process, but rather to highlight the integration of these central activities with other aspects of pharmacometrics workflow, and to reflect on elements where gains can be made in efficiency and quality.

Pharmacometricians have many tools at their disposal to perform analyses. In addition to specialized software programs designed for the specific modeling methodology to be used, such as nonlinear mixed-effects, PBPK, or QSP modeling, a variety of other tools may be used during the execution of an analysis, such as: text editors for model coding; run management tools for model execution and organization, as well as real-time documentation for subsequent reporting activities (e.g., key model table); tools to facilitate automated covariate search algorithms; post-processing software for extracting model results and creating TLFs; and specialized simulation tools. Tools used to support model building and simulation should be carefully selected and curated, because the selection of these tools has workflow consequences both upstream and downstream of these activities. For example, modeling software may require analysis datasets to be formatted in a certain way with unique variable names specific to that software. Naturally, this impacts the data specifications and other aspects of data management. Similarly, the analysis output, including directory structure, output file names, and file type, will be packaged in a manner specific to the modeling software. These, as well as the analysis dataset format and naming conventions, will impact code for post-processing and subsequent simulation applications which leverage a standardized model output.

Automation of mundane and repetitive tasks during the model building and simulation process can greatly improve pharmacometrics workflow efficiency. Traditionally, “automation” has been used only to execute a particular procedure within the process; one example may be the automatic execution of a validated template script to create standardized goodness-of-fit diagnostics or parameter tables after each model runs. Perhaps the most implemented type of automation in pharmacometrics is the covariate search procedure [20-23]; the application of these procedures which automatically construct, execute, and document the statistical significance of tested covariate-parameter relationships have led to substantial time savings compared to manual execution.

Automated methods for structural model development for population PK models have also been developed [24, 25]. More recently there has been interest in automation of the entire model building process from dataset creation to reporting. This has been demonstrated for the standard concentration-QTc analyses as well as exposure-response analysis for binary outcomes, whereby entire analyses can be executed and reports generated in a single step after selecting appropriate options in a control script [26, 27]. The automation in these types of analyses leverage tools like R Markdown to incorporate analysis code and supporting text in one executable file which can render polished reports. These reports can be easily and efficiently re-rendered if control script options need to be modified or if source datasets are updated.

While the efficiency gains obtained from automated procedures are obvious, the gains in quality may be even more important. Automated procedures have the potential to reduce mistakes and errors frequently perpetuated by humans (e.g. parameter numbering typos in model code). In addition, automated procedures can require substantially less quality control activities. Reviewers need only to check the input, setup, and output components rather than various intermediate model runs and objective function calculations.

It is important to note that model building and pharmacometrics workflows, in general, will continue to evolve based on advancements in AI/ML and availability of tools that utilize this techology. AI-assisted coding and code review technologies are already widely available and routinely used. In addition, the use of AI agents and agentic workflows [28] to perform specific tasks with varying degrees of autonomy continue to gain traction within our field; these will almost certainly occupy a key role once fully integrated with existing methodologies and infrastructure, and once more experience with their use has been collected.

Reporting

Traceable, reproducible, and (semi-)automated modeling analysis reports (MARs) are critical to improve efficiency, increase consistency, and reduce time for documenting pharmacometrics analyses. Another benefit of semi-automated reporting is a reduced quality control (QC) burden by using standardized text and modularized scripts with reusable and QC'd functions.

A standardized report template that meets an individual organization's needs and internal documentation standards is an important first step towards automation, and is aligned with regulatory expectations [29-31] as well as the MIDD International Council for Harmonization (ICH) initiative across global regulatory and pharmaceutical organizations [32]. Several automated reporting tools and packages based on LaTeX [8, 9] or Markdown (Quarto or R Markdown) have been developed to support automated pharmacometrics report generation. These tools can automatically incorporate tables and figures from modeling outputs into a template without manually copying and pasting them, or even script entire reports in code, enabling efficient and less error-prone reporting over multiple iterations of data updates and model developments. A significant challenge to successful implementation of this "literate programming" approach lies in the reliance of the pharmaceutical industry's internal authoring and review systems requiring DOCX-formatted documents, which have traditionally been less well-supported by the automation tools listed above (compared to PDF and HTML outputs). The advent of AI-driven coding agents may accelerate the development of explicitly DOCX-centric solutions.

A list of sections and contents for population pharmacokinetic reports are included in the current Population Pharmacokinetics Guidance for Industry [30]. As pharmacometrics analyses are expected components of regulatory submissions, it is also recommended to create executive summaries of MARs which can be used as a basis to support prescribing labels and Module 2 documents (clinical summary, especially module 2.7.2), as well as other sections as appropriate of the CTD. Unbalanced focus on technicality without assessing clinical relevance and regulatory questions/decisions such as labeling were identified as barriers to hamper the impact of MIDD [7]; therefore, we recommend a balanced assessment of clinical and regulatory aspects of the analysis with technical details in MAR or other clinical summary modules as deemed most appropriate when supporting regulatory submissions.

Quality control

As an essential component of the workflow, QC is a form of quality management focused on providing confidence that quality requirements of pharmacometrics analyses have been fulfilled. Key components of a pharmacometrics analyses that require QC include data, model development, reporting, and process. Bonate and colleagues [33] provide a detailed overview of this topic; although they present it from the point of view of a NONMEM analyst, the principles laid out are broadly applicable to pharmacometrics analyses in general.

When conducting the QC, the overarching goal is to ensure that the entire analysis and all outputs are reproducible and meeting the expected quality standard. Where applicable, the QC activities should prioritize models/programs and output that are used to generate content for the MAR and any communications that will be submitted to regulatory agencies for review. To attain this goal, a series of QC-related milestones are proposed as detailed in Table 2. This is not an exhaustive list but reviews the key QC considerations. It is also focused on an industry setting; considerations in regulatory or academic settings may be different. The rapid development of AI-assisted tools, particularly for code and data review, is likely to have a significant impact on QC processes, although at the time of writing experience is relatively limited.

Data QC

An accurate and complete analysis dataset is the single most important prerequisite for all downstream activities. The

Table 2: Scope and considerations for QC.

Stage of PMx	Key files for QC	QC considerations
Data: analysis data management	• Scripts that import source data and assemble the study level and pooled analysis-ready datasets.	• Correct input data version was used. • Data processing logic was appropriate. • Common errors (e.g. duplicate dose records) were not present. • Decisions about data imputation and exclusion were justifiable, clearly documented, and in line with analysis plan. • Variables in the dataset were coded in agreement with data specification.
Model development: key milestones for model development, evaluation and application	• Key model programs and output (e.g. base model, full model and final model) • Key model evaluations that support the utilization of the model • Simulation and application scripts	• Code is correct (no coding errors) • Model runs and simulations are reproducible and use correct input data. • Model files were sufficiently annotated • Mapping of data fields in model code to data file was accurate • Data filtering was applied correctly • Model outputs (such as parameter estimates) correctly captured in simulation scripts
Reporting	• Slide decks (exploratory analyses, preferably scripted) • Report/s (preferably scripted)	• Editorial check of scientific clarity and flow of work (peer review) including justification for model development decisions. • Captions/headings for figures and tables are unique, accurate and complete. • Citations and cross-references are accurate. • Numbers in the text, tables and figures are correct, traceable and reproducible. • Report is aligned with the MAP: all objectives were addressed, deviations were documented, analysis methods were consistent, etc.
Process	All	• MAP has been adhered to • SOPs have been adhered to • Workflow and analyses are reproducible to the extent practical

level of stringency required for QC of datasets is, however, considered situational and should incorporate a risk-based programming approach. The most rigorous level of QC is double programming, in which two individuals create the dataset independently from the source data and specification, and the results are compared; the dataset is accepted only when both versions match. It is recommended to apply this approach where practical given available resources. Often, however, a balance between stringent and practical aspects of data QC must be struck when resources and time are limited. As a less onerous alternative, data management scripts and outputs can be thoroughly reviewed by a second analyst, ensuring that the correct input data is used, that outputs are reasonable and reproducible, that the code correctly implements the intended data strategy, and that the intended data strategy is appropriate for the analysis. Tools have been developed to improve the efficiency of data QC through an interactive system that automatically identifies and reports potential issues in the data. Note that the validity of the source data (e.g., unrealistic covariate values) should be continually assessed and queried during exploratory data analysis and subsequent model development.

Model development QC

For model development, double programming is neither practical nor appropriate given the almost-infinite variations possible when developing a bespoke model with a specific dataset. In this situation, code review of base structural and final covariate models and any additional scripting that was done to inform model selections (e.g., PsN stepwise covariate model building scripts) is recommended, as well as careful inspection of the outputs by a scientist with experience in the relevant software tool.

Report QC

This QC should be both editorial and scientific content-based. Besides scientific peer review, the QC should check all quoted results, tables, figures and listings to ensure that the analysis results have been appropriately and accurately reflected and the workflow and decisions made at every model development step have been clearly communicated. Reports can be scripted and automatically generated in PDF and other common document formats using an array of readily-available tools, which reduces the chances of error and the QC burden.

Process QC

Finally, it is essential to ensure that the analysis as reported reflects the MAP accurately and completely, that it is reproducible to the extent practical, and that it complies with applicable standard operating procedures [SOPs].

It is beyond the scope of this article to provide recommendations for good practice for pharmacometrics programming coding [7]. Generally, however, using standardized code and

programs that have been previously validated or qualified may substantially reduce the amount of QC time required and the number of potential errors that might be made, or missed during QC.

A pharmacometrics analysis is a complex process with many closely inter-related steps, with each step dependent on those coming before. The timing of QC activities is therefore critical. The scientist(s) performing QC should be identified *a priori* and should have sufficient expertise on the required data structures, modeling methods, report requirements, software utilized, and any applicable SOPs. The analyst and QC scientist(s) should be in regular contact to communicate the analysis background, scope, intended strategy, and evolving timelines.

We recommend that QC activities be started as soon as the analysis dataset becomes available and continue in parallel until the report is finalized, analysis results are communicated to stakeholders, and conclusions have been endorsed. Conducting QC at key milestones—such as after building the base model and again with the final model—helps catch errors and inefficiencies early. The QC process is inherently iterative and should be integrated throughout the model development lifecycle, versus delaying these activities until the final stages. Importantly, QC findings should be communicated in real time, enabling timely interventions and adjustments. This proactive approach ensures that issues are identified and addressed before they become critical, reducing the risk of late-stage setbacks. QC activities may be documented in a brief QC report, which might be as simple as a checklist. Such a document is intended to ensure the QC deliverables (location and version of a final report, location of sources, for example) were clearly defined and QC findings and agreement on resolutions have been reached between the analysts and the QC reviewers.

Efficient QC also requires seamless and real-time file sharing and communication between the analyst and the QC scientist; manual transfer of files is prone to errors and security issues. A shared analysis platform (described in the next section) is strongly recommended to facilitate more rapid and efficient QC, since reproducibility cannot be assured where these differ.

Analysis environment

In the pursuit of efficient, high-quality, and reproducible pharmacometrics analyses, the establishment of a stable, qualified, and secure computational environment is critical. A stable environment refers to one in which the software, operating system, package versions, system dependencies, computing infrastructure, security, and access permissions required to execute an analysis are documented, controlled, and available such that the work can be reproduced or extended by others with minimal effort. Ideally, this environment should follow the principles of Good Automated Manufacturing Practice (GAMP) [34] and align with regulatory standards including 21 CFR Part 11 [35] and good clinical practice (GCP). Appropriate documentation of the analysis environment, including validation activity, is helpful to ensure the integrity of the computational platform setup and maintenance.

While some modeling activities may be conducted on a PC, the computational demands of pharmacometrics analyses often require a dedicated, high-performance computing infrastructure, such as a physical or a cloud-based server. Within pharmacometrics teams, the computational environment, including the operating system, CPU architecture, and software tools and versions, should be standardized and controlled. The exact environment used for an analysis should be available to new and existing team members throughout the analysis, but also accessible for months or years in the future, when analyses may need to be revisited or extended in new directions.

Particular attention should be given to reproducible installation of specific versions of add-on software packages (e.g., dplyr or ggplot2 for R) that may be used in the analysis. Rapid development cycles can produce substantial changes in these packages compared to other software, creating the potential for problems with reproducibility if the exact set of package versions used in the analysis cannot be easily identified and (re)installed. It is recommended to use a per-project, version-controlled dependency lockfile (such as that provided by renv for R projects) that records the exact direct and transitive package versions used in the analysis and is committed alongside the code, thereby enabling the analysis environment to be recreated from the project itself. Frozen repositories (e.g., Posit Package Manager snapshots identified by date) may be used as a complementary or backup mechanism to support package installation and reproducibility. These add-on packages may also require certain system dependencies (e.g., fonts or other utilities), emphasizing the need for comprehensive specification of the compute environment. For long-term reproducibility, containerization technologies (e.g., Docker or Apptainer) may also be considered to capture the complete software environment, including system-level dependencies.

Also integral to reproducible pharmacometrics workflows is the ability to trace changes in analysis code, inputs, and outputs over the course of the analysis. This is readily accomplished through a version control system (most commonly Git or validated enterprise equivalents). These systems document the date, time, and user identity for any change that is made to project-related files over the course of the analysis. Tracking this history enables team members to (1) obtain the most up to date version of any analysis artifact (e.g., script, model, or data set) and (2) investigate incremental changes in code or outputs at any given time. This allows team members to better understand analysis decisions over the course of the project and to identify the point in time when a bug or regression was introduced in the code base. Finally, version control systems enhance collaboration within a team, allowing multiple users to simultaneously work on the same set of files, letting the version control software manage and merge multiple changes as they are committed to the repository.

Table 3: Workflow recommendations.

Workflow components	Recommendations
Analysis Planning	• Align on key clinical and regulatory questions with key stakeholders • Start with detailed planning of data acquisition. • Choose the format based on purpose, a full, report-ready MAP as seen in regulatory submissions, or a concise slide deck for exploratory analysis • Use standardized templates to facilitate automation and streamline reporting. • Maintain plan flexibility to adapt to evolving data and project needs.
Data Management	• Make use of ADPPK dataset construction recommendations and naming conventions etc. • Commit to using a standard data structure and file storage structure to facilitate collaboration, organization, and automation. • QC and create data specification and define.pdf data prior to initiating modelling
Model Building and Simulation	• Consider use of detailed run records (programs/homemade) • Utilize QC'd template code for standard output including parameter estimates, demographic tables, etc. • Utilize standardized naming and numbering convention and output extensions to support use of automated software and templated code for common activities.
Reporting and Archiving	• Incorporation of automation in reporting via LaTeX/Quarto/R Markdown • Agree on a standard reporting format (headings, etc) and use it • Construct reports such that specific sections of report can be dropped into sections of the CTD or briefing documents
QC	• Data QC, model QC and report QC are the three aspects of QC activities. • QC activities should be started when the analysis dataset becomes available and continue in parallel until the report is finalized, analysis results are communicated to stakeholders and conclusions have been endorsed. • Document QC activities with a brief QC report. Such a document is intended to ensure the QC deliverables were clearly defined and agreement has been reached between the analyst and the QC reviewer. • QC should be performed by a second, qualified modeling and simulation scientist.
Environment	• Establish a validated & secure environment to ensure compliance, system integrity, and software performance through proper documentation. • Implement a file storage system with version control, including a back-up or recovery mechanism. • Use high-performance computing with standardized local or cloud-based infrastructure. • Ensure interoperability with commonly used pharmacometrics tools.

Of note, version control repositories are generally most useful for code, model files, specifications, workflow documentation, and environment configuration files. Larger datasets, rendered outputs, or other system-generated artifacts may require alternative storage approaches based on organizational requirements, but should remain traceable to the workflow steps that produced them.

As a final step, following project or task completion, datasets as well as other modeling inputs and outputs should be archived in a secure location with controlled access privileges for safe and prolonged storage to meet organizational and regulatory requirements. Archived materials should include the datasets, model files, analysis scripts, reports, QC documentation, and sufficient information about the computational environment to enable future reproduction of the analysis. Consideration should also be given to legal and contractual retention requirements, protection against unauthorized modification, and procedures for restoring archived materials when needed.

Artificial intelligence-enabled workflow support

AI-enabled tools are increasingly being incorporated into pharmacometric workflows (28). Current applications include code generation, code review, exploratory data analysis, analysis documentation, report drafting, and QC activities. These tools have the potential to improve efficiency, and reduce repetitive manual effort when incorporated into well-defined workflows. AI agents and agentic workflows may further extend these capabilities by coordinating multiple tasks across analysis planning, data processing, model execution, and reporting.

From a workflow perspective, AI-enabled tools are most valuable when applied to standardized or repeatable activities. The use of AI should not, however, alter the fundamental principles discussed in this article. Outputs generated by AI systems should be considered as intermediate work products with potential flaws or errors that require review by qualified scientists. Scientific judgment remains essential for defining analysis objectives, selecting modeling approaches, evaluating biological plausibility, interpreting results, assessing clinical relevance, and guiding regulatory suggestions [36, 37]. Likewise, AI-generated code, analysis documentation, and QC findings should be reviewed to ensure they are accurate, reproducible, consistent with the analysis plan, and appropriate for their context of use.

Organizations incorporating AI into their workflows should establish clear expectations regarding acceptable use, review requirements, and accountability for final deliverables. As with any pharmacometric tool, the focus should not be the technology itself, but rather the delivery of analyses that meet the expected standards of quality and scientific rigor.

SUMMARY OF RECOMMENDATIONS

A "one-size-fits-all" pharmacometrics workflow does not and cannot exist. Individual pharmacometricians and organizations should tailor their workflow to balance their own specific needs; the workflow for a small pharmacometrics consulting company with a handful of modelers might look very different to the workflow for a large multi-national pharmaceutical company employing 200 pharmacometricians. While institutional workflows will surely differ, the core principles for efficient, reproducible, high-quality analyses of complex, multidimensional data are universal. The recommendations set out in this document, summarized in (Table 3), provide a foundation for pharmacometrics practice upon which pharmacometricians and institutions can build their own optimized solutions.

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CONFLICT OF INTEREST

None.

SUPPLEMENTAL FILES

Additional supporting information can be found online in the Supplemental Information tab in the Quantitative Medicine collection.

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