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Authors

Solans, Belén
van Wijk, Rob
Imperial, Marjorie
et al.

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TUTORIAL

Pharmacokinetic analysis across studies to drive knowledge-integration: A tutorial on individual patient data meta-analysis (IPDMA)

Rob C. van Wijk[1,2] | **Marjorie Z. Imperial**[1,2] | **Radojka M. Savic**[1,2] | **Belén P. Solans**[1,2]

[1]University of California San Francisco Schools of Pharmacy and Medicine, San Francisco, California, USA

[2]UCSF Center for Tuberculosis, University of California San Francisco, San Francisco, California, USA

Correspondence
Belén P. Solans, 1700 4th Street, UCSF Box 2552, Rm 503C, San Francisco, CA 94143, USA.
Email: belen.perezsolans@ucsf.edu

Abstract

Answering challenging questions in drug development sometimes requires pharmacokinetic (PK) data analysis across different studies, for example, to characterize PKs across diverse regions or populations, or to increase statistical power for subpopulations by combining smaller size trials. Given the growing interest in data sharing and advanced computational methods, knowledge integration based on multiple data sources is increasingly applied in the context of model-informed drug discovery and development. A powerful analysis method is the individual patient data meta-analysis (IPDMA), leveraging systematic review of databases and literature, with the most detailed data type of the individual patient, and quantitative modeling of the PK processes, including capturing heterogeneity of variance between studies. The methodology that should be used in IPDMA in the context of population PK analysis is summarized in this tutorial, highlighting areas of special attention compared to standard PK modeling, including hierarchical nested variability terms for interstudy variability, and handling between-assay differences in limits of quantification within a single analysis. This tutorial is intended for any pharmacological modeler who is interested in performing an integrated analysis of PK data across different studies in a systematic and thorough manner, to answer questions that transcend individual primary studies.

INTRODUCTION

With growing attention and appreciation for data sharing and open access availability, and increasingly powerful pharmacological analysis tools in drug development, there is an enormous potential to answer challenging questions through the analysis of integrated data across clinical studies. At the same time, analyzing data across studies comes with additional methodological criteria that should be met for the results to be reliable. By analyzing pharmacokinetic (PK) data thoroughly and systematically across multiple studies, we integrate knowledge to ensure that

Rob C. van Wijk and Marjorie Z. Imperial authors contributed equally to this work.

robust and generalizable models are built, which improve informed decision making within the context of model-informed drug discovery and development (MID3).[1]

Relying on data presented in single published reports only has its limitations toward generalizing results and answering questions that were not necessarily the focus of the single study. Inconsistent reporting of the parameters of interest, incompatible data across studies, heterogeneous populations with respect to patient characteristics and disease status, and small sample sizes limit the ability of drawing robust conclusions out of single studies. In consequence, any quantitative analysis with an objective or research question of a more general nature, but that may be based on only a single or an incomplete subset of published studies, is potentially prone to bias. Even though some of the caveats might not apply if results from large phase III studies are presented, multiple sources of information and variability are desirable, if available, to reflect the intended population in its full diversity.

Therefore, if one wants to obtain reliable, robust answers to the scientific question of interest, it is highly recommended to go beyond the results sections of publications by replacing summary data for individual data and perform an integrated analysis across studies.

Different approaches to integrated analysis of PK data across studies can be defined. A convenient or opportunistic approach is to pool data from different studies that are already accessible to the investigator, for example, pooling data from a single ascending dose and a multiple ascending dose clinical trial for the compound of interest to answer a question on dose recommendations in a similar population. This pooled analysis is a statistical technique for combining results from multiple studies and can be used as long as the included studies have a similar design resulting in homogeneous patient populations that are the subject of the research question.[2] A more systematic approach is model-based meta-analysis, which has been defined as a quantitative knowledge management approach that exemplifies pharmacology-inspired and statistically rigorous meta-analytical data integration to inform decision making.[3] An example could be systematically searching and including all clinical trials for the compound of interest to formulate general dosing recommendations. Both approaches can be used to answer similar research questions (e.g., a dosing recommendation; Table 1), but the direction, applicability or population, and depth of research will depend on the type of data available and the quantitative analysis implemented.

This tutorial is intended for scientists performing an integrated analysis of PK data across studies and/or obtained from different sources. We will do so by providing guidance on how to successfully do an individual patient data meta-analysis (IPDMA). This tutorial assumes that the researcher knows and follows good practices for standard PK model building, and we refer the reader to previously published tutorials in order to build a good PK model, whether the data comes from one or more studies.[4–8] For the analysis of pharmacodynamic data, an approach with a similar structure can be followed, but a detailed description is out of the scope of this tutorial.

WHAT ARE INDIVIDUAL PATIENT DATA?

The term individual patient (or participant) data (IPD) is defined as the information obtained for each specific patient in a given study. It is the most detailed level of information on the individual patient available. Individual patient data would consist of a specific patient's demographic characteristics (e.g., age, weight, and gender), both assigned treatment and actually taken treatment

TABLE 1 Comparison between different methods to analyze data across clinical trials.

	MBMA			
	IPDMA			
	One-stage	Two-stage	Aggregated data meta-analysis	Pooled analysis
Data collection	Systematic review IPD	Systematic review IPD	Systematic review Aggregated trial data (summary statistics)	Available or in-house data
Analysis	Model-based re-analysis across trials, accounting for trial-specific sources for variability	Model-based re-analysis of IPD per trial Statistical meta-analysis	Model-based reanalysis of aggregated trial data accounting for trial-specific sources for variability	Model-based reanalysis of IPD/aggregated trial data accounting for trial-specific sources for variability
Reporting	Outcome of interest Heterogeneity across trials			

Abbreviations: IPD, individual patient data; IPDMA, individual patient data meta-analysis; MBMA, model-based meta-analysis.

if those data are available (e.g., drug used, specific dose, and dosing schedule), disease characteristics (e.g., disease stage and baseline biomarker) and the individual drug exposure measurements (e.g., longitudinal concentration over time data points, maximum concentration [C_{max}], and area under the concentration time curve [AUC]).

This concept contrasts with aggregate data, which refers to averaged information obtained across all (or a subgroup) of the participants in a study. Therefore, aggregate data are derived from the individual participant data. Inherent to the nature of summation, the level of detail, number of datapoints, and statistical power decreases. Taking the same example of a PK study, aggregate data would consist of summary metrics, such as median demographic characteristics (e.g., median age, weight, and the most common gender or percentage of women), the protocol administered treatment, median disease characteristics (possibly stratified), and summary metrics of drug exposure (e.g., median C_{max}, median AUC, median average plasma concentration).

WHAT IS AN INDIVIDUAL PATIENT DATA META-ANALYSIS?

The use of IPD, rather than aggregate data, has been described as the gold standard approach for systematic reviews and meta-analyses (MAs).[9] Analysis of IPD typically improves the quality of the type of analysis that can be performed as it relies on the most detailed level of data available. Further, the results from the analysis of IPD, compared to aggregate data, is the least biased and most reliable in addressing questions that have not been satisfactorily resolved by individual clinical trials. IPD analysis consist of central collection, validation, and reanalysis of the individual data from multiple trials that have addressed a common research question. Therefore, in IPDMA, the ultimate goal is to summarize evidence across studies to address a specific question, such as effective drug exposure across populations. Both IPDMA and aggregate-level MA can also explore relevant sources of heterogeneity between the related studies. However, a thorough and systematic covariate investigation can only be performed through an IPDMA, because it requires the IPD level data that is lacking in an aggregate-level MA.

For IPDMA, two strategies are possible: one and two-stage approaches. The one-stage approach is more powerful, but the two-stage approach has been more widely used.[10] Focusing on the two-stage approach first, in the first stage, the individual data are analyzed within the trial, and therefore trial-level summary statistics are generated. In a second step, these results from each of the included trials are then combined using conventional MA methods. This second step would therefore be similar to an aggregate-level MA, and the advantages of using individual patient data would be therefore diminished.

In contrast, a one-stage approach considers all the individual data in a single analysis, considering the different data sources. Random effects are then used to identify and quantify the different sources of heterogeneity in the data, thus separating variability at the study-level from the individual-level variability.[11–13] One-stage models have more ability to control bias and may provide deeper insights into the data by allowing testing of different assumptions about model structure and adjustment for multiple covariates.[14–16] With increased and more diverse study population and treatment scenarios, it is possible to identify and quantify different predictors of the variability in a more robust way. However, this is conditioned on the way the included studies are selected. The selection of studies is paramount, and therefore an appropriate initial search is essential for the analysis.

Having the correct selection of included studies in mind, and with an increased sample size and more diverse study population and larger variability in treatment scenarios obtained when integrating individual patient data from different studies, it is sometimes possible to quantify the extent of associations and covariate effects more robustly than in the individual primary studies. It allows detailed patient-level exploration of treatment exposure in relation to an individual's characteristics, such as age or stage of disease.

INCIDENCE OF INDIVIDUAL PATIENT DATA META ANALYSIS COUPLED WITH PHARMACOKINETIC ANALYSIS OVER TIME

We defined an "individual patient data meta-analysis coupled with a pharmacokinetic analysis" as one applying population PK analysis techniques to a pooled dataset from multiple studies or with data from multiple collaborating research groups, not using an aggregate-data approach.

To explore the incidence of individual data pooled analysis coupled with population PK analysis, and to evaluate the change over time in the publication frequency, we performed a systematic review of the published literature. We searched PubMed on October 15, 2022, for articles published up to October 2022 using the following set of search terms: "pooled" AND "pharmacometric," "pooled" AND "population pharmacokinetic," "individual patient data" AND "pharmacokinetic," "Meta-Analysis" AND "population pharmacokinetic," "individual patient data" AND

"pharmacokinetic," "individual patient data" AND "pharmacometric." Methodological articles, commentaries, or discussion articles regarding IPDMA were excluded. No other restriction on the studies included in the systematic review were implemented.

Our review identified 243 pooled analyses of PK data published up to October 2022. Only 36 (15%) articles were published before 2010, of which only three (1%) were published before 2000 (Figure 1). This increase is probably due to an increased interest and appreciation for data sharing, and correspondingly in doing interstudy analysis and getting the answers those can give.

WHAT RESEARCH QUESTION WILL THE IPDMA ADDRESS AND WHAT SPECIFIC INFORMATION WILL THE IPDMA PROVIDE?

Before performing an IPDMA, the specific research question that will be addressed and expected information to be gained from the analysis should be prespecified in an analysis plan. Possible objectives that can be studied by IPDMA that are coupled with population PK analysis include:

1. Characterization of PK parameters across diverse regions and ethnicities.
2. Characterization of PK parameters in special population, for example, pediatrics, pregnant women, geriatrics, or subpopulations with comorbidities.
3. Quantification of heterogeneity across multiple clinical trials and clinical settings.
4. Identification of risk factors (e.g., covariates such as demographics: e.g., age and weight; medical history: e.g., renal or hepatic impairment and obesity,) or co-medication: (e.g., enzyme or transporter inducers/inhibitors) associated with suboptimal drug exposures and/or overexposure; and
5. Development, evaluation, and validation of dosing recommendations in diverse settings.

HOW TO OBTAIN INDIVIDUAL PATIENT DATA FOR A META-ANALYSIS

To minimize bias in IPDMA, a systematic review should be performed to obtain IPD data for analysis. This approach involves searching all relevant databases, including published and unpublished studies and data sharing repositories and platforms. The search needs to be transparent, systematic, thorough, and typically involves multiple researchers in the screening, review, and selection of the key studies.[9] Another approach to collect data for IPDMA is to establish a relationship and collaboration with other research groups to combine resources to answer a specific research question. A major advantage to such collaborations is that analysis and population PK models could potentially be revised and updated as new data are generated within these collaborations. However, a major drawback to this approach, is that other sources of data that can address the question of interest may not be part of the collaboration leading to potential bias in results of the analysis if these other datasets cannot be accessed, or data agreements prevent different datasets to be integrated.

Overall, to successfully perform an IPDMA, data sharing is critical throughout the research community and must be promoted. Data sharing encourages collaboration and knowledge integration between researchers that can lead to new important findings not addressed with single

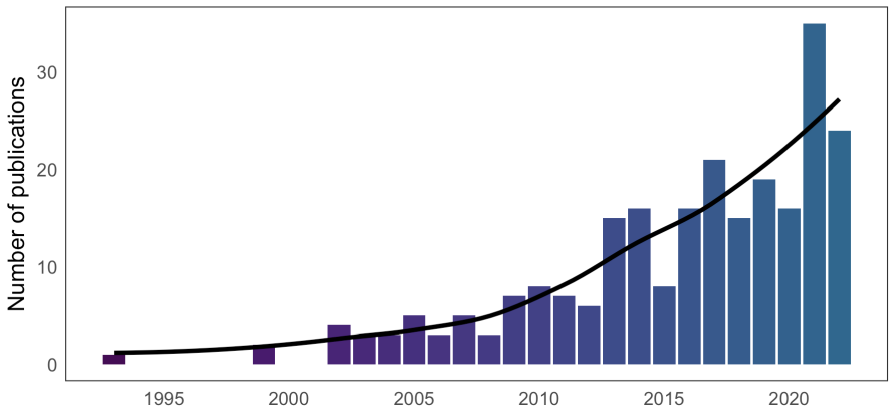

FIGURE 1 Number of publications over time as a result of systematic review through PubMed with search terms "pooled" AND "pharmacometric," "pooled" AND "population pharmacokinetic," "individual patient data" AND "pharmacokinetic," "Meta-Analysis" AND "population pharmacokinetic," "individual patient data" AND "pharmacokinetic," and "individual patient data" AND "pharmacometric."

studies.[17] Furthermore, data sharing is efficient and cost saving because it combines resources to address specific research questions. A successful example of a data sharing platform is that of the Critical Path initiative, which has several datasets containing clinical data available for different indications. For other indications than tuberculosis, the Critical Path may only have access to placebo arm data. A recent analysis based on these available data for drug-sensitive tuberculosis resulted in a risk-stratification algorithm to identify a patient with tuberculosis at higher or lower risk of unfavorable outcome which supports their personalized therapy.[18,19] Other examples include TansCelerate, Yale YODA, Vivli, Supporting Open Access for Researchers initiative (SOAR), or ClinicalStudyDataRequest.com.[20–26]

After the IPDMA strategy has been decided upon, the individual data themselves need to be obtained. In principle, data can be obtained through two different approaches, either contacting the study authors/sponsors directly or accessing the data through a data repository.[27] If data are going to be obtained via study authors, one should (1) clearly define the scope of the project in case additional institutional or ethical clearance is required, (2) come with the author or sponsor to a data transfer agreement to transfer the data, (3) request appropriate data dictionary or metadata on collected variables, (4) find a suitable data transfer method, especially for larger datasets, and (5) consider scheduling a follow-up call after exploring the data to resolve any queries. Direct, concise, friendly requests that minimize additional responsibilities for the study authors, and attempt to establish a personal connection would be more likely to receive a positive response.[28] Moreover, and especially if the results have been published, many journals have the data-sharing requirement to publish, and many companies are willing to share the individual-level data, if a detailed proposal is presented.

Study authors and data curators who generate, manage, and share the data, and provide commentary on findings make efforts that should be recognized. Authorship or acknowledgments on relevant publications should be offered.

After a connection has been made, and when a positive response is received, data sharing agreements should be set up. A good data sharing agreement should describe study rationale, analysis plan, contents exchanged, timing and deadlines, third party data sharing, intellectual property rights, and publication plans, at least.[29]

When any of the above specified steps fail and data cannot be included as a result, the analysis might be biased. The potential bias should be assessed based on the available information from the primary publication and reported. Therefore, the authors recommend including in the publication when reporting the results that certain study or studies' data could not be analyzed.

HOW TO CURATE THE IPDMA DATASET?

Figure 2 visualizes the workflow for an IPDMA. After the research question has been established, systematic

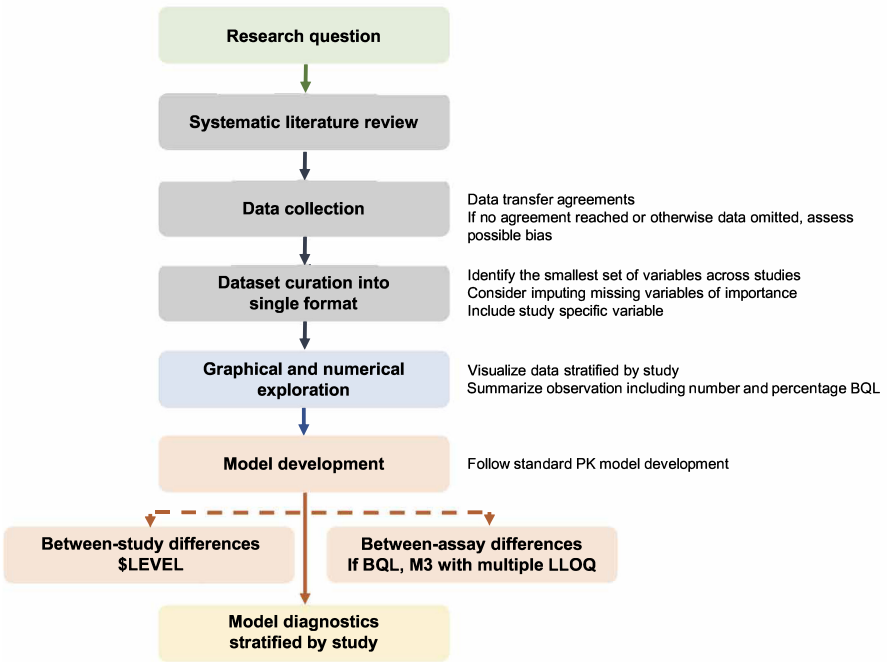

FIGURE 2 Proposed framework to integrate PK knowledge across studies. BQL, below the quantification limit; LLOQ, lower limit of quantification; PK, pharmacokinetic.

literature review has been performed, and the appropriate data have been collected, the next steps are to integrate all data into a single dataset. Curation of this dataset requires handling missing data and difference between, which are described in more detailed below. Graphical and numerical exploration of the integrated data, including stratified by primary study and other relevant variables, will support these decisions in data curation.

Managing the obtained data

Reviewing, reading, and adapting datasets is a time-consuming and resource intensive task. The nature of an IPDMA itself requires that multiple datasets from different sources are integrated together. Because data will be from various sources, it is expected that shared datasets may be on different formats, may contain different information, or even if they do contain the same information, that might be recorded in different ways. It is good practice to review study protocols, clinical trial reports, and publications before and alongside data extraction to understand the dataset, ensure accuracy, and plan on how to harmonize datasets in advance. Collecting individual patient data allows data checking to ensure consistency and quality. Inconsistencies can be resolved through conversations with study stakeholders, and unresolved inconsistencies should be annotated and be described in the publications, reports, and presentations.

A unified database should be created across studies, and at least two independent reviewers should verify it to ensure quality standards and identify any errors. Ensuring quality data with accurate data representation is critical to avoid any modifications of the dataset after it has been created, and during the analysis. Good practice is to reproduce the tables and/or figures from primary publications or reports based on the individual datasets and compare them for consistency. After the unified database has been created, the data should be explored graphically and numerically to assess quality and consistency. For PK analysis, graphical exploration will include at least the following plots: (1) concentration over time across studies, and stratified by dose level and by study, (2) dose-normalized concentration over time to assess dose-nonlinearities, (3) concentration over time compared to concentration over time after dose and/or stratified by occasion to assess interoccasion variability and/or time-dependent elements, and (4) concentration over time stratified by potential covariates relevant to the project (e.g., race/ethnicity and region). In the case of a project involving (active) metabolites, the relationship of parent and metabolite over time and dose should also be explored, whereas a project involving monotherapy compared to combination therapy should explore the concentration-time profiles per regimen compound with its corresponding monotherapy to assess drug–drug interactions. Numerical exploration will include at least (1) number of subjects and number of observations per dose level and per study, (2) number and percentage of subjects per demographics and other relevant covariates, (3) number and percentage of observations below the lower limit of quantification (LLOQ) of the method of each corresponding primary study, and (4) number and percentage of missing variables (dose, concentration, timepoints, and covariates). Additional assessments on data quality assurance and quality control, with a focus on pharmacological analysis, is described elsewhere.[30,31] Overall, typical assessments that apply to single study analysis should also apply to IPDMA.

Dealing with missing data

During data curation, the investigator might identify missing, inaccurate, or unreliable data. The approach for handing such data inconsistencies can substantially impact the interpretation of results. Before conducting an IPDMA, and as part of the dataset building process, the investigator must decide how to deal with such data. The number of occurrences and the reason for each missing data should be considered to establish appropriate methods to handle each missing datapoint. Missing data are typically divided into three categories: missing completely at random, missing at random, and missing not at random.[32] The difference among these three categories is the underlying mechanism causing the data to be missing, which can be non-dependent on any data (observed or unobserved), dependent on the observed data, or dependent on the unobserved data, respectively. The underlying mechanism is usually unknown, but it can really affect the predictability of the model if wrong assumptions are made. If data are not missing because of randomness, but a pattern is causing data to be missing (e.g., missing doses because of nonadherence, missing concentrations, or timepoints because no-show related to treatment), that should be taken into account into the modeling and result interpretation. Irby et al. provided guidance in more detail for dealing with missing clinical and nonclinical data and other data curation issues.[33]

Concentration versus time data

Population PK analyses should be developed from a dataset where all exact dosing times, concentration measurements, and sampling times are known, and IPDMAs should be no exception to this statement. If exact dosing

or sampling timepoints are missing and no other informative variable is available, the nominal timepoints from the protocol should be used. Missing concentrations should preferably not be imputed in the population approach. In addition to missing data, data can also be inconsistent, most commonly in population PK analysis (1) errors in sampling times (e.g., incorrect sampling times or failure to capture actual sample times), and (2) errors in concentration measurements (e.g., wrong units or recorded value). Causes for the latter ones may include errors in the recorded data or problems with the bioanalytical assay. Both measured drug concentrations and recording sampling times are key components of PK studies, and any deviation from the true condition of these values should be identified and adjusted. One additional challenge is that errors in concentration measurements can sometimes be difficult to distinguish from errors in sample times. More information on how to handle these missing data with a special focus on PKs can be found in the tutorial published by Irby et al.[33]

As a general rule, and similarly to a single study population PK dataset, if erroneous time data or concentration data are either identified or suspected, these must be replaced with correct data. If the investigator has access to the correct original data, this should replace the mistake found. In the event of not having access to the correct data or it is unknown, those must be handled appropriately in the analysis, as has been described elsewhere in much more detail.[33,34] In the case of an IPDMA, the complexity increases if missing of exact concentration or time data is not equally distributed between studies, which would show up in the graphical and numerical exploratory analysis. Data from studies with an unequal influence of missing concentration or time data should be interpreted with care, and sensitivity analyses on the corresponding variables should be considered.

Dose data

A critical piece of information needed in any PK analysis, and therefore also in an IPDMA coupled with population PK analysis, is dosing history information. Studies conducted within a general clinical setting or programmatic setting tend to have higher rates of dosing information gaps than controlled clinical trials. Furthermore, many times individual-level dosing histories are not available and the only information available is the planned dosage administration described in the general protocol. In the case of missing data or questionable dose information on the amount of dose, dose time, or even treatment duration as a result from the exploratory analyses, it is important to distinguish between nonadherence (i.e., patient did not take the drug) and a missing dosing record (i.e., patient may or may not have taken the drug). In practice, whether a missing dose was due to nonadherence or a missing dosing record, can be difficult to distinguish. All information from study protocols, clinical trial reports, and publications must be reviewed, and clinical trials, sponsors, and researchers of original studies should be contacted to attempt to resolve any missingness in the dosing histories. If missingness can be resolved, then, nonadherence, which impacts the PK analysis,[35] can be handled by simply not including drug administration at the time of the missing data. However, for a missing dosing record, we do not know whether a patient took a dose or not and different approaches to control missing information and to assess reliability can be explored.[36] Given the importance of this type of data, the choice of method for handling missingness in dosing histories can heavily impact the quality and output of the PK data analysis. In this case, ignoring all missing records is never acceptable, because observed drug concentrations are a direct result of the administration, and influenced by drug distribution and elimination. Methods for handling mistaken or missing dosing information have been extensively reviewed elsewhere.[36–42] All the methods adopt one or more assumptions that will inevitably impact the results of the analysis. Assumptions for the various methods of handling missing data should always be stated in the analysis report and should be evaluated with sensitivity analyses.

Covariates

Within the population approach, the use of covariates to explain interindividual variability is important in understanding the pharmacology and supporting decisions in drug development and clinical practice toward individualized medicine. However, it is a common scenario to find when integrating datasets that studies may not record the same covariate information (different definitions of the same covariates, different cutoffs, or even studies not including covariates that other studies have), covariate information is missing for subsets of patients within a study, or different assays are used to measure covariate information. As with other data types (dose records, outcomes, and drug levels), missing or erroneous covariate data can really impact the results of the analysis.

There are different ways for dealing with missing covariates, but the most common strategies include: elimination of the entire patient from the dataset; imputing the missing value to a reference value (mean, median, mode for continuous; and most common value for categorical); and joint or mixture modeling to estimate the

covariate value for continuous or categorical covariates, respectively.[32,33]

The choice of method to handle the missing data is also affected by the extent of missing information on the dataset.[43] The fraction of missing information depends on both the quantity of missing data and the importance of the missing data itself. This means that covariates that are more important for the performance of the analysis (e.g., body weight) require more advanced methods of imputation to avoid bias in parameter estimates, whereas if the missing covariate is of less importance (e.g., glomerular filtration rate for a drug that is not renally cleared), the method of imputation would be less important as well, as long as it is correct.[32]

Handling interassay bias

Ideally, assays for measuring plasma drug concentrations should be cross validated, meaning that the measurements obtained from the different assays could be interchanged. Still, in the case of IPDMAs, the interchangeability of results from different laboratories assays should be evaluated. Exploratory analysis should reveal analytical discrepancies, especially graphical concentration over time stratified by dose, or dose-normalized concentration in case studies do not have overlapping dose levels, as well as numerical metrices about median and variability differences between studies for the same doses. Additionally, assay difference between studies could impact the estimation of some PK parameters, when using a one-stage analysis (e.g., clearance value in some low doses). Analysis-wise, the potential impact of the variability between assays can be taken into account in the analysis by including a different residual error models for each assay.[44] To perform this type of analysis, a variable in the dataset identifying the assay methodology must be included and used as a flag to specify the residual error model. This approach can help reduce the unexplained residual variability, therefore reducing bias in parameter estimates, and improving model predictions. Alternatively, bias between assays can be characterized by estimating a covariate effect of the assay on the relevant parameters. If bias is evident, then they should be handled appropriately.[44]

HOW TO DO THE IPDMA PK ANALYSIS

Based on the curated and finalized dataset and informed by the exploratory graphical and numerical analysis, the PK model can be developed. PK model development will follow the standard model development strategy, with the additional elements of accounting for data clustering by the different studies, and accounting for observations below different quantification limits for different assays. Both will be described here in detail.

When integrating all the datasets it is very important to maintain clustering on the data. Individual data allows straightforward clustering of individuals for subgroup analysis defined by single or multiple factors. Keeping the study source of the data, and even the site or sites at which the original study took place, are essential.

The population approach utilizes stochastic elements in addition to fixed elements to characterize variability within the population. In addition to interindividual variability (IIV) and interoccasion variability (IOV), pooled analyses and IPDMAs will describe an additional level of variability considering interstudy and/or intersite variability. These random effects should be incorporated hierarchically, reflecting their nature of IIV and IOV nested within the intersite and/or interstudy variability. Through this hierarchical structure, the variance of the IIV and/or IOV is scaled by site or study, based on the assumption interstudy and/or intersite variability would only be observed in parameters that already have IIV and/or IOV.

Modeling hierarchical levels of variability is possible in various nonlinear mixed effects modeling software packages. Here, we exemplify coding using NONMEM, in which the $LEVEL record and functionality should be used.[44,45] The dataset must contain, therefore, a column identifying the study and/or site (SID, after study ID, or add columns as needed based on the information available), and individuals from that study and/or site would therefore share the same variance for the interstudy or intersite variability. An example dataset for four individuals belonging to two sites, and the code can be seen below:

```
ID TIME DV SID BLOQ LLOQ
1 2 5 1 0 0.1
1 6 15 1 0 0.1
2 2 4 1 0 0.1
2 6 13 1 0 0.1
3 2 6 2 0 0.5
3 6 17 2 0 0.5
4 2 5 2 0 0.5
4 6 16 2 0 0.5
$LEVEL
SID = (3 [1], 4 [2])
(...)
$PK
TVCL = THETA(1)
CL = TVCL * EXP(ETA(1) + ETA(3))
(...)
$OMEGA
```

```
0.09 ;IIV CL
0.09 ;IIV V
0.09 ;interstudy variability CL
0.09 ;interstudy variability V
```

In this case, ETA(1) representing IIV in clearance (CL) is nested within ETA(3) representing study-level variability associated to a parameter in the model, for example, CL. In a similar way, ETA(2) is nested within ETA(4) but for a different parameter, for example, volume of distribution (V). SID is the name of the outer level variable (e.g., SID = study ID) listed in the $INPUT on the NONMEM control stream (i.e., the name of the column of the dataset).

More than one additional level of clustering can be included, as is described on the NONMEM user manual, when describing the $LEVEL functionality.[44]

The inclusion of the different levels of variability systematically allows for description of differences in variance between studies and sites, without assuming parameters show equal variability across studies or sites. It can also help reduce the unexplained variability when analyzing data from individuals from different original datasets. Additional nested levels of random effects may be added, following reasonable rationale, and including parsimonious consideration.

Dealing with data below the limit of quantification

Data below the limit of quantification (BLOQ) are often found during population PK analyses. Beal et al.[46] described seven methods for handling BLOQ data in 2001, several of which have been adopted as standards in modeling BLOQ data ever since. Several researchers have evaluated these approaches.[33,47–52] The selection of the appropriate method to handle BLOQ data is a very important point for consideration during model development.

In general, in all PK analyses, when the proportion of BLOQ is low compared with the rest of the data (≤5%), ignoring such observations should not affect the results, whereas simplifying the procedure. However, if the percentage of BLOQ exceeds 5%, the M3 method has been accepted as the default method for generating the least biased results.[33] For an analysis with multiple studies, this percentage holds for each individual study, as the percentage BLOQ across studies can be <5%, whereas informative studies, for example, lower dose levels have larger proportions of BLOQ datapoints that warrant the use of the M3 method to prevent bias across the IPDMA. In this example, not using the M3 method would indeed bias the PK findings against the lower dose level studies.

Given that data come from different studies in an IPDMA, the data will likely be analyzed in different laboratories and on different assays. Therefore, the limit of quantification may vary between studies, and the percentage of data BLOQ might vary as well. The different LLOQs used in each study should be reported and maintained in the IPDMA. In this way, the analysis should not be affected by the difference in assay sensitivities. If the numerical exploratory analysis results in larger proportions BLOQ data, the M3 method should be applied. This holds also if the overall proportion of BLOQ is below 5%, but individual studies have proportions above 5%, to limit bias for these specific studies.

Different LLOQs can be incorporated by including an LLOQ column in the dataset (see above), and referring to that in the $ERROR section of the NONMEM code[51]:

```
$ERROR
SIG1 = THETA(1) ; additive residual error
SIG2 = THETA(2) ; proportional residual error
IF(BQL.EQ.1) THEN
W = SQRT(SIG1*SIG1 + F*F*SIG2*SIG2)  ;  combined
RUV model to illustrate
DUM = (LLOQ – F)/W ; LLOQ specific to each study
from dataset
CUMD = PHI(DUM)
F_FLAG = 1
Y = CUMD
ENDIF
```

REPORTING INDIVIDUAL PATIENT DATA META-ANALYSES

Even though the number of IPDMA studies in the context of population PK analysis is increasing, there is still no clear reporting of the methodology and results being found. Like all good research, these types of studies should be protocol driven, and should always be conducted with a clear and prespecified objective, or, as it has been referred to before in this tutorial, with a clear and prespecified relevant clinical question to answer in mind.

The included studies in the IPDMA should also be clearly reported following the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) or Meta-analysis Of Observational Studies in Epidemiology (MOOSE) for randomized controlled trials or observational studies, respectively.

There is additional information that should be reported to supplement the above-mentioned guidelines. That includes whether ethic approval was necessary, and, if so, granted, and if there is protocol for the project where it can be found.

In this type of studies, it is also very important to report why and how the IPDMA was done. Therefore, the research question of interest needs to be clearly stated and answered in the report. In addition, information on the methods and approaches used in the IPDMA should be described. It should include: (1) the process used to identify the relevant studies included in the analysis and how original authors were contacted, (2) the number of authors initially approached for data, (3) the number of authors that did not provide individual data and the reasons why, and (4) the number of authors who provide individual patient data and whether all available data was provided, or, if not, why data were omitted.

Focusing on the data that were included on the IPDMA, a good report should include a summary of the number of patients and patients' characteristics within each of the original studies, along with an overall overview of all the data together, and how many patients per study were included. In the specific case of IPDMA with PK analysis, specific technical details from the individual studies should also be included, such as how many samples were included from every trial, differences in study design (e.g., sampling schedules and doses given), limit of quantification of different assays or percentage of samples BLOQ. A detailed report of the population PK modeling and statistical analysis to obtain the results is also required. Details of any missing data and how that was handled must be also reported.

Suggested information to report include whether the individual participant data results for each study were comparable with the published results, and, if not, why not (e.g., did the IPDMA performed contained updated information on the matter of interest?).

Because the nature of an IPDMA implies that the number of data that you are going to be managing is usually higher to what you would be with an original study, visual explorations and analysis are very important. Data visualization can be understood as the practice of translating information into a visual context, to make data easier for the human brain to understand and pull insights from, and therefore graphical representations of the data are essential tools to comprehensively represent data and raise the readability of the analysis. Input individual data should always be presented, using different stratifications of interest, if applicable (e.g., figures showing the input individual data, visual predictive checks [VPCs], including original data and not only summary statistics). Similarly, figures showing the results would also be needed. Good visual representations of the data and results are always going to boost the reader's interest and are going to make science more accessible to all. Results tailored to the peculiarities of the data that are being analyzed should be shown. If, for instance, the modeler is dealing with different BLOQ levels per study, the diagnostic plots should also reflect that. There is no automated tool, to our knowledge, capable of dealing with multiple LLOQs to generate VPCs to diagnose the model. Therefore, to create them, one should do simulations with the final model and plot the VPCs accordingly, creating a tailored VPC code that reflects the characteristics of the integrated analysis.

Going back to the research question of interest, good figures and visualizations that back up the obtained answer and carry important messages on their own should be included in the report, meaning that the figure itself needs to provide a clear message. If, for example, the project's objective is to provide dosing recommendations in a pediatric population, and the IPDMA found postnatal age as a significant covariate, one wants to include exposure visualizations stratified by that covariate (e.g., boxplots stratified by grouped age values) to highlight how the covariate can be utilized in the dosing recommendation to adjust the dose for a certain age group. This will be more informative than, for example, a VPC stratified by age group, which could be supplementary for the reader to assess the model fit.

It is important to have in mind that a PK IPDMA should follow the good reporting recommendations for PK studies, in addition to specific details that have been mentioned above. These good reporting practices have been published before, and collect guidelines on how PK studies should be reported.[53–55] In addition, a checklist of what to include when reporting IPDMAs is shown in Appendix S1.

WHAT ARE THE ADVANTAGES AND DISADVANTAGES OF A META-ANALYSIS OF INDIVIDUAL PATIENT DATA?

IPDMA in the context of population PK analysis has many potential advantages over analysis of aggregate data or PK analysis using just data from one study. The first advantage is the increased sample size of analysis for the same compound as compared to single-study analysis. Furthermore, IPDMA in the context of population PK analysis have richer data available than the data in single studies, and the power to detect significant covariates affecting model parameters can be higher. This is especially relevant when doing analysis in special populations, because the individual studies tend to enroll small sample sizes in each study, notoriously the case for pediatric PK studies. Therefore, IPDMAs shed more light into the covariate-parameter relationship and may allow more subgroup analyses,

which can be difficult to perform with data from single studies. In addition, the results presented in the original publications can be verified (or not), and consequently, the model assumptions each original publication made can be assessed and the integrated dataset can be used as a validation or models. If the IPDMAs are done appropriately, the results generated from these analyses are more robust than the ones reported in the individual studies. Integrating data can also help reduce bias in population PK analysis. For example, with the large diverse datasets included in IPDMAs, there is more opportunity to the ability to control bias in the analysis and improve precision compared to a PK analysis from single studies, as described in this tutorial. IPDMA also provides an opportunity to improve consistency and explore reasons for inconsistency among different studies. Finally, with the exception of some additional considerations for integrating datasets described in this tutorial, the methodology and software used in IPDMA in the context PK analysis is typically the same as the performing PK analysis of a single study.

The decision to undertake IPDMA coupled with PKs also presents some disadvantages. In general, they are more resource intensive, especially time-consuming because substantial time is required to contact authors, obtain data, prepare datasets, and resolve data inconsistencies. The required time will clearly vary depending on the complexity of the analysis and the number of included studies. Such factors need consideration before embarking on an IPDMA. Obtaining the data itself is a time-consuming step and can inevitably cause project delays. How to contact study stakeholders to start collaborations and maintain those relationships and negotiate data sharing agreements is required for an IPDMA to be successfully done. Broader issues, including data sharing models and platforms, data request review panels, and recognition of primary study investigators, must also be understood prior conducting an IPDMA in an appropriate scientific, ethical, and legal standard.[56–59] In addition, research on the effectiveness of data acquisition techniques,[60] good practices on data formatting, and platform features that could facilitate data sharing are needed. Even when individual patient data are fully available, obstacles may still remain. For instance, previously published reports or trials might be of poor quality. It is possible that the design of the initial study already has intrinsic bias. Often, they may not have recorded the individual variables of interest, having to deal with missing data, or those might be recorded with less granularity than needed, or are reported differently across trials. It is essential to remember that the quality of individual patient data is dependent on the quality of the original studies themselves.

FURTHER RECOMMENDATIONS

The decision to undertake an IPDMA should always be driven by the research question of interest, and it is the investigator's responsibility to assess whether that question can be answered with a simpler analysis. However, in many situations, an IPDMA analyzing PK data from different sources will provide numerous advantages over single-study data analysis, which is one of the reasons why these analyses are increasingly being applied. In the case that only one study is available for a specific compound, well-performed analyses on single studies are always encouraged. In that case, the research question of interest is different, and the methodology of an IPDMA does not apply.

The way individual patient PK analyses are reported should be of the highest quality, in order to live up to the standards that you may want to see in those individual trials. The importance of data visualization and effective reporting of results should never be underestimated.

With respect to published studies[61–67] that have undertaken individual PK data meta-analyses, diversity on the methods used can be observed. There are clear differences on the way the data are obtained, with the majority of studies using pooled analysis with available data in house, or from different selected studies, whereas only few of the reported studies actually perform a literature search to identify available studies to include in their analysis. Another big difference encountered is in the data analysis itself. Accounting for interstudy variability was rare in the reported studies, and often the analysis was done as if a single dataset with numerous individuals was obtained from a single trial. Interstudy heterogeneity is a key element of these types of analyses, and bias could be included if heterogeneity is not accounted for.

In addition, these techniques will gain further importance given the US Food and Drug Administration's (FDA's) efforts on diversity and inclusion in the past few years, which will enrich the diversity of the patients included in the clinical trials.[68] The covariate analysis would be more robust when data in the minority population can be increased as a consequence of pooling the datasets obtained from much diverse clinical trials.

With more data sharing initiatives available, it is important to incorporate standardized dataset formats to facilitate harmonization and integration of datasets, in contrast to handling datasets in very different formats. The study data tabulation model (SDTM) defines a standard structure for clinical trial datasets that are to be submitted as part of a product application to a regulatory authority.[69] This provides a standard for organizing and formatting data that, if taken in, it would be a way to

streamline processes in collection, management, analysis, and reporting data. Implementing SDTM supports data aggregation and warehousing, fosters data mining and reuse, and facilitates data sharing, and data sharing platforms, such as Critical Path already incorporates this.

There are clear trade-offs between analysis complexity and including potential problems on the answers provided, such as bias, but once the decision to undertake these types of analyses is done, they should be done appropriately. Standardized guidelines both for the best approach to use as well as ways to report are needed in this area. Transparency of assumptions and applied rules at study level and analysis level throughout the analysis is something that should be provided and non-negotiable in these analyses.

CONCLUSION

An IPDMA is a powerful tool to analyze PK data across studies. With the increased willingness and possibility to share clinical data, pharmacological researchers will have more opportunities to perform IPDMAs and answer clinical questions that remain unanswered by individual studies on their own. We must be prepared to undertake such projects in a systematic, timely, and accurate manner, leveraging all tools in the modeler's toolbox adequately. This tutorial contributes to performing systematic and standardized IPDMAs, as part of the MID3 framework to integrate knowledge and support informed decision making in drug development.

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ORCID

Rob C. van Wijk https://orcid.org/0000-0001-7247-1360
Belén P. Solans https://orcid.org/0000-0003-4621-5480

REFERENCES

1. Marshall S, Madabushi R, Manolis E, et al. Model-informed drug discovery and development: current industry good practice and regulatory expectations and future perspectives. *CPT Pharmacomet Syst Pharmacol*. 2019;8(2):87-96.
2. Blettner M. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol*. 1999;28(1):1-9.
3. Upreti VV, Venkatakrishnan K. Model-based meta-analysis: optimizing research, development, and utilization of therapeutics using the totality of evidence. *Clin Pharmacol Ther*. 2019;106(5):981-992.
4. Mould D, Upton R. Basic concepts in population modeling, simulation, and model-based drug development. *CPT Pharmacomet Syst Pharmacol*. 2012;1(9):6.
5. Mould D, Upton R. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. *CPT Pharmacomet Syst Pharmacol*. 2013;2(4):38.
6. Byon W, Smith M, Chan P, et al. Establishing best practices and guidance in population modeling: an experience with an internal population pharmacokinetic analysis guidance. *CPT Pharmacomet Syst Pharmacol*. 2013;2(7):51.
7. Keizer R, Karlsson M, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. *CPT Pharmacometrics Syst Pharmacol*. 2013;2(6):e50.
8. Nguyen THT, Mouksassi M, Holford N, et al. Model evaluation of continuous data pharmacometric models: metrics and graphics. *CPT Pharmacomet Syst Pharmacol*. 2017;6(2):87-109.
9. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane, 2022. Available from: https://www.training.cochrane.org/handbook
10. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. *PLoS ONE*. 2012;7(10):e46042.
11. Riley RD, Steyerberg EW. Meta-analysis of a binary outcome using individual participant data and aggregate data. *Res Synth Methods*. 2010;1(1):2-19.
12. Turner RM, Omar RZ, Yang M, Goldstein H, Thompson SG. A multilevel model framework for meta-analysis of clinical trials with binary outcomes. *Stat Med*. 2000;19(24):3417-3432.
13. Simmonds MC, Higginsa JPT, Stewartb LA, Tierneyb JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials*. 2005;2(3):209-217.
14. Fisher DJ, Copas AJ, Tierney JF, Parmar MKB. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. *J Clin Epidemiol*. 2011;64(9):949-967.
15. Smith CT, Williamson PR, Marson AG. Investigating heterogeneity in an individual patient data meta-analysis of time to event outcomes. *Stat Med*. 2005;24(9):1307-1319.
16. Bowden J, Tierney JF, Simmonds M, Copas AJ, Higgins JP. Individual patient data meta-analysis of time-to-event outcomes: one-stage versus two-stage approaches for estimating the hazard ratio under a random effects model. *Res Synth Methods*. 2011;2(3):150-162.
17. Conrado DJ, Karlsson MO, Romero K, Sarr C, Wilkins JJ. Open innovation: towards sharing of data, models and workflows. *Eur J Pharm Sci*. 2017;109:S65-S71.

18. Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med*. 2018;24(11):1708-1715.
19. Imperial MZ, Phillips PPJ, Nahid P, Savic RM. Precision-enhancing risk stratification tools for selecting optimal treatment durations in tuberculosis clinical trials. *Am J Respir Crit Care Med*. 2021;204(9):1086-1096.
20. Forum on Drug Discovery, Development, and Translation, Forum on Neuroscience and Nervous System Disorders, National Cancer Policy Forum, Roundtable on Genomics and Precision Health, Board on Health Sciences Policy, Board on Health Care Services et al. In: Wizemann T, Khandekar E, Hinners J, Shore C, eds. *Reflections on Sharing Clinical Trial Data: Challenges and a Way Forward: Proceedings of a Workshop [Internet]*. National Academies Press; 2020 [cited 2023 Mar 29]. Available from: https://www.nap.edu/catalog/25838
21. Bierer BE, Li R, Barnes M, Sim I. A global, neutral platform for sharing trial data. *N Engl J Med*. 2016;374(25):2411-2413.
22. TransCelerate Biopharma INC. [Internet]. [cited 2023 May 6]. Available from: https://www.transceleratebiopharmainc.com
23. Yale University. The YODA project [Internet]. [cited 2023 May 6]. Available from: https://yoda.yale.edu
24. Vivli. Center for global clinical research data [Internet]. [cited 2023 May 6]. Available from: https://vivli.org
25. Pencina MJ, Louzao DM, McCourt BJ, et al. Supporting open access to clinical trial data for researchers: the Duke Clinical Research Institute–Bristol-Myers Squibb supporting open access to researchers initiative. *Am Heart J*. 2016;172:64-69.
26. Clinical Study Data Request [Internet]. [cited 2023 May 6]. Available from: https://clinicalstudydatarequest.com
27. Polanin JR, Williams RT. Overcoming obstacles in obtaining individual participant data for meta-analysis: obtaining IPD for meta-analysis. *Res Synth Methods*. 2016;7(3):333-341.
28. Wolfe N, Gøtzsche PC, Bero L. Strategies for obtaining unpublished drug trial data: a qualitative interview study. *Syst Rev*. 2013;2(1):31.
29. Tudur Smith C, Hopkins C, Sydes MR, et al. How should individual participant data (IPD) from publicly funded clinical trials be shared? *BMC Med*. 2015;13(1):298.
30. Bonate PL, Strougo A, Desai A, et al. Guidelines for the quality control of population pharmacokinetic–pharmacodynamic analyses: an industry perspective. *AAPS J*. 2012;14(4):749-758.
31. Data Quality Management In Clinical Research [Internet]. [cited 2022 Jul 2]. Available from: https://oir.nih.gov/system/files/media/file/2021-08/data_quality_management-2015_05_15.pdf
32. Johansson ÅM, Karlsson MO. Comparison of methods for handling missing covariate data. *AAPS J*. 2013;15(4):1232-1241.
33. Irby DJ, Ibrahim ME, Dauki AM, et al. Approaches to handling missing or "problematic" pharmacology data: pharmacokinetics. *CPT Pharmacomet Syst Pharmacol*. 2021;10(4):291-308.
34. Thanneer N. Data standards for population pharmacokinetic analysis (POPPK) and non-compartmental analysis (NCA). *Compart AnalAnnual Conference Pharma Software Users Group*. 2018; AA16.
35. Garcia-Cremades M, Solans BP, Strydom N, et al. Emerging therapeutics, technologies, and drug development strategies to address patient nonadherence and improve tuberculosis treatment. *Annu Rev Pharmacol Toxicol*. 2022;62(1):197-210.
36. Nedelman JR. On some "disadvantages" of the population approach. *AAPSJ*. 2005;7:E374-E382.
37. Soy D, Beal S, Sheiner L. Population one-compartment pharmacokinetic analysis with missing dosage data. *Clin Pharmacol Ther*. 2004;76(5):441-451.
38. Kumar VVP, Duffull SB. Methods to account for inaccuracies in the dosing history when performing population pharmacokinetic analysis. *Pharm Res*. 2008;25(12):2740-2749.
39. Gupta P, Hutmacher MM, Frame B, Miller R. An alternative method for population pharmacokinetic data analysis under noncompliance. *J Pharmacokinet Pharmacodyn*. 2008;35(2):219-233.
40. Friberg LE, Isbister GK, Hackett LP, Duffull SB. The population pharmacokinetics of citalopram after deliberate self-poisoning: a Bayesian approach. *J Pharmacokinet Pharmacodyn*. 2005;32(3–4):571-605.
41. Mu S, Ludden TM. Estimation of population pharmacokinetic parameters in the presence of non-compliance. *J Pharmacokinet Pharmacodyn*. 2003;30(1):53-81.
42. Gibiansky L, Gibiansky E, Cosson V, Frey N, Stark FS. Methods to detect non-compliance and reduce its impact on population PK parameter estimates. *J Pharmacokinet Pharmacodyn*. 2014 Jun;41(3):279-289.
43. Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol*. 2013;64(5):402-406.
44. ICON Development Solutions. *NONMEM Users Guide*. ICON Development Solutions; 2006.
45. Bauer RJ. NONMEM tutorial part II: estimation methods and advanced examples. *CPT Pharmacomet Syst Pharmacol*. 2019;8(8):538-556.
46. Beal SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn*. 2001;28(5):481-504.
47. Hing JP, Woolfrey SG, Greenslade D, Wright PMC. Analysis of toxicokinetic data using NONMEM: impact of quantification limit and replacement strategies for censored data. *J Pharmacokinet Pharmacodyn*. 2001;28:465-479.
48. Keizer RJ, Jansen RS, Rosing H, et al. Incorporation of concentration data below the limit of quantification in population pharmacokinetic analyses. *Pharmacol Res Perspect*. 2015;3(2):e000131. doi:10.1002/prp2.131
49. Xu XS, Dunne A, Kimko H, Nandy P, Vermeulen A. Impact of low percentage of data below the quantification limit on parameter estimates of pharmacokinetic models. *J Pharmacokinet Pharmacodyn*. 2011;38(4):423-432.
50. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. *AAPS J*. 2009;11(2):371-380.
51. Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J Pharmacokinet Pharmacodyn*. 2008;35(4):401-421.
52. Duval V, Karlsson MO. Impact of omission or replacement of data below the limit of quantification on parameter estimates in a two-compartment model. *Pharm Res*. 2002;19:1835-1840.
53. Wade JR, Edholm M, Salmonson T. A guide for reporting the results of population pharmacokinetic analyses: a Swedish perspective. *AAPS J*. 2005;7(2):E456-E460.
54. Dykstra K, Mehrotra N, Tornøe CW, et al. Reporting guidelines for population pharmacokinetic analyses. *J Clin Pharmacol*. 2015;55(8):875-887.
55. Kanji S, Hayes M, Ling A, et al. Reporting guidelines for clinical pharmacokinetic studies: the ClinPK statement. *Clin Pharmacokinet*. 2015;54(7):783-795.

56. Berlin JA, Morris S, Rockhold F, Askie L, Ghersi D, Waldstreicher J. Bumps and bridges on the road to responsible sharing of clinical trial data. *Clin Trials*. 2014;11(1):7-12.
57. Huser V, Shmueli-Blumberg D. Data sharing platforms for de-identified data from human clinical trials. *Clin Trials*. 2018;15(4):413-423.
58. Sydes MR, Johnson AL, Meredith SK, Rauchenberger M, South A, Parmar MK. Sharing data from clinical trials: the rationale for a controlled access approach. *Trials*. 2015;16(1):104.
59. Bertagnolli MM, Sartor O, Chabner BA, et al. Advantages of a truly open-access data-sharing model. *N Engl J Med*. 2017;376(12):1178-1181.
60. Veroniki AA, Straus SE, Ashoor H, Stewart LA, Clarke M, Tricco AC. Contacting authors to retrieve individual patient data: study protocol for a randomized controlled trial. *Trials*. 2016;17(1):138.
61. Francis J, Barnes KI, Workman L, et al. An individual participant data population pharmacokinetic meta-analysis of drug-drug interactions between lumefantrine and commonly used antiretroviral treatment. *Antimicrob Agents Chemother*. 2020;64(5):e02394-19.
62. Jacqz-Aigrain E, Leroux S, Thomson AH, et al. Population pharmacokinetic meta-analysis of individual data to design the first randomized efficacy trial of vancomycin in neonates and young infants. *J Antimicrob Chemother*. 2019;74(8):2128-2138.
63. Dolton MJ, D'Argenio DZ. Population-based meta-analysis of roxithromycin pharmacokinetics: dosing implications of saturable absorption and protein binding. *J Antimicrob Chemother*. 2016;72:dkw553.
64. Grassin-Delyle S, Semeraro M, Foissac F, et al. Tranexamic acid through intravenous, intramuscular and oral routes: an individual participant data meta-analysis of pharmacokinetic studies in healthy volunteers. *Fundam Clin Pharmacol*. 2019;33(6):670-678.
65. Ocampo-Pelland AS, Gastonguay MR, Riggs MM. Model-based meta-analysis for comparing vitamin D2 and D3 parent-metabolite pharmacokinetics. *J Pharmacokinet Pharmacodyn*. 2017;44(4):375-388.
66. Zufferey PJ, Lanoiselée J, Graouch B, Vieille B, Delavenne X, Ollier E. Exposure–response relationship of tranexamic acid in cardiac surgery. *Anesthesiology*. 2021;134(2):165-178.
67. Naik H, Zhao Y, Forrestal F, Cleall S, Bockbrader H, Chapel S. Population pharmacokinetics of Vixotrigine in healthy volunteers and subjects with trigeminal neuralgia, painful lumbosacral radiculopathy and erythromelalgia. *Eur J Drug Metab Pharmacokinet*. 2021;46(3):395-404.
68. Food and Drug Administration (FDA). Clinical Trial Diversity fact sheet [Internet]. Clinical trial diversity. [cited 2023 Mar 24]. Available from: https://www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity
69. CDISC Submission Data Standards Team. Study Data Tabulation Model (SDTM) [Internet]. 2021. [cited 2023 Mar 28]. Available from: https://www.cdisc.org/system/files/members/standard/foundational/SDTM_v2.0.pdf

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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