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LEADING ARTICLE

Reporting a Population Pharmacokinetic–Pharmacodynamic Study: A Journal's Perspective

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Abstract The key purpose of performing pharmacometric research is to aid optimization of drug dosing strategies. The statistical techniques required for this research are advanced, which can make interpretation of results difficult to convey to the target audience if they are unfamiliar with pharmacometric concepts. This article provides a basic guide for authors who wish to publish pharmacometric analyses in peer-reviewed journals. This guide is intended to enhance the readability, reproducibility and understanding of the work for a general readership, which may include clinicians, pharmacists and pharmacometricians. Presentation techniques and examples are offered, as well as a checklist of suggested contents for the manuscript.

1 Introduction

An understanding of the time-course of effects of a drug, in particular a high-risk drug, is important to help optimize subject outcomes in the clinical setting. Pharmacometrics can be described broadly as the quantitative science behind the time-course of drug effects. Pharmacometric research is often undertaken in the early stages of a drug's clinical development, with an aim to support approval applications to regulatory bodies, where the manufacturer seeks a 'standard' dosage regimen for the majority of subjects in a select population. Additionally, pharmacometrics can assist with identifying subject-specific factors that may influence the time-course and associated effects of a drug, which can be valuable for informing dosing recommendations for subject subgroups, such as patients with renal impairment or obesity. Thus the key purpose of performing pharmacometric research is to aid optimization of a drug dosing strategy to produce the best possible therapeutic response in individual subjects.

Pharmacometric research requires population pharmacokinetic and/or pharmacokinetic–pharmacodynamic models (i.e. nonlinear mixed-effects models) to be fitted to subject data. These models aim to describe the concentration–time course and associated effect(s) of a drug for both the study population and individual subjects. Although these models can be very useful for achieving study objectives, the advanced statistical concepts they encapsulate can make interpretation of results difficult to convey to a general readership. For instance, a hospital-based clinician will on most occasions have no formal training in pharmacometrics. Basic biostatistics is found in most health science curriculums; however, for those health professionals with no ongoing involvement in clinical trials, an advanced understanding of pharmacometrics cannot be assumed. Thus for pharmacometric research to be comprehensible and hence utilized, it is imperative that authors present their work in a logical, readily interpretable format that can be understood by all subgroups of the target audience.

The objective of this article is to offer authors of pharmacometric research a basic guide/framework for the reporting of their work such that it is appropriate for the general reader (who may be a clinician, pharmacist, statistician or other pharmacometrician) and is suitable for

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publication in a peer-reviewed journal. Presentation techniques with examples are given, which aim to assist authors with enhancing the readability, reproducibility and understanding of their work. A checklist that summarizes this guide is also provided.

2 Presentation of Research

A document that reports a pharmacometric analysis is best presented by following a standard scientific structure, which consists of 'Introduction', 'Methods', 'Results' and 'Discussion/Conclusion' sections. Ensuing recommendations presented by Wade et al. [1], the following sections offer guidance for the contents of each of these sections, with examples demonstrating some approaches that may be used to present pharmacometric material.

2.1 The 'Introduction' Section

The 'Introduction' section describes clearly the motivation for and objective(s) of the pharmacometric research. The motivation for the analysis is pivotal, as the pharmacometric techniques performed will vary depending upon the goal(s) of the analysis. This section might include prior background material about the pharmacokinetics–pharmacodynamics of the drug(s) and should indicate the knowledge gap that the analysis intends to address. To be palatable to a broad readership, the wording of the motivation should be concise and explained in terms that a general reader who is not familiar with the drug or disease/condition can understand (i.e. avoid discipline-specific jargon). If population pharmacokinetic or pharmacokinetic–pharmacodynamic modelling is introduced in this section, it is recommended that the material is presented from a conceptual point of view rather than with mathematical equations, as many readers might have only a passing knowledge of the topic. For instance:

> Population pharmacokinetic models utilize data from all subjects simultaneously to characterize the concentration time-course of a drug for both the study population and individual subjects.

The introduction should conclude with an unambiguous statement of the objective of the study, which relates logically to the motivation. For example:

> The aim of this study was to develop a population pharmacokinetic model for drug X in adults and children with disease Y, that can be used to simulate concentration–time profiles under different dosing strategies to match exposure across subjects of different ages.

2.2 The 'Methods' Section

The 'Methods' section is presented with a clear, concise description of how the study was performed such that the general reader could repeat the study either in reality or via simulation. Essential information in this section includes descriptions of ethics approval, the study population, dosing, the sampling schedule, analytical methods and the pharmacometric/statistical analysis to be undertaken. The following bullet points offer suggestions for the reporting of each of these items:

- *Ethics*: Ethics approval for the study can be stated, such as:

  > The current study was approved by the Z ethics committee and was carried out in concordance with ICH Guidelines for Good Clinical Practice [2].

  If applicable, details of study registration can also be provided.

- *Study Population*: A clear description of the study population is imperative for the reader, since pharmacometric analyses are dependent upon the study population in which they were conducted. Details regarding the study subjects (e.g. adult cancer patients), study location(s) (e.g. hospital, field clinic, etc.), dates when the study took place and inclusion/exclusion criteria are essential for study reproducibility. An example description could be as follows:

  > Adult subjects with disease Y were recruited from hospitals A, B and C from May 2011 to June 2012. Subjects were eligible if … Subjects with … were excluded from the study.

  Additionally, a clear demographics table presented in the 'Results' section can complement this statement (see below). If the subjects were a subgroup of a larger clinical trial, it can be helpful to provide a brief summary of the larger trial, with citations. If data from multiple studies were included in the analysis, a table describing each study may be appropriate to summarize information including subject details, inclusion/exclusion criteria, dosing and sampling schedules (see more below and Table 1). Further, if the analysis is to be performed on a set of data that has been published previously, then the demographics table can be displayed or cited in the 'Methods' section.

- *Dosing:* Dosing regimen information includes the drug(s) administered (including a reference to the patent holder of the drug, and the trademark symbol, if applicable), route of administration, frequency of administration (e.g. twice daily) and the intended target dose for all subjects (which may include details of dose

Table 1 Example study information table providing a summary of clinical trials

Study (study code)	Drug dose and administration (dose, administration method and drug formulation)	Subjects [number of subjects, health status (healthy or patients?), age (e.g. adults, children, neonates, elderly)]	Study description [phase of the trial (if applicable), description of the study objectives]	Sampling design [were the data rich (e.g. >XX samples per subject) or sparse (i.e. 1–XX samples per subject/dose interval)?]
001	XX mg intravenous infusion; XX mg orally as the tablet formulation	12 healthy adults	Phase 1, single-dose study of [DRUG] XX mg to determine oral bioavailability of [DRUG]	Rich sampling, XX samples per subject
002	XX mg orally as the tablet formulation	50 healthy adults	Phase 2, multiple-dose study of [DRUG] XX mg	Rich sampling, XX samples per subject
003	XX mg orally as the tablet formulation	100 adult patients	Randomized controlled trial [etc.]	Rich and sparse sampling, XX samples per subject for sparse sampling, with XX samples from XX subjects in the rich-sampling substudy

DRUG drug name

escalation or reduction). For a randomized controlled trial, the randomization procedure should be described (e.g. treatment/placebo allocation ratio, single- or multi-centre, etc.), as well as all information above for each group. For more on the reporting of randomized controlled trials, see the CONSORT statement (http://www.consort-statement.org). Further, it can be informative to the reader to report how the dosing times were recorded (e.g. diaries, medication event monitoring systems, etc.). For example, the description of the dosing strategy for an open-label randomized study (two groups) could be as follows:

> In this open-label trial, eligible subjects were randomized to receive a single oral dose of drug X® [pharmaceutical company name and location] at either 10 mg/kg or 5 mg/kg. Drugs were administered by study clinicians and nurses, with dosing times recorded in case report forms.

A comprehensive description of the dosing strategy can assist readers to replicate the study (in practice or via simulation) and compare studies of the same drug.

- *Sampling Schedule*: Details of the blood sampling schedule include the scheduled sampling times after a specified administration of the drug (e.g. 1 h after the initial dose) and possibly the volume of the sample. For studies with less stringent sampling designs (e.g. a target number of samples per person but no specific sampling times, or retrospective data collection from hospital records), a summary of the general sampling strategy can greatly assist the reader to understand how subjects were actually sampled. An explanation of a protocol sampling schedule could be as follows:

> Blood samples (X mL) were taken at 0.25, 0.5, 1, 2, 4 and 8 h after drug administration.

If the sampling schedule was determined using quantitative methods (e.g. by simulation–estimation or optimal design), a description of these methods is justified. The length and depth of this description may depend on the focus of the analysis. For instance, if a key objective of the study was to determine an optimal design for the analysis (requiring rigorous evaluation), then it can be helpful for readers to provide an extensive description of the derivation of the design, which may span over both the 'Methods' and 'Results' sections. Alternatively, this description could be placed in an appendix or supplementary file. On the other hand, if the sampling schedule was only partially informed by an optimal design that was not evaluated extensively, and the focus of the study was primarily on modelling, then the description can be shorter and limited to the 'Methods' section.

Regardless of how the sampling schedule was determined, an accurate description is important for reproducibility of the study and can also help readers to assess and critique reported models.

- *Analytical Methods*: Specification of the analytical method used (e.g. liquid chromatography tandem mass spectrometry [LC–MS/MS]) can assist readers who wish to repeat the study to achieve comparable measurements of concentrations and/or effects. The make and model of the equipment used and assay variability can also be helpful to readers, as well as details regarding storage and collection. Further, the lower limit of quantification (LLOQ) for drug concentrations and/or effects should be stated. If applicable, the inter- and intra-day percentage coefficients of variation (%CVs) and LLOQs can be provided. An

example description of the analytical methods is given below:

> Blood samples were analysed using liquid chromatography–tandem mass spectrometry (LC–MS/MS), using the method reported in (cite the relevant reference OR include all details required for reproducibility of results). The lower limit of quantification (LLOQ) was 20 ng/mL.

This information can be helpful to explain any differences in observed concentration/effect variability across studies, as measurement accuracy can vary across analytical methods. Also, reporting the LLOQ can assist readers to assess the simulation properties of a reported model.

- *Pharmacometric Modelling:* This section describes the model-building process in a clear, logical manner. Typically, it includes a description of base model development, which indicates the software package(s) (including version numbers) used for analysis, candidate structural models attempted (e.g. one- and two-compartment models), justification for the candidate models (previously published models, prior knowledge, visual inspection of the data, etc.) and methods for comparing the candidate models. It can also be helpful to provide tables describing the method(s) used for structural model determination, which can be placed in an appendix or supplementary file. Furthermore, for reproducibility of results, it is important to state the assumptions of the distributions of individual model parameters (e.g. lognormal) and the residual error structure (e.g. additive, proportional, etc.), and justification for these specifications (e.g. previously published models, biological plausibility, etc.). If applicable, methods for handling missing data (e.g. drug concentrations below the LLOQ), the accuracy and precision of the assay (e.g. adjustments to the residual error structure) and between-occasion variability (in the case of multiple dosing) should also be described. An example description of the pharmacometric modelling section could be as follows:

> On the basis of visual inspection of the data and a review of the literature, one- and two-compartment models were considered to describe the concentration–time data. Both models assumed lognormal distributions of the individual pharmacokinetic parameters. Data were modelled using a log-transform both sides (LTBS) approach whereby the residual error was incorporated as an additive error on the log scale. Models were compared using the objective function value (OFV), computed as -2 times the log-likelihood. All modelling was performed using software package X version Y [give the manufacturer name and location or cite the relevant reference], using the ABC estimation method.

An unambiguous description of base model development can greatly assist the reader to understand the determination of the structural form of the model, which promotes transparency and can be advantageous for comparing studies of the same drug.

For studies that specify a structural model a priori (i.e. other candidate models are not considered), the choice of the model should be justified on the grounds of biology, drug mechanism, prior literature, etc. Further, if this model is mechanistic in nature, a schematic diagram is recommended and, if possible, the associated mathematics (e.g. sets of differential equations) can be made available in an appendix or supplementary file for the article. Figure 1 displays an example of such a schematic for a two-compartment model with $n = 2$ transit absorption compartments. A justification could be as follows:

> The choice of the model in Fig. 1 was based on a previous study [cite the relevant reference], which consisted of 200 subjects who were sampled intensively.

Providing a concise description of the methods used for evaluation of the derived base model (e.g. observed concentrations/effects versus population and individual predictions, histograms of subject-specific random effects, visual predictive checks [VPCs], etc.) can help readers to comprehend the level of rigour undertaken to assess the fit of the model. For example:

> Standard goodness-of-fit plots were generated during model development and to evaluate the fit of the base model to the data. These included plots of the observed concentrations versus population- and individual-predicted concentrations, plots assessing the conditional and individual weighted residuals and plots of the distributions of estimated subject-specific random effects. A visual predictive check (VPC) was also performed to ensure that simulations from the base model could reproduce the observed data [details of the VPC method can be described here, e.g. percentiles specified, inclusion of prediction bands, etc.].

A more thorough description of the pivotal model-building steps, including a table of models that were considered, could be provided in a supplementary file. Additionally, if standard errors (SEs) were used as part of the evaluation procedure for the base model, it is recommended that the method for obtaining the SEs (e.g. parametric, bootstrap,

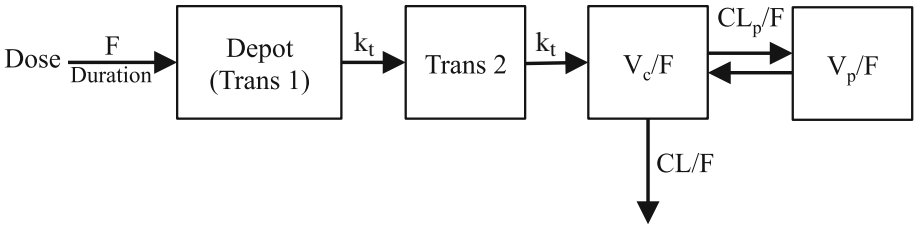

Fig. 1 Example schematic diagram for a two-compartment model with $n = 2$ transit absorption. [Define any abbreviations used in the figure here, e.g. *CL/F* apparent total body clearance, CL_p/F apparent intercompartmental clearance, *Duration* duration of input into the depot compartment, *F* bioavailability, k_t transit rate constant, *Trans 1* transit compartment 1, *Trans 2* transit compartment 2, V_c/F apparent central volume of distribution, V_p/F apparent peripheral volume of distribution]

etc.) is stated. Further, the method for obtaining SEs for the final model should also be stated.

To assist the reader with understanding consideration of potential covariates, it is helpful to list all covariates that were considered for potential inclusion in the model, as well as the parameterization (or candidate parameterizations) of each covariate. Such a description could be as follows:

> Covariates were normalized to the population median values, with continuous covariates modelled using the general equation (Eq. 1):
>
> $$\theta_i = \theta_{pop} \cdot (cov_i/cov_m)^{\theta cov} \quad (1)$$
>
> where θ_i is the individual model-predicted pharmacokinetic parameter (e.g. clearance) for an individual with covariate value cov_i, θ_{pop} represents the population central tendency for the pharmacokinetic parameter θ, cov_m represents the population median value of the covariate and θ_{cov} represents the covariate effect.
>
> A table of example parameterizations of continuous covariate relationships can be found in McLeay et al. [3]. Any covariates that are included in the model a priori should be indicated (with their respective parameterizations) when describing base model development, and should be justified on the grounds of biology, prior literature, etc. Further, in some cases, it may be important to mention covariates that were not considered for the analysis, and provide justification for excluding them from potential inclusion in the model (biological plausibility, etc.). If any covariate parameterizations involve long and/or complicated formulae (e.g. incorporating the glomerular filtration rate into apparent clearance), for ease of reading it is suggested that these parameterizations are reported in an appendix or supplementary file.
>
> A concise yet complete statement describing the determination of which covariates are included in the final model can convince the reader that the final model was developed such that it provided the best description of the variation of the data. This description may include explanations of any screening techniques used (e.g. plotting individual estimates of random effects against potential covariates), methods for comparing models (e.g. the Bayesian information criterion, stepwise selection, etc.) and selection criteria specified (e.g. *p* values for forward and/or backward stepwise selection). An example description could be as follows:
>
> Random effects of parameters of interest were plotted against covariates to identify possible relationships. Covariates with a visually apparent relationship were singly added to the model, i.e. a univariate analysis, to determine if they improved the fit of the model to the data. Covariates in the univariate analysis that were deemed statistically significant on the basis of a change in the objective function value (OFV) of 7.9 ($p < 0.005$) were included in a full covariate model. A backwards elimination process was then performed, where covariates were deleted singly from the full model with the OFV computed from the reduced and full models. Covariates that could be deleted from the full model without an associated increase in the OFV of 10.8 ($p < 0.001$) were sorted according to the OFV, and the covariate with the smallest OFV was removed from the model. This process was repeated until no more covariates could be removed.

Table 2 Example subject demographics table: continuous covariates

Covariate	N[a]	Mean	SD	CV	Median	Range[b]
Age (years)	20	36.9	10.7	0.290	35.4	21.4–61.1
Weight (kg)	20	78.0	15.0	0.193	79.7	50.0–120
CL_{CR} (mL/min)	18	121	5.63	0.047	121	112–133

Define any footnotes and abbreviations here, e.g. CL_{CR} creatinine clearance, *CV* coefficient of variation, *SD* standard deviation

[a] Sometimes some covariates are not available for all subjects. It is therefore useful to include the number of subjects from which the summary statistics were derived

[b] If space allows, consider inclusion of percentiles (e.g. the 10th–90th percentile range) or quartiles

Table 3 Example subject demographics table: categorical covariates

Covariate	Value
Sex [*n* (%)]	
Male	11 (55)
Female	9 (45)
Race [*n* (%)]	
White	14 (70)
African American	4 (20)
Asian	2 (10)

Lastly, it is recommended that final model diagnostic/evaluation procedures are declared, and any procedures used that were not part of the base model development should be stated.

To elaborate on diagnostic/evaluation procedures, it is recommended that descriptions (and presentation) of these procedures be restricted to those that are relevant to the purpose of the derived model, as suggested by the European Medicines Agency (EMA) [4] and Brendel et al. [5]. For instance, if the derived model is to be used for simulation purposes, the simulation characteristics of the model must be presented. On the other hand, if the derived model is to be used to determine individual exposure, the presentation of non-biased individual predictions may be all that is required. Presentation of model evaluation procedures that are not entirely necessary for the purpose of the derived model can make for a long read and may distract the reader from the overall objective of the analysis.

Furthermore, from a pragmatic perspective, the information above regarding the reporting of each highlighted item in the 'Methods' section (ethics, study population, etc.) can be structured in several ways. Each item could be presented as a separate subsection or combined into themed paragraphs, depending on how much explanation is required. For example, information on ethics approval, the study population, dosing, blood sampling and the analytical method could be presented in two or three paragraphs, and the rest of the 'Methods' section could be devoted to describing the modelling.

2.3 The 'Results' Section

The 'Results' section is devoted to displaying the results of the analysis specified in the 'Methods' section. It is essential to begin with the number of subjects and concentration/effect observations used in the analysis, as well as the median, minimum and maximum number of observations per subject. A table of summary statistics of subject demographics and clinical variables can provide readers with a concise description of the subjects included in the study. The table can be read easily if the full names of the demographic and clinical variables are used (i.e. not abbreviations), but if abbreviations are necessary they should be explained in a footnote. Provide units of measurement for all clinical and demographic variables.

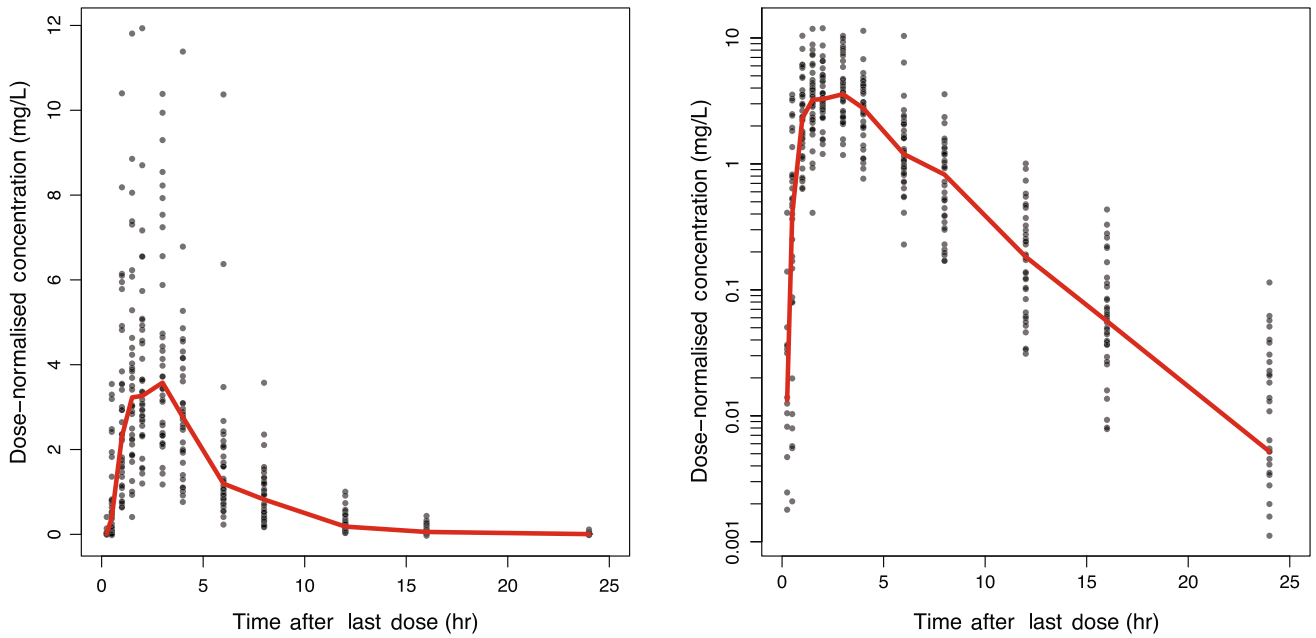

Fig. 2 Example of a concentration–time plot of data used for a population pharmacokinetic analysis. [Define anything relevant here, e.g. the *red solid lines* display Loess smooth lines, the *circles* represent the observed data and *darker colouring of the circles* indicates multiple/overlapping observations]

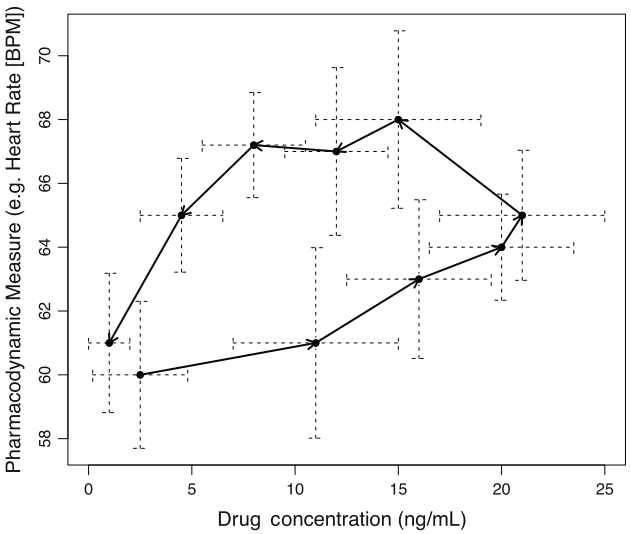

Fig. 3 Example of an effect versus concentration plot of data used for a population pharmacokinetic–pharmacodynamic analysis. [Define anything relevant here, e.g. the *black lines* represent the mean pharmacodynamic change from baseline against the drug concentration, with *arrows* indicating the direction of time, the *dashed vertical lines with error bars* represent the standard deviations of the mean pharmacodynamic value changes from baseline and the *dashed horizontal lines with error bars* represent the standard deviations of the drug concentrations. *BPM* beats per minute]

Table 4 Example table describing univariate covariate analysis

Covariate	OFV	ΔOFV	Covariate effect	Included in multivariate analysis
Base model	72.483			
Weight on CL/F[a]	30.745	41.738	0.656	Yes
Weight on V_c/F[a]	43.020	29.463	0.670	Yes
Effect of solution formulation on F[b]	47.989	24.494	1.32	Yes
Effect of Black race on CL/F[c]	71.322	1.161	1.08	No

CL/F apparent total body clearance, *F* bioavailability, *OFV* objective function value (presented to three decimal places), *ΔOFV* difference in OFV from base model, V_c/F apparent central volume of distribution

[a] Estimated exponent on weight, i.e. the covariate effect (θ_{cov}) in Eq. 1, centred around the population median presented in Table 2 or the fractional shift from the reference group

[b] Compared with the tablet formulation

[c] Compared with subjects of White race

Summaries of continuous variables can include the number of observations, mean, standard deviation, median and range, with the latter four summaries being reported according to journal requirements (e.g. to three significant digits). Percentages of categorical variables (e.g. male/female, healthy weight/overweight/obese, etc.) should indicate clearly what category the percentage refers to (e.g. the percentage of males), and the number of subjects that the percentage is based on should also be displayed. Examples are provided in Tables 2 and 3. If the data are from multiple studies, consider presenting demographics by study (e.g. to match Table 1) in addition to overall demographics. Furthermore, it is important to highlight any protocol deviations (e.g. with respect to dose timing, sampling times, dropouts, etc.) at the beginning of the 'Results' section. The number of concentration/effect observations below the LLOQ should also be stated. This information can assist the reader to understand differences in subject/observation numbers between the demographics table and the study design description in the 'Methods' section.

Table 5 Example table of parameter estimates for the final covariate model

Parameter	Estimated value [%RSE]	BSV, as %CV [%RSE]
CL/F (L/h)	32.1 [8.9]	44.1 [17.2]
Effect of weight[a]	0.64 [2.8]	
V_c/F (L)	112 [10.2]	52.6 [20.9]
Effect of weight[a]	0.67 [13.2]	
CL_p/F (L/h)	45.3 [9.3]	60.5 [23.5]
V_p/F (L)	298 [13.7]	56.4 [22.9]
t_{lag} (h)	0.21 [0.2]	18.0 [24.1]
k_a (h^{-1})	0.98 [15.1]	
Correlation between CL/F and V_c/F (R^2)	0.61	
Proportional residual unexplained variability	0.33 [21.0]	

BSV between-subject variability, *CL/F* apparent total body clearance, CL_p/F apparent intercompartmental clearance, *%CV* percentage coefficient of variation, *F* bioavailability, k_a absorption rate constant, *%RSE* percentage relative standard error, t_{lag} absorption lag time, V_c/F apparent central volume of distribution, V_p/F apparent peripheral volume of distribution

[a] No units [refer to the equation in the 'Methods' section where parameterization of covariates was defined, i.e. Eq. 1)]

Further, if the derived model is to be used for simulation, it is also recommended that the relationships among these clinical/demographic variables are reported, either in the table or in an appendix or supplementary file. This may include covariances between continuous variables (e.g. height and weight for each sex), two-by-two tables of categorical variables (e.g. sex and disease status) or results of regression analyses. This information is essential for readers interested in simulating subjects from the reported study population.

To assist readers to understand choices for candidate structural models and specifications for between-subject and residual variability, it is strongly recommended that a plot of drug concentrations versus time in all subjects is

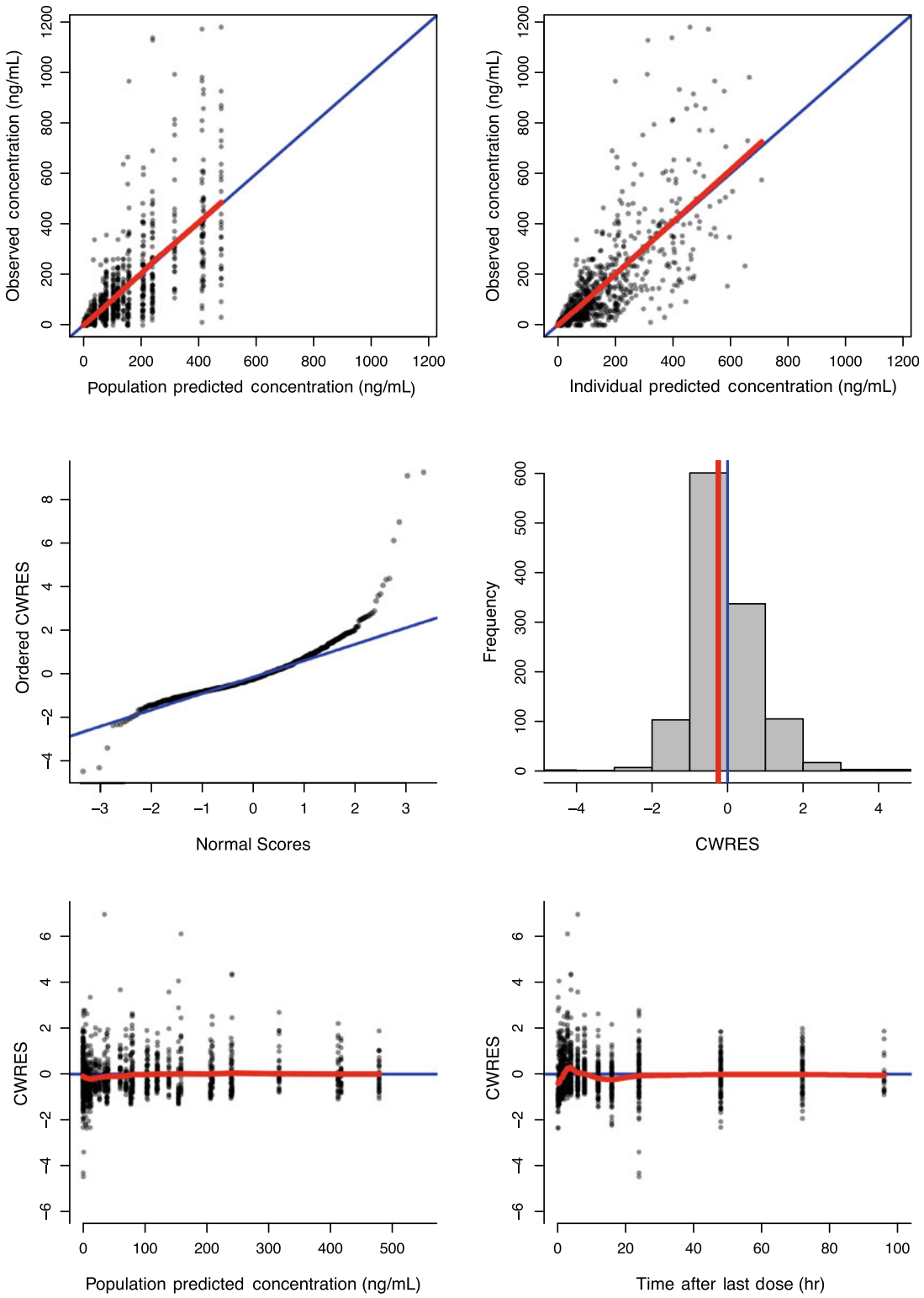

Fig. 4 Example of a figure displaying diagnostic plots. [Define anything relevant here, e.g. the *red lines* display the trend of the data, the *blue lines* indicate the expected trends, the *black circles* represent the observed data and *darker colouring of the circles* indicates multiple/overlapping observations. *CWRES* conditional weighted residuals]

displayed, on a normal and/or log scale as appropriate. Also consider whether the data would be more informative if normalized on the *y*- or *x*-axis (e.g. dose-normalized concentrations, if the pharmacokinetics are linear) or time normalized (i.e. time since last dose rather than actual time if multiple doses), respectively. The plot(s) should indicate the units of the drug concentration (e.g. ng/mL) and time (e.g. hours). A brief summary of the plot(s) in the text can further assist readers with an initial assessment of the raw data. If the study is investigating a pharmacokinetic–pharmacodynamic relationship, a plot of drug effects versus concentrations should also be presented, again indicating the units of measurement. Figure 2 shows an example plot of hypothetical drug concentrations versus time in both the original and log scale, and Fig. 3 displays a hypothetical effect versus concentration (across time) plot. Example descriptions of Figs. 2 and 3 could be:

> It can be seen in Fig. 2 that the median concentration–time profile indicated a mono-exponential decay following absorption, with the maximum (peak) concentration occurring approximately 3 h post-dose. The hysteresis loop in Fig. 3 provides support for considering an effect-site compartment or turnover model to describe the delay in the pharmacodynamic effect.

If subgroups are displayed in any of the plots, they should be indicated by different symbols and/or colours, and a legend should be included. To conserve space, these plots could also include the derived typical profile from the final model.

The results of the model-building process described in the 'Methods' section can be summarized briefly. For example, this can be encapsulated in a table (or a small number of tables), including the results from the best base model, univariate covariate analysis (Table 4), covariate selection (pivotal steps) and the final model, along with succinct, supportive descriptions in the text. Relevant model evaluation/diagnostic plots (for base and final models) should be displayed in close proximity to these tables. Furthermore, a schematic of the final structural model can help readers visualize how the model characterizes drug absorption, distribution and elimination, and should be included if at all possible, especially for mechanistic models (e.g. Fig. 1).

All final model parameter estimates should be listed in a table. If model parameters are not provided in an article, the model is useless to others. Confidence intervals or percentage relative standard errors should also be reported, as they indicate the precision of parameter estimates. For easy reading, it is helpful for all model parameters in the table to have meaningful names that indicate clearly what the parameter represents (e.g. V_c/F for the apparent volume

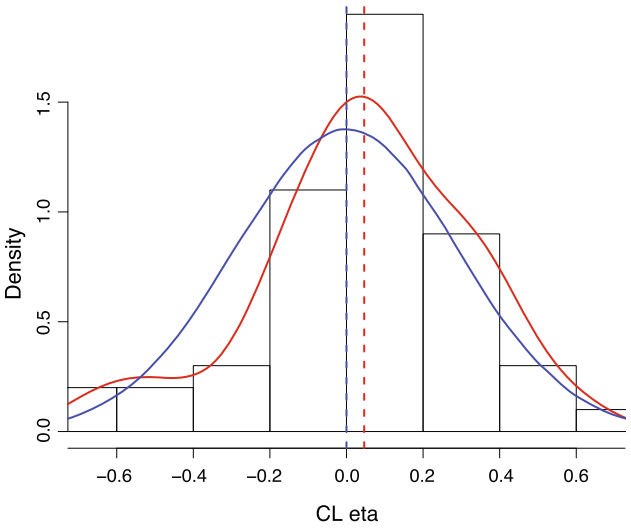

Fig. 5 Example of a figure displaying a plot of the distribution of estimated random effects for a pharmacokinetic parameter. [Define anything relevant here, e.g. the *solid red line* shows the trend of the data, *the blue line* shows the expected trend, the *dashed red line* shows the mean of the data and the *dashed blue line* shows the expected mean of zero. *CL* apparent total body clearance]

of distribution in the central compartment). These names can be further explained in a footnote and/or in the text describing the final model. Software-specific parameter names, such as those used in NONMEM® [6], should be avoided. If covariate effects are included in the final model, it can be helpful to readers if the parameterization is provided in the table (or otherwise if equations presented in the 'Methods' section are referred to). For between-subject and between-occasion variability parameters, it should be stated whether they are expressed as %CVs or variances. For covariance parameters, it should be stated whether they are reported as covariances or as correlation coefficients. Residual variability parameters should be clearly identified as additive, proportional, etc., and it should be stated whether they are expressed as variances or standard deviations. Table 5 displays an example of a table reporting parameter estimates for a final population pharmacokinetic model.

Lastly, in regard to presentation of model diagnostic/evaluation procedures, effort should be taken to conserve space on the page, which can be achieved by grouping several graphs of a similar theme into a single figure. For example, one could display a set of diagnostic plots (Fig. 4), distribution of random effects (Fig. 5) or other diagnostics such as a VPC (Fig. 6). Figures should always be accompanied by a brief description and interpretation to assist readers with their meaning and purpose. Note that consideration should be given to the presentation of the data—for example, a VPC (Fig. 6a) may be more informative presented on a non-log scale (Fig. 6b), with the

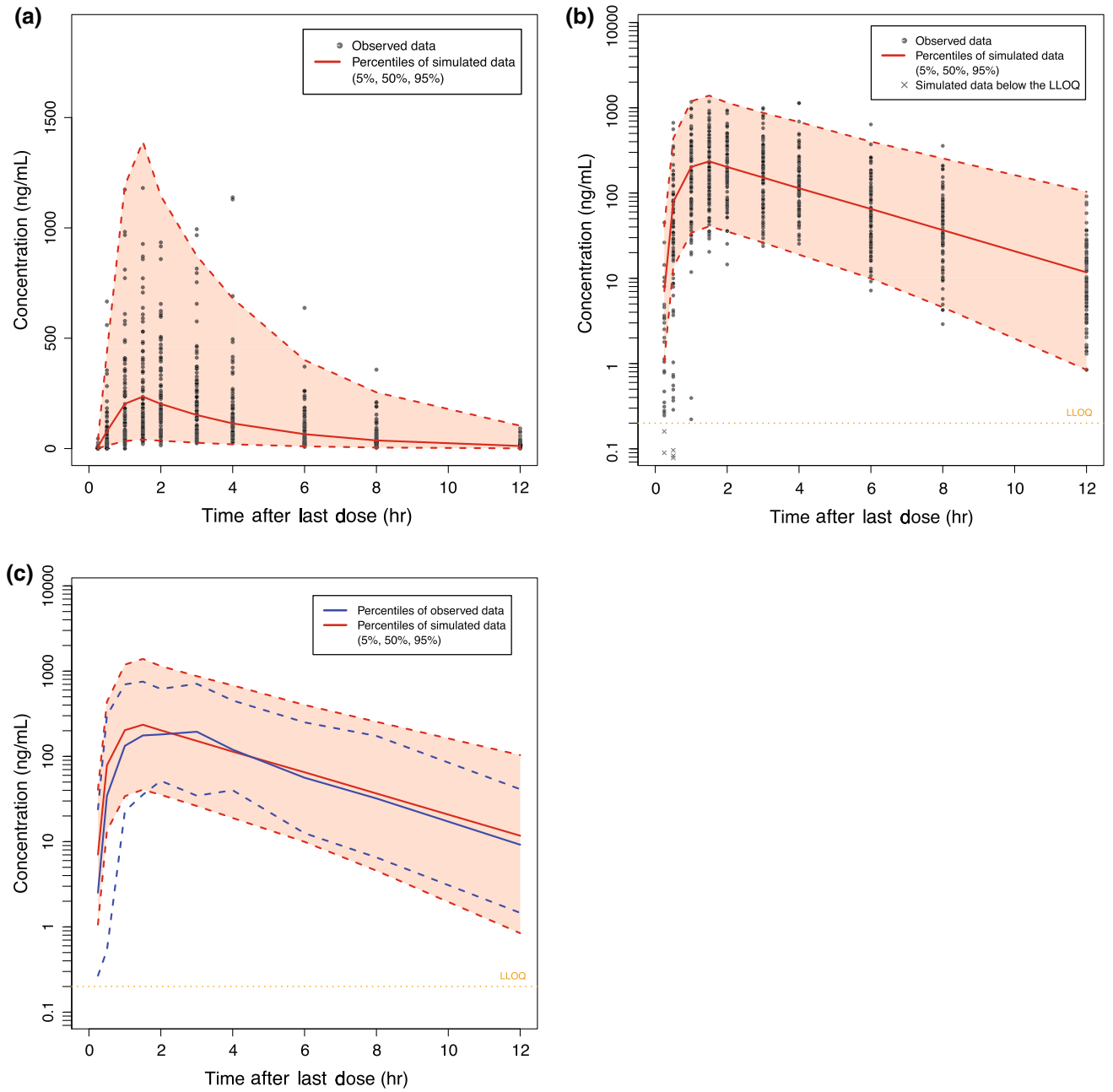

Fig. 6 Example of a figure displaying visual predictive checks (VPCs). [Define anything relevant here and/or include a legend, e.g. the data were binned according to the time after the last dose. *LLOQ* lower limit of quantification]

addition of a second plot with only overlaid percentiles when the data are densely overlapping (Fig. 6c). Example descriptions of Figs. 4, 5 and 6 could be:

> The plots displaying observed versus population- and individual-predicted values in Fig. 4 show a trend consistent with the line of unity; however, variability in the observed values increased with higher predicted concentrations. The distribution of the conditional weighted residuals (CWRES) closely resembled a normal distribution and was symmetrically distributed on zero across population-predicted values and actual time after the last dose. These plots therefore suggest that the model fitted the data adequately at the population and individual levels.
>
> Figure 5 shows that the distribution of random effects (etas) for clearance (CL) was approximately normal and centred on zero, which is consistent with the model assumptions.
>
> Figure 6c shows that the model described the observed data well with no systematic bias, although

Table 6 Checklist of suggested contents for the 'Introduction', 'Methods', 'Results' and 'Discussion/Conclusion' sections of an article reporting a pharmacometric analysis

Section	Suggested contents
Introduction	Motivation for and objective(s) of the pharmacometric research
Methods	Sufficient information for the general reader to repeat the study: • Ethics approval • Study population • Dosing • Sampling schedule • Analytical methods and lower limit of quantification • Pharmacokinetic or pharmacokinetic–pharmacodynamic modelling strategy: – Candidate structural models – Distribution of individual model parameters – Residual error structure – Methods for handling missing data – Methods for base model determination – Methods for base model evaluation – Covariate analysis strategy – Methods for final model evaluation – Software package(s) used for the analysis – Estimation method(s) used
Results	Presentation of analyses described in the methods: • Numbers of individuals and observations included in the analysis • Table of patient demographic and clinical variables • Plot of concentrations versus time and/or effects versus concentrations • Summary of the model-building process and the derived final model • Schematic of the final model • Table of the final model parameters • Final model evaluation plots
Discussion	Highlight what the study achieved, implications of the work, suggestions for future work and limitations of the study
Conclusion	Briefly answer questions posed by the objectives

variability in concentrations was slightly overpredicted.

2.4 The 'Discussion' and 'Conclusion' Sections

The purpose of the 'Discussion' section is to provide the reader with a summary of what the study achieved, the implications of the work and suggestions for future work. Specifically, key findings should be summarized, which can include how well the model described the variation in the observed data and if the model fulfilled its intended purpose. References to previous work can be made, with emphasis on how the current study sheds new light on the topic addressed. Clinical implications of the research—particularly implications for clinical practice in pharmacotherapy—should be stated, such as how the findings can inform dosing schedules. The limitations of the study should be clearly noted, which is important for general readers wishing to critique the study and compare it with prior literature.

The 'Conclusion' section should be brief and answer the questions posed by the objectives. For instance, if the objective of the study was to develop a population pharmacokinetic model for drug X in adults and children with disease Y, that can be used to simulate concentration–time profiles under different dosing strategies (i.e. the example objective in the 'Introduction' section), then the 'Conclusion' section should address these points only.

3 A Checklist for Authors

Table 6 displays a checklist for reporting a pharmacometric study, which summarizes the suggestions made in the previous sections.

4 Concluding Remarks

This article offers a basic guide to authors of pharmacometric research on how they might report their work in a manner that is appropriate for a general readership, which may include clinicians, pharmacists and other pharmacometricians.

It is important to reiterate that the focus of this article is on the reporting of pharmacometric research, and not on the promotion of any particular methodologies. Therefore the examples provided in this article should be viewed from a reporting/presentation perspective only, and not from a methodological perspective. For recent educational articles on basic pharmacometric techniques and practices, see references [7–11]. Furthermore, it is recommended that readers seek published manuscripts of pharmacometric (or related) research in their fields of interest for further examples of currently used methodologies.

Additionally, it can be helpful for authors of pharmacometric research to develop skills in critical appraisal of published work, as this can provide further insight into the reporting of their research. For information on basic critical appraisal concepts, see references [12, 13]. Lastly, the current article can be read in conjunction with several other articles that offer guidance for scientific writing (see references [14–19] for some recent examples), as well as articles that propose guidelines for the reporting of different types of trials [20–24].

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References

1. Wade JR, Edholm M, Salmonson T. A guide for reporting the results of population pharmacokinetic analyses: a Swedish perspective. AAPS J. 2005;7:456–60.
2. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). http://www.ich.org.
3. McLeay SC, Morrish GA, Kirkpatrick CMJ, Green B. The relationship between drug clearance and body size: systematic review and meta-analysis of the literature published from 2000 to 2007. Clin Pharmacokinet. 2012;51(5):319–30.
4. Committee for Medicinal Products for Human Use, European Medicines Agency. Draft guideline on reporting the results of population pharmacokinetic analyses [online]. http://www.emea.eu.int/pdfs/human/ewp/18599006en.pdf. Accessed 28 Dec 2006.
5. Brendel K, Dartois C, Comets E, Lemenuel-Diot A, Laveille C, Tranchand B, Girard P, Laffont CM, Mentré F. Are population pharmacokinetic and/or pharmacodynamics models adequately evaluated? Clin Pharmacokinet. 2007;46(3):221–34.
6. Beal SL, Boeckmann AJ, Sheiner LB. NONMEM users guide. Parts I–VIII ICON Development Solutions.
7. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol. 2012;1:e6. doi:10.1038/psp.2012.4.
8. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development—part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2013;2:e38. doi:10.1038/psp.2013.14.
9. Holford N. A time to event tutorial for pharmacometricians. CPT Pharmacometrics Syst Pharmacol. 2013;2:e43. doi:10.1038/psp.2013.18.
10. Byon W, Smith MK, Chan P, Tortorici MA, Riley S, Dai H, Dong J, Ruiz-Garcia A, Sweeney K, Cronenberger C. Establishing best practices and guidance in population modeling: an experience with an internal population pharmacokinetic analysis guidance. CPT Pharmacometrics Syst Pharmacol. 2013;2:e51. doi:10.1038/psp.2013.26.
11. Karlsson MO, Mentre F. Best practices in population modeling should always be evolving. CPT Pharmacometrics Syst Pharmacol. 2013;2:e52. doi:10.1038/psp.2013.37.
12. Young JM, Solomon MJ. How to critically appraise an article. Nat Clin Pract Gastroenterol Hepatol. 2009;6(2):82–91.
13. Fowkes FGR, Fulton PM. Critical appraisal of published research: introductory guidelines. BMJ. 1991;302:1136–40.
14. Melina R, Kibbe MD. How to write a paper. ANZ J Surg. 2013;83(1–2):90–2.
15. Knottnerus JA, Tugwell P. How to write a research paper. J Clin Epidemiol. 2013;66(4):353–4.
16. Masic I. Ethical aspects and dilemmas of preparing, writing and publishing of the scientific papers in the biomedical journals. Acta Inform Med. 2012;20(3):141–8.
17. Popham K, Calo WA, Carpentier MY, Chen NE, Kamrudin SA, Le YCL, Skala KA, Thornton LR, Mullen PD. Reporting guidelines: optimal use in preventive medicine and public health. Am J Prev Med. 2012;43(4):e31–42.
18. Davidson A, McD Taylor D, Babl FE. Review article: a primer for clinical researchers in the emergency department: part III. How to write a scientific paper. Emerg Med Australas. 2012;24(4):357–62.
19. Lin P, Kuo Y. A guide to write a scientific paper for new writers. Microsurgery. 2012;32(1):80–5.
20. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Ann Intern Med. 2010;2010(152):726–32.
21. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999;354:1896–900.
22. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for Reporting of Diagnostic Accuracy. BMJ. 2003;326:41–4.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7.
24. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. JAMA. 2000;283:2008–12.