Handling Missing Dosing History in Population Pharmacokinetic Modeling: An Extension to MDM Method

Yuhuan Wang and Xiaoxi Liu*

A major challenge in population pharmacokinetic modeling is handling data with missing or potentially incorrect dosing records. Leaving such records untreated or “commented out” will cause bias in parameter estimates. Several approaches were previously developed to address this challenge. Published in 2004, the missing dose method (MDM) demonstrated its robustness in handling missing dosing history in pharmacokinetic (PK) modeling. In this study, we presented two new extensions: a modified MDM method (MDM2) and a compartment initialization method (CIM). Their performance was examined with a large batch of simulated PK studies. For each method, 8,000 models were run, including different model structures, dosing routes, and missing dosing record scenarios. Both MDM2 and CIM exhibited robust performance and improved parameter estimation results. Specifically, CIM consistently outperformed other methods in fixed-effect and random-effect PK parameter estimation. The new methods demonstrate great potential in addressing missing dosing records challenges in PK analysis.

Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

☑ Several methods are available in handling missing dosing records in PopPK analysis, including MDM, extrapolation-subtraction method, PDM, and OM. MDM is very robust in handling missing dosing history.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

☑ This study proposed two extensions to the MDM method, which address the missing dosing records under complex situations in addition to missing dosing history.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

☑ The proposed methods extend the application of MDM based methodology. They provide new tools to pharmacometricians for handling missing dosing records in PK analysis.

**HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?**

☑ With the robust performance and easy implementation, the proposed new methods demonstrated great potential for their applications in PopPK model development during drug development and clinical therapeutics.
prescriptions. Although easy to apply, this method can be bias potent, due to the fact that dosing regimens are constantly adjusted by clinicians and may vary from prescriptions.\(^5\) The extrapolation-subtraction method creates a "subtraction curve" by extrapolating from previous doses.\(^6\) It parameters the residual concentration assuming a first-order elimination and poses it to current observation. This method completely ignores dosing history and produces more biased estimates compared with other methods.\(^5,6\)

Soy et al.\(^5\) proposed the use of the missing dose method (MDM), which performed well in the published "one-compartment, steady-state" case. The MDM method "ignores" the missing dosing history, but accounts for the leftover drug amount from it. The residual amount (before the current dose) in the studied compartment is introduced as an individual-specific parameter \(A_0\). The \(A_0\) is estimated the same way as other PK parameters (such as clearance, volume of distribution, etc.). A later report by Gupta et al.\(^6\) re-investigated this approach and used the baseline concentration \(C_0\) as an alternative individual parameter. Both studies shared the essential idea of estimating the individual baseline drug amount resulting from the dosing history. With the inclusion of two extra parameters (\(A_0\) or \(C_0\), and an associated population variability term) in the model, both methods have shown to perform sufficiently well in demonstrated cases.

In this study, we further developed the methodology proposed by Soy et al.\(^5\) and Gupta et al.\(^6\) Although still adjusting for baseline drug amounts in the system, we aimed to reduce the model parameterization. This was achieved by initializing the model status with the first available observation records. We also aimed to expand the simulation scenarios of missing dosing history and examine the performance of each method in realistic settings.

**METHODS**

**PK data simulation**

This study was based on computer-simulated datasets. PK profiles of hypothetical drugs were simulated in virtual populations. Consistent with previously published methods, we simulated the PK data assuming a one-compartment model structure, with first-order absorption and first-order elimination. Five sets of parameter values were used to simulate different PK characteristics representing slow to fast clearance.\(^1\) Combined additive and proportional residual error model was assumed. Complete absorption was assumed and fraction absorbed \(F\) was fixed to 1. Body weight was assumed as a significant continuous covariate on clearance and volume with a power relationship. Sex was assumed as a significant categorical covariate on clearance with a linear relationship. The mathematical construction of an individual PK parameter is expressed as below:

\[
\theta_i = \theta_{\text{pop}} \times \left( \frac{\text{Cov}}{\text{Median}} \right)^{\alpha} \times (1 + \alpha) \times e^{\beta_i}.
\]

In this equation, \(\theta_i\) is the individual parameter for the \(i\)th subject; \(\theta_{\text{pop}}\) is the covariate-adjusted population mean of this parameter; \(\beta_i\) is the individual deviation from the population mean in the \(i\)th subject; Cov is the continuous covariate value of the \(i\)th subject; Median is the median value of the continuous covariate in the dataset; \(\beta\) is the exponential term for the corresponding continuous covariate; and \(\alpha\) is the linear term corresponding to the alternative level of a categorical covariate (i.e., sex effect on men).

For each parameter set, 100 replicates of PK datasets were simulated using random seeding. In each PK dataset, 100 virtual subjects’ (50 men and 50 women) PK profiles were simulated. Weight followed normal distribution, with the mean \((\pm SD)\) of 70 ± 10 kg for men and 60 ± 10 kg for women.\(^2\) Base models and covariate models were separately simulated.

**Simulated trial design**

The hypothetical drug is prescribed as an oral or i.v. bolus dose of 8 mg with a 12-hour dosing interval. The simulated trial features three consecutive visits, during which a single i.v. or oral bolus dose was administered. To simplify the case, the dosing interval was strictly 12 hours for each patient. The dose amount varied from 5–10 mg on each visit. Blood samples were collected during visits and later analyzed for drug concentrations (ng/mL). Dosing and sampling times, dose amounts, and blood concentrations were available, unless the record was missing, as defined in each case.\(^2\) In this study, we implemented a relatively rich sampling strategy and assumed no missing concentration data. This was done to avoid potential model identifiability issues due to complications from data sparsity and missing data. Four different cases were simulated, varying in missing record situations.\(^1\) For case 1, only the first dosing record was missing. For case 2, only the second dosing record was missing. For case 3, only the third dosing record was missing. For case 4, one of the three dosing records was missing randomly on the individual level.

The PK data was simulated using parameters listed in Table 1 and trial design listed in Table 2. The dose amount...
(mg) was simulated as a random number, assuming a uniform distribution between 5 and 10. This design was implemented to simulate the situation under which the exact dosing records can only be obtained from available data. When a dosing record is missing, there is no way to trace it back. Under this situation, “guessing” based on prescribed doses would inevitably bring in errors. The observed concentration data was generated using customized R codes (R packages, version 3.2.2) and the $SIMULATION$ module in NONMEM 7.3 (ICON Development Solutions, Ellicott City, MD).

**Methods of analysis**

Data were analyzed using several methods to compare the outcomes. The complete dataset for each trial (no records missing) was analyzed to obtain the “ideal” estimates of the parameters (ideal method (IDM)). These estimates served as the reference for comparison. Base model estimates and covariate model estimates were obtained and examined separately. First-order conditional estimation method with interaction from NONMEM 7.3 was applied to run the models (demo codes in Code Examples S1 and Data Examples S1).

**Omit method.** The OM method represents the practice of “commenting out unusable records.” Both the missing dosing records and the subsequent observation records (before a new available dosing event) were excluded from analysis.

**Prescribed dose method.** The PDM method fills in the missing dosing records with prescribed dosing time and amount. No other formatting of the dataset or modification of the model control files are applied.

**Missing dose method.** The MDM method ignores missing dosing records. A new individual parameter $A_0$ corresponding to the “unknown” drug amount in the compartment, was introduced and estimated. More details of this method are described by Soy et al. $^5$ The initial amount $A_0$ is defined with the following formula:

$$A_0 = A_{0\text{pop}} \times e^\eta_i.$$  

$A_0$ is the initial amount in the central compartment for the $i$th subject; $A_{0\text{pop}}$ is the population mean value for this amount; and $\eta_i$ is the individual specific random deviation from the population mean.

**Modified missing dose method.** In the original publication by Soy et al. $^5$ the MDM was only examined in a simplified scenario, in which only one PK event is being studied. To

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**Table 2 Summary of trial design**

|               |           |
|---------------|-----------|
| Number of patients | 100       |
| Number of observations | 1,200     |
| Dosing time, hour    | 0, 12, 24 |
| Sampling time, hour  | 11.83, 12.25, 12.75, 13, 17, 23.83, 24.25, 24.75, 25, 27, 31, 35 |
| Missing dosing records |         |
| Case 1            | 1st       |
| Case 2            | 2nd       |
| Case 3            | 3rd       |
| Case 4            | At random |

The missing dosing record situation for each case is listed.

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**Figure 1** Missing dosing record case examples. The i.v. dosing situation is illustrated. (a) Complete record case. (b) First dosing record missing (case 1). (c) Second dosing record missing (case 2). (d) Third dosing record missing (case 3). Arrows indicate events of dosing. Circles represent drug concentrations at sampling points. Solid lines, pharmacokinetic (PK) events with available dosing records; dashed lines, PK events with missing dosing records.
adapt appropriately to our current multi-PK event settings, we expanded the MDM with several modifications.

First, under cases 2–4, for each patient after the missing dosing records, the records were treated as from a different patient by assigning a modified ID (e.g., from ID = 1 to ID = 1.1). This was done to avoid the conflicts in estimating the initial amount before and after the missing dosing records within the same patient.

Second, we added a mixture model structure in the PopPK model. This adaption was only necessary for case 3 and case 4, in which the initial compartment amount stratifies in patient PK profiles. In the mixture model, two populations were parameterized. The mixture effect only applies to \( A_0 \), whereas all other PK parameters are shared by the two populations. Both the population-specific \( A_0 \)s (and associated between-subject variability variances) and the population proportion were estimated in the model. All other parameterization was the same as the original MDM.

**Compartment initialization method.** This new compartment initialization method (CIM) is an extension to the MDM method. It takes advantage of the compartment initialization feature in NONMEM and is further optimized to handle missing dosing records. Rather than “estimate” the initial drug amount before an available dosing event, the gist of this method is to use observation data (especially those after missing dosing records) to “back calculate” the compartment initial state. Minor modification of existing dataset structure may be necessary, depending on specific cases. The central compartment is initialized with the following mathematical definition:

\[
A_{0i}(t) = \text{Conc}_i(t) \times V_i.
\]

\( A_{0i}(t) \) is the initial amount in the central compartment for the \( i^{th} \) subject at time \( t \); \( \text{Conc}_i(t) \) is the first available concentration record right after the missing dosing record; \( t \) is the corresponding time to that concentration; and \( V_i \) is the volume of distribution for the \( i^{th} \) subject. The compartment initialization is performed only once after each missing dosing record. All other PK parameterization and model structure follows the convention of building PK models.

**Method evaluation metrics**

Relative estimation errors (RERs), root mean squared errors (RMSEs), and standardized RMSEs (sRMSEs) were used to assess the precision of estimation by each method. The mathematical definitions of these metrics are listed as below:

\[
\text{RER}^{(\hat{\theta})} = \frac{\hat{\theta} - \theta_p}{\theta_p} \times 100,
\]

\[
\text{RMSE}^{(\theta_p)} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\hat{\theta}_i - \theta_p)^2},
\]

\[
\text{sRMSE}^{(\theta_p)} = \frac{\text{RMSE}^{(\hat{\theta})}}{\text{complete (RMSE}^{(\hat{\theta})})}.
\]

\( \hat{\theta} \) is the estimate of parameter \( \theta \) by method \( a \). \( \theta_p \) is the true value of parameter \( \theta \) used for simulation. For each parameter \( \theta \), the sRMSE is calculated by dividing RMSE (returned by method \( a \)) by the complete case RMSE (IDM) for parameter \( \theta \).

**RESULTS**

The method performance was evaluated based on RER and sRMSE statistics. RER measures the estimation bias relative to true simulation values, whereas sRMSE (normalized to IDM estimation) examines the estimation precision relative to the complete case analysis. The RER statistics are presented in box plots for each parameter estimate (Figures 2 and 3). The sRMSE statistics are stratified by case, dosing route, and parameter categories (Tables 3 and 4).

Overall, the performance of OM and MDM methods was case sensitive. In contrary, PDM was quite inert to different cases. The modified missing dose method (MDM2) and CIM performed similarly to each other and superior to all other methods in most cases.

**Omit method.** In almost all cases, dosing routes, and parameter sets tested, OM gave the most deviated estimates to true parameter values. The only exception was case 3. In this specific case, the distribution of OM RER exhibited comparable pattern to IDM (Figures 2 and 3). The sRMSE of OM was also one of the highest among all tested methods (Tables 3 and 4).

**Prescribed dose method.** The performance of PDM was consistent across tested cases. Compared with other methods, it was neither the best nor the worst in reducing the estimation bias (Figures 2 and 3). The bias of PK parameter estimates (fixed and random effects) was within 10% relative to true values. However, the residual error was systemically overestimated.

**Missing dose method.** The performance of MDM varied greatly between cases. In case 1, the MDM method returned parameter estimates with comparable accuracy and precision as IDM (Figures 2 and 3, Tables 3 and 4). This is in agreement with previous publications in which dosing history is missing previous to current observations. However, greater bias was observed in cases 2–4, in which the dosing records were missing between observation records.

**Modified missing dose method.** This extended MDM performed robustly in all tested scenarios. The estimations of PK parameters (fixed-effects and random-effects) were slightly inferior to CIM, but still very close to IDM. For i.v. routes (Figures 2a and 3a), however, the residual error estimation by MDM2 outperformed the CIM and was consistently the closest to IDM in all scenarios.

**Compartment initialization method.** CIM was the most accurate method (Figures 2 and 3) and produced the smallest variances in fixed-effect and random-effect parameter estimations in almost all stratifications (Tables 3 and 4). For all tested scenarios, the median RERs by CIM for fixed-effect
and random-effect parameters were consistently well below 5% compared with true simulation values (Figures 2 and 3). The distributions of RERs were almost identical between CIM and IDM for these parameters. CIM outperformed the other tested methods in estimation accuracy and precision in almost all scenarios. The only exception was the estimation of proportional error variance in cases 2 to 4 for i.v. dosing (Figures 2a and 3a). Under this scenario, CIM tended to overestimate the proportional error variances. Zoomed-in plots of residual error variance RERs are presented in Figures S1 and S2.

**DISCUSSION**

In this study, we proposed two new extensions to MDM and systematically examined their performance in handling...
missing dosing records for PopPK model development. Using simulation techniques, we created a representative test space of multiple dimensions (5 parameter sets × 2 dosing routes × 4 missing situations × 100 replicates). By evaluating the estimation accuracy (RER) and precision (RMSE) of each method, we have demonstrated the differential method performance under a series of conditions. Overall, both extensions (MDM2 and CIM) were robust, whereas CIM performed especially well for estimating key PK parameters.

In this study, we used four simplified cases to represent the elementary exhibition of missing dosing records in the PK dataset. Case 1 represents the scenario when proceeding dosing records are missing and a “baseline” drug concentration exists before the currently available PK events. Case 2 represents when the dosing records in the middle of treatment are unavailable, whereas the proceeding and following records are intact. Case 3 represents when only following dosing records are missing. Case 4 is a more “realistic” representation when dosing records are missing at random. Although simplified, these simulated cases covered the most typical situations of missing dosing records. Real-life data conditions are usually different combinations of these cases. Therefore, knowledge generated from this
Figure 3  Relative estimation error (RER) of all parameter estimates (covariate model). RERs for each parameter are stratified by case. Y-axis: RER (%) for each parameter. X-axis: method names. (a) The i.v. dosing routes. (b) Oral dosing routes. CL_SEX, linear term of sex effect on clearance; CL_WT, power term of weight effect on clearance; V_WT, power term of weight effect on volume. All other annotations are the same as in Figure 2.
Figure 3 Continued
study should be readily translatable to practical PK model development efforts.

Since the publication of the Soy et al. article in 2004, there have not been many updates to the MDM. Four years later, Gupta et al. presented the MDM in a different angle and focused on addressing the baseline concentration. In the same year, Dansirikul et al. reported a series of similar methods (B1–B3) to address baseline effects in pharmacodynamic modeling, which can be considered as (extended) implementations of MDM for pharmacodynamic models specifically. Nonetheless, the essence of MDM (and similar methods) is to parameterize the initial state of the central compartment, either as the total drug amount or drug concentration. The method recognizes the existence of an initial drug amount before current dosing records, which results from the missing dosing history. Assuming a certain distribution among patients, this initial amount is parameterized and estimated the same way as other individual PK parameters (such as CL, V, etc.). Upon model convergence, its population mean and distribution variance are estimated, and, hence, the missing dosing history issue is addressed. In this study, case 1 (in which only the first dosing record was missing) was a representation of this scenario. Under this case, MDM performed as well as the IDM as if no dosing records were missing.

However, the performance of MDM has not been tested in scenarios that are more complex since the original publication. As demonstrated by cases 2–4 in this study, the original MDM was not robust enough in these settings. This can be attributed to several methodological factors. First, MDM assumes each patient has a specific “initial status” of drug amount by estimating an individual parameter $A_0i$. Under current methodology (e.g., NONMEM syntax), the assignment of this parameter occurs at the first record in patients or in a reset record. For case 2 (in which the second dosing record was missing), the same $A_0i$ was assigned twice with the same value: one at the first record and the other at the missing dosing record. Apparently, this results in contradiction within patients, because the first assignment should not be as high as the second one. In MDM2, we addressed this by assigning a new patient ID after the missing dosing record, which gave the model freedom to adjust the initial amount estimates before and after the missing dosing records. Second, the initial amount may not be described appropriately with a simple distribution. For case 1, because the first observation was a trough concentration (as originally published by Soy et al.), a single population distribution of initial amount was sufficient. For cases 2–4, the assumption of “a certain distribution” is no longer valid. Theoretically, a patient either has an initial drug amount (if previous dosing records are missing), or not (if the missing records are after current PK events). A stratification of initial status existed in the population (the later trough was higher than the earlier one). Therefore, parameterization of a single $A0$ in population leads to contradiction between patients. This influence was not very obvious under case 2 because the second trough was not much higher than the first one. However, the stratification was much more influential under cases 3 and 4. Therefore, we implemented the mixture model structure in MDM2 to adapt to this situation. The population was then divided into two groups, one with lower initial amount and the other with higher initial amount. For each group, the mean and distribution of the initial amounts were separately estimated. As demonstrated by the results, these

### Table 3 Summary of sRMSE by each method (base model)

| Method   | Case 1 | Case 2 | Case 3 | Case 4 |
|----------|--------|--------|--------|--------|
| OM       | 3.86   | 4.21   | 1.28   | 3.11   |
| PDM      | 1.98   | 4.91   | 6.95   | 4.36   |
| MDM      | 1.00   | 12.59  | 13.12  | 8.59   |
| MDM2     | 1.06   | 1.73   | 1.70   | 1.24   |
| CIM      | 1.02   | 1.08   | 1.91   | 1.55   |

Average sRMSE pooled across all parameters obtained by different methods stratified by case, dosing route, and parameter type.

CIM, compartment initialization method; MDM, missing dose method; MDM2, modified missing dose method; OM, omit method; PDM, prescribed dose method; sRMSE, standardized root mean squared error.

### Table 4 Summary of sRMSE by each method (covariate model)

| Method   | Case 1 | Case 2 | Case 3 | Case 4 |
|----------|--------|--------|--------|--------|
| OM       | 4.48   | 4.39   | 1.21   | 3.28   |
| PDM      | 2.10   | 3.50   | 4.73   | 3.27   |
| MDM      | 1.07   | 15.38  | 15.19  | 10.03  |
| MDM2     | 1.06   | 1.51   | 1.47   | 1.19   |
| CIM      | 1.03   | 1.64   | 1.68   | 1.41   |

Average sRMSE pooled across all parameters obtained by different methods stratified by case, dosing route, and parameter type.

CIM, compartment initialization method; MDM, missing dose method; MDM2, modified missing dose method; OM, omit method; PDM, prescribed dose method; sRMSE, standardized root mean squared error.
adaptons were able to maintain the performance of MDM2 and returned parameter estimates very close to the ideal cases (IDM). It is also worth noting that the MDM2 is different from the missing dose mixture method (MDMM) published by Soy et al.\(^5\) MDMM assigned the studied population to either MDM or PDM methods. Considering the mediocre performance of PDM alone, MDMM is expected to perform inferior to MDM2 in studied cases.

However, MDM2 exhibited some artificial effects on parameter estimate uncertainty. The standard errors of some PK parameters were moderately underestimated compared with IDM (Figures S3 and S4). This was a result of the patient ID renaming, which consequently increased patient numbers in each dataset. In addition, because of the extra parameterization, the model run times were longer when using MDM2 methods (Table S2).

If MDM2 seems like “patching holes in the roof” of the MDM, then the new method CIM is a much more elegant extension to MDM. The gist of CIM is to “back calculate” the initial drug amount using available concentration records and the current estimate of individual volume. It has some advantageous features over the MDM and MDM2 methods. First, the calculation is dynamic. The concentration records used for calculation are allowed to vary in time and are specific to each individual subject. Therefore, the subjects are assigned their own initial amounts. The initial amount is parameterized with individual volume and, therefore, is updated at each iteration of model running. Second, the implementation of the CIM method is very simple. There is no need to parameterize the initial amount \(A_0\) with an additional PK parameter. The same number of parameters is needed as in the ideal case because no extra parameters will be estimated. There is also no need to assign special attention to stratified initial amount distribution among population (cases 3 and 4). This is automatically taken care of by formulating \(A_0\) using the available concentration records, which are stratified already. As an extension to MDM, the CIM allows the maximum utilization of PK information in observation records without extra parameterization. As demonstrated by the RER and sRMSE metrics, CIM returned comparable outcomes as MDM2 and IDM. Additionally, CIM outperformed all other methods in the fixed-effect and random-effect PK parameter estimations.

However, like every method, CIM has its limitations. First, the implementation of CIM (also for MDM and MDMM) may require moderate modification of dataset format depending on specific cases. For cases 2, 3, and 4, a reset event record (EVID = 3 in NONMEM) had to be created in the data. This was necessary in NONMEM because the compartmental initial amount \(A_0\) can only be assigned a value when EVID = 1 or 3, or at the first record of a subject.\(^9\) But no extra data formatting is required for case 1. After the first dosing record being missing, the next available concentration record becomes the first record of a subject. Second, not all of available observation records after missing dosing records can always be utilized. In oral dosing scenarios, only observation records (after a missing dosing record) after five absorption half-lives (5 × ln2/\(ka\)) were included. This was necessary to minimize the influence of the remaining drug amount in the dosing depot \(A_0\) (1). With prior knowledge of absorption rate constants (which can be roughly estimated using OM method), \(A_0\) (1) could be considered as negligible (3% of dose) after five absorption half-lives. Third, the estimation of proportional residual error variances is not the best compared with MDM2. This was largely due to the utilization of observation records when initializing the compartment, because the observed concentrations already contain residual errors. For large (close to peak) concentrations, the proportional residual error can be large in number. Therefore, an additional error is introduced during the compartment initialization. The higher the concentration record, the bigger the error. This phenomenon was most manifested in i.v. dosing scenarios (except case 1), in which the first available concentration record after the missing dosing record was near the peak. Currently, we are still investigating ways to fix this issue. Nonetheless, the influence only resided in the estimation of proportional residual error variances. This should not mask the overall outstanding performance of the method. Compared with other methods, the CIM still returned the most accurate and precise estimates of all other fixed-effect and random-effect parameters and additive residual errors.

Last, there are situations in which application of CIM will be considered as “overshoot.” Case 3 is an example of such situations in which CIM does not necessarily have to be applied. When only the third dosing record was missing, the OM returned parameter estimates with similar accuracy as IDM. This is because the rich observation records after the first two doses (especially the second dose) were sufficient to define the drug PK. Therefore, simply “commenting out” the third dosing and subsequent observation records was effective enough. For such cases, OM is recommended for the ease of use. For studies with a flat dosing plan, PDM should just be sufficient because the dose is known or can be easily reconstructed for every patient. In addition, there are some very specific conditions in which other methods may be more appropriate to apply. For example, a “partial dosing history” condition was described by Kumar and Duffull.\(^6\) Under this condition, the dose amount is known but the dosing time is not available. A concentration time method was reported and was suggested as an appropriate method to address that specific data condition. Last, if a drug exhibits very short half-life (e.g., 1 hour) but is administered with a large dosing interval (e.g., 12 hours), it may not be critically necessary to apply MDM, MDM2, or CIM for case 1. After 12 half-lives, there is about 0.02% drug left that remains to be cleared from the circulation, which can be safely considered as all cleared. Then any “baseline” effect from previous missing dosing history should be very minimal. For cases 2–4, however, one can still choose to apply CIM or MDM2, if there are PK data after missing dosing records and including them in modeling analysis is desired. The method performance should be similar as demonstrated in this study.

**CONCLUSION**

In this study, we presented two new methods based on MDM. Both MDM2 and CIM exhibited robust performance and improved the parameter estimation results. Specifically, CIM consistently outperformed all other methods in fixed-effect and random-effect PK parameter estimation. The
The implementation of CIM was also easier than MDM2. The new methods demonstrate great potential in addressing challenges of missing dosing records in PK analysis.

**Supporting Information.** Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

**Figure S1.** Relative estimation error (RER) of residual error estimates (base model).
**Figure S2.** Relative estimation error (RER) of residual error estimates (covariate model).
**Figure S3.** Standard errors of PK parameter estimates (base model).
**Figure S4.** Standard errors of PK parameter estimates (covariate model).
**Table S1.** Virtual population demographics.
**Table S2.** Model run CPU time (seconds).
**Code Examples S1.**
**Data Examples S1.**

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