PERSPECTIVE

Model-Informed Precision Dosing at the Bedside: Scientific Challenges and Opportunities

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The development of model-informed precision dosing (MIPD) tools, especially in the form of native or web-based applications to be used at the bedside, has garnered marked attention in recent years. Their potential clinical benefit can be large, but it should be ensured that such tools make optimal use of available clinical data and have adequate predictive ability. Unique scientific challenges specific to MIPD remain, which may require adaptation of commonly used diagnostics in pharmacometrics.

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In 1969, Lewis B. Sheiner[1] published a paper that can now only be described as seminal, as it launched the field of pharmacometrics as we know it. This paper, and similar work done in the early 1970s by Roger Jelliffe and his group at USC, demonstrated the rudimentary concepts of how clinical pharmacokinetic (PK) data can be fed into computer-based algorithms to optimize drug treatment for patients. In the ensuing 5 decades, the field of pharmacometrics has grown markedly. Although model-informed precision dosing (MIPD), a recently introduced label, has always attracted a subset of clinical researchers, it seems to have gained renewed attention from the modeling community, evidenced by the release of new software tools, the publication of opinion papers,[2–4] the scheduling of various dedicated conference sessions (ASCPT, PAGE, ACoP, and ACCP), and the creation of a Special Interest Group within ISoP ("Applied Clinical Pharmacometrics").

MIPD generally requires custom-made software tools because generic modeling software, such as MATLAB or NONMEM, is too cumbersome and complex for most practicing clinical providers to learn and apply. Dedicated tools are likely to come in the form of a mobile or web-based application that contains algorithms for drawing inference from available clinical data and evaluating future personalized treatment courses. For any academic or commercial MIPD tool to be applied successfully at the point-of-care, a considerable number of technical, organizational, regulatory, and financial hurdles need to be overcome, some of which have been highlighted before.[2] Furthermore, to drive adoption of these tools in the clinic practice, it is essential to provide proper education of the intended end-user, and provide proof of improved efficacy, reduced toxicity, and/or reduced costs, preferably from prospective clinical trials.[5] Finally, even though the science of pharmacometrics has progressed considerably, within the subfield of MIPD, a considerable number of scientific challenges still remain.

MODEL SELECTION

An obvious first question that should be answered for any MIPD tool concerns the selection of the underlying model or models. Intuitively, one needs to select a model that matches the intended population. In practice, this usually means matching age groups (neonate, pediatric, adult, and geriatric), body composition (normal, cachectic, and obese), indications and comorbidities, and potentially genetic makeup (e.g., cytochrome P450 genotype), as well as dose levels studied and analytical assay(s) used.[6] For some drugs, models have been developed that scale over a wide age range, but most often models are developed over limited ranges, making it potentially hazardous to extrapolate or generalize. Similarly, many clinical datasets only contain limited numbers of a certain subgroup (e.g., obese patients), thereby making it challenging to capture the specific impact of the characteristics for that subgroup.

Even once we have identified an appropriate model to use in a specific patient population, and we have made sure its numerical performance is the same (or highly similar) to the platform on which it was developed, we are still not in the clear. Naively implementing such a model into point-of-care software would assume that the population on which the model was built will be exactly the same as the intended population (e.g., when drawing inference based on maximum *a priori* estimates), one will be making the bold assumption that the model is unbiased and that population parameters follow distributions with the same magnitude as observed in the studied population (which is usually from a different hospital, often from a different country). These assumptions often do not hold and limit the scalability of a given model across institutions. We have seen several cases in which published models did not perform well for individual patients, an observation reported before, for example, by Neef *et al.*[7] Therefore, we recommend evaluation of the

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predictive ability of the intended model for its intended use before applying it in the clinic, and to continuously monitor it once deployed. Specialized analytic dashboards could be implemented to inform clinical providers and hospital management on the population-level performance of the implemented MIPD tool, for example, in terms of favorable clinical outcomes or, for antibiotics, target attainment rates.

MODEL QUALIFICATION

Evaluation of model performance in the same clinical setting and scenario of application is critical. Such a qualification step can be done using historical data drawn from the clinical records of the institution in which the tool is meant to be implemented. For example, when implementing a decision tool to determine the optimal starting dose, the *a priori* predictive value is important: ensuring that the model has good predictive value using only the information that will be available for patients at the time of starting dose selection. When the intention is to use the model in the setting of biomarker-based dosing, such as therapeutic drug monitoring, the *a posteriori* predictive performance is more important: the predictive ability after biomarker data has been used to inform the model parameters, which can, for example, be obtained by forecasting future exposure from repeated subsetting and fitting of subjects' historical data. Many diagnostic tools that have been developed for model development can also be used in this context, but often do not directly answer whether the model is fit for purpose. New dedicated tools will be necessary to allow easy and standardized evaluation of the predictive or prognostic ability of models within their intended clinical application.

MITIGATING MODEL BIAS AND IMPROVING PREDICTIVE VALUE

Even when a model has been selected and has shown acceptable performance in a fit for purpose qualification procedure, it is likely that when used in clinical practice the model will be challenged by patients with more "extreme" PK/pharmacodynamic characteristics than expected (i.e., "outliers" that deserve special attention). To some extent, this is expected due to the fact that, for example, (i) the model is only a product of the limited number of patients it was built on, (ii) the distribution of model parameters might be misspecified or its magnitude overestimated or underestimated, (iii) the magnitude of process noise (e.g., errors in sample or dose timing) is often higher in clinical practice than in a trial setting, (iv) the model has inherent bias (e.g., from missing data), but was deemed acceptable in qualification, and/or (v) selection bias (e.g., from selectively applying biomarker dosing tools to patients), which show toxicity or poor response.

One way to mitigate poor fit and potentially poor predictive ability for extreme patients is to flatten or downweigh the model priors in the likelihood function. This will allow for more extreme individual parameter estimates to be estimated for the patient, thus, to rely more on the observed data, and potentially improve predictive ability. If possible, gathering more data on the patient should of course be a priority in such a case to confirm or disprove the outlying individual parameter estimates. Although somewhat arbitrary, this approach does provide more flexibility in using existing models for patients that are showing more extreme behavior or are outside the scope of the original study's population. We do need to keep in mind that a better fit does not necessarily result in better predictive ability, so some degree of reliance on prior estimates is required to avoid overfitting, and this approach should be explored during qualification before it can be recommended generically. A similar approach of prior modification to optimize fit and predictive ability has been advocated in the nonparametric setting, in which the grid of support points has been proposed to be extended with a second grid around the maximum *a priori* Bayesian estimates.[8]

Additionally, although a chosen model might in some cases show suboptimal predictive performance when first applied in clinical practice, data collected in the tool could subsequently be used to update the model structure or model parameters to match the intended clinical population better (i.e., a "learning model"). Over time, the need for strategies to improve fit and predictive ability, as discussed above, should then be reduced. If implemented in a (semi-) automated manner, this will result in a cycle where the model is updated continuously, as shown in **Figure 1**. Clinical data is often messy and incomplete, so curation and data cleaning should be key considerations in such a workflow, whereas one should also be careful that the use of routinely collected data does not introduce bias in the model.[9]

CHANGES OVER TIME

A third challenge concerns the handling of the interoccasion variability (IOV) arising from the time-varying nature of individual patient physiology and PK and pharmacodynamics. A first aspect is the interpretation of covariates and individual parameter estimates from previous visits: do these historical data points have predictive value for future treatment courses? Should data with potential predictive value from

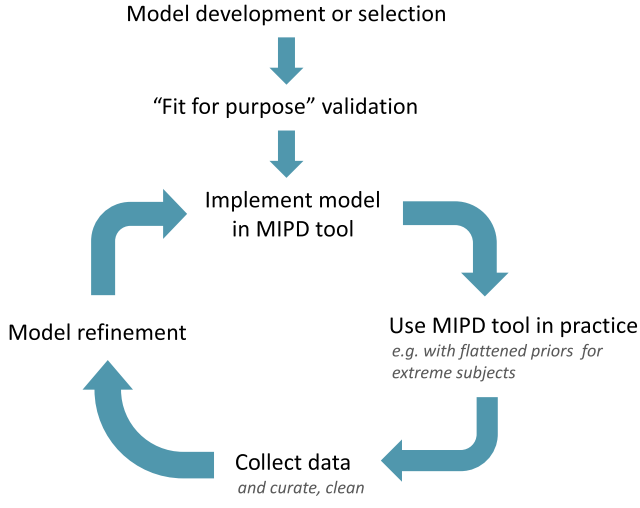

Figure 1 Proposed workflow for model-informed precision dosing (MIPD) tools at the bedside.

more recent visits be given more weight? In pediatrics, in which physiology is changing more rapidly than in adults, should we allow a shorter time span of historical data to inform future treatment? We and several other groups (e.g., Abrantes *et al.*,[10] Wicha *et al.*[11]) are investigating such questions, but little work on this topic has been done to date.[12] Incorporation of IOV is important for characterization of both short-term (e.g., within-day, for the same visit or treatment course) and long-term (between-visit) treatment scope. If IOV is not properly accounted for, downweighing or ignoring historical data might be needed to avoid bias in individual parameter estimates, which, again, should ideally be evaluated during model qualification.

CONCLUSION

We have highlighted several practical scientific challenges commonly encountered when developing and implementing MIPD tools at the point-of-care. "Fit for purpose" qualification is a key step when developing and implementing MIPD tools for use at the bedside, in which conventional model diagnostics are often only of limited value. Further methodological research into this area is needed, especially around diagnostics for model qualification and the weighing and proper interpretation of historical data and model priors.

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