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Big world challenges for pharmacometrics

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Aims: From the outset, the aim of pharmacometrics has been to improve patient therapy through model-based methods. The focus of these efforts have shifted over time. Initially, in the 70's and 80's, targeting the data collected during routine use of drugs in the target patient population to providde better dosing recommendations. In the 90' and 00's the focus shifted towards improved clinical drug development, whereas in the present decade the additonal focus has been towards translation between different stages throughout drug development as well as allowing improved societal use of drugs. Thus, today the overall aim remains the same, but the scope of activities has widened considerably. Specific aims and challenges for activities of different maturity need to be identified and addressed. The performance in core activities needs to improve while also exploring and implementing the utilization of pharmacometric methods and models in new areas of application where the benefit/cost is high or promising.

Methods: For core development activities, assure efficient utilization of resources and appropriate impact on decision-making through increased communication and integration with other disciplines. The sibling disciplines statistics and systems pharmacology that together with pharmacometrics consititute the quantitative aspects throughout drug development require particular attention. Methodologies that bridge gaps need to be developed. For example, to better bridge towards systems pharmacology, methods to utlize both prior information and new data are required and to bridge towards statistics in late stage clinical development, more methods for prespecified use of pharmacometric models are desired. For core clinical use activities, there is a opportunity to develop the utilization of models in areas beyond therapeutic drug monitoring. The increased access to, and possibility to develop, models for clinical endpoints can provide not presently available decision-support in management of patient care. Such models may become particularly important with increasing access to of patient-specific information through new technologies. Models may act as notification- and decision-support when data amounts prohibit systematic in cerebro synthesis. Increased access to or generation of large databases from different populations: the general population, patients with specific diseases and/or treatments comes from registries, health care providers or through multi-institutional collaborations. Such data can provide information on (patho)physiological and functional charateristics from more patients than would ever be possible to study in clinical trials. However, efficient utilization of these databases will involve collaboration with new disciplines, e.g. epidemiologists and health economists.

Results: In its core application area of clinical drug development, pharmacometrics is becoming a mature discipline. However, its implementation still displays a large heterogeneity between and within organisations. Community consensus, including regulatory acceptance, is only slowly being generated. Data sharing, common in many other disciplines has made little or no progress to the detriment of better-based models, in particular in rare, orphan and slowly progressing diseases. Good practises documents, model-sharing mechanisms, standards development and other community-led efforts have only recently started to emerge. Short-comings of existing estimation methodologies and software are impediments in developing otherwise desireable models, especially mechanistic models and models for large databases. Educated and trained pharmacometricians remain a scarce resource. PhD programs and training on the job remains the main influx of new pharmacometricians, while undergraduate programs intentionally set up to suit the need of the disciplines are rare.

Conclusion: To consolidate the use of pharmacometrics in core areas and expand its use to new opportunities there is a need for development in a large number of areas: education, methodology, software, interdisciplinary collaborations, intradisciplinary infrastructure to name a few.

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Challenges in treating infectious disease - linking epidemiology with pharmacometrics

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Aims: In pharmacometric analyses, a goal is to quantify the impact of a therapeutic agent on a population of patients with a disease who will take the drug, with a particular focus on understanding the factors that contribute to individual variability that exists across patients within the population. In epidemiologic analyses, a goal is to quantify the primary risk factors that contribute to the spread of a disease across a population, similarly with a focus on understanding individual factors that may enhance the susceptibility or protection of members of the population to the disease. Combining these two methods presents an opportunity to understand how to get the right treatment intervention to the right patients at the right time to be able to impact the spread of infectious disease and potentially lead towards disease elimination.[1] In essence, this is the basis for the emerging area called Precision Public Health.

In Precision Public Health, the right treatment intervention may not only include using therapeutics but could also include other interventions that in total contribute to effective treatment of infectious disease. An illustrative example comes from efforts to treat malaria infection. A meta-analysis of individual subject level data from children who had participated in studies with the anti-malarial combination agent Arthemther-Lumafantrine uncovered an interesting and perhaps counterintuitive result.[2] It was noted that patients who were underweight for their age – a surrogate indicator of possible malnutrition- showed a higher rate of treatment failure than matched children who were the appropriate body weight for their age. These underweight children received the same mg dose as their normal weight counterparts and thus had a larger mg/kg dosage. Traditional pharmacometric analyses identified the primary covariate to identify which children more likely failed therapy. Epidemiological analyses pointed to factors that could be measured to address this problem using a simple method for assessing malnutrition in the field. A subsequent study using an intervention to address acute malnutrition then showed the ability to correct this problem which was ultimately due to poor absorption of the drug dose.

A second illustrative example is an effort by Bershteyn and Eckhoff to assess the impact of variation in host immunity along with patient adherence to drug regimens as levers that impact the likelihood of a developing drug resistance in a population receiving prophylaxis for prevention of HIV infection.[4] Coupling an epidemiologically based within-host viral dynamics model with individual subject PK/PD model that is affected by dosing adherence, the relative contribution of host specific biological factors and behavioral factors related to adherence to the development of resistant virus could be estimated. This allows the opportunity to plan an intervention for a particular community of patients and develop effect means for assessment of treatment to intervene before inadequate dosing can contribute to the development of resistance.

A final example from treatment of tuberculosis will be discussed. In a meta-analysis review of clinical trials to explore the use of treatment shortening regimens for TB therapy, Wallis et al explored sentinel indicators that could be used to explore the likelihood that patients would successfully be treated based on initial results after 2 months of therapy.[5] This review identified factors related to treatment regimen and duration that increased the probability of success of clinical trials to show non-inferiority to standard of care therapy. The analysis is being extended to explore the individual subject level covariates that can predict who among a treated population is more likely to succeed with a particular regimen of a different durations. These results will allow the population tailoring of tuberculosis therapy to maximize success across a range of patients.

Conclusion: Pharmacometric analyses of individual subject level data from infectious disease treatment studies can provide valuable information for identifying key factors that will contribute to successful treatment of a maximum number of patients. When coupled with epidemiological models to assess factors that impact the spread of disease, effective strategies for treating patients emerge that form the basis for Precision Public Health interventions.

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Developing next-generation malaria medicines to address drug resistance and increase the operational feasibility of malaria elimination efforts

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Aims: In 2015 the World Health Assembly endorsed the WHO Global Technical Strategy for Malaria 2016-2030[1], which aims to reduce global malaria incidence and mortality rates by 90%. While progress towards malaria reduction and elimination can be made using existing tools, there is general consensus the operational feasibility and impact of malaria elimination efforts will be enhanced by the availability of improved interventions, including drugs. Furthermore, new drugs are needed to address the increasing prevalence of drug resistant parasites. The Malaria Eradication Research Agenda (malERA) published a target profile for the 'ideal' malaria elimination/eradication drug[2] - a Single Encounter Radical Cure and Prophylaxis (SERCaP) intervention capable of achieving rapid reduction in parasitemia, sterilizing the human host of all forms of the parasite, reducing/preventing onwards transmission and providing some degree of post-treatment protection against reinfection. The aim of this talk is to provide an update on the strategy and progress of the Medicines for Malaria Venture (MMV) and its partners in developing novel anti-malarial medicines that meet these requirements.

Methods: MMV's current efforts focus on delivering improved interventions for children and pregnant women, including chemo-prevention, drugs to address resistance and improved drugs for relapsing malaria, all ideally as single dose medicines. MMV works with a consortium of partners to screen chemical libraries, initially via high throughput screening (HTS) against whole parasites. Compounds that are confirmed as active in the HTS are then 'finger-printed' using a selection of assays covering the various lifecycle stages of the parasite[3]. PK/PD data obtained in a humanized SCID mouse model for *P. falciparum* are used within lead optimization to support the first human dose prediction required at preclinical candidate selection[4]. Clinical development of novel malaria agents now utilizes a controlled human infection model[5] for blood stage *Pf* infection, allowing early assessment of PK/PD in humans, facilitating early portfolio de-risking and dose selection.

Results: To date more than 7 million compounds have been screened against whole parasites. Over 25,000 compounds with EC50<1 uM have been identified. Importantly, many of these compounds are active against targets different from the currently approved anti-malaria medicines. To date, drug candidates covering six novel targets have been selected for development. Twenty-five compounds have been identified where no drug-resistance phenotypes could be generated. The most recent compound to enter Phase IIa studies is DSM265 a triazolopyrimidine-based highly selective inhibitor targeting *Plasmodium's* dihydroorotate dehydrogenase (DHODH). Data obtained from the HuSCID mouse model and the controlled human infection model for *Pf* malaria were used to estimate the MIC and efficacious dose for DSM265. Data obtained from the Phase IIa monotherapy study in malaria-infected patients showed strong concordance with predictions, with a single 400mg dose of DSM265 sterilizing the majority of patients of *Pf* infection out to 28 days follow-up.

Conclusion: MMV and its partners have bought forward a portfolio of novel antimalarial drugs focused on addressing key unmet medical needs, including compounds to address drug resistance and support malaria elimination efforts. Through these efforts, pathways to kill the parasite have more than doubled over the last 10 years, providing the potential to address drug resistant parasites. Early PK/PD assessment in the HuSCID mouse model, coupled with the use of the controlled human model for *Pf* blood-stage infection has identified potent compounds with rapid parasite clearance kinetics and long half lives, supporting their potential inclusion into future SERCaP regimens for malaria elimination.

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Pharmacometric modelling of antimalarial drugs in development: from challenge to clinics

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Aims: guide the dose finding in clinical studies based on the Induced Blood Stage Malaria (IBSM) challenge studies and population pharmacokinetic-pharmacodynamic (PKPD) modeling.

Methods: Two compounds (OZ439 and DSM265) were tested in IBSM challenge studies[1]. In these studies, P*. falciparum* was inoculated to healthy volunteers. When parasitemia had developed to a level detectable by real-time quantitative polymerase chain reaction (qPCR) but below the level of detection by microscopy, the treatment was administered. PK concentrations were measured and parasite densities were assessed by qPCR. Typically, each cohort comprised of 8 subjects. OZ439 was tested at 3 single doses (100, 200 and 500 mg) in one challenge study. DSM265 was tested at 2 single doses (150 and 400 mg) in two challenge studies. A population PKPD model was built based on the generated PK and PD data. For DSM265, PK concentrations from First-In-Human studies were added, allowing coverage of a wider range of dose levels. Based on the developed model, parasitemia profiles in patients were predicted for a number of dose level combinations. The underlying assumption was that the model, developed based on IBSM data is valid also for patients, when using higher baseline parasitemia values. The model was then used to predict the parasitemia profiles in patients assuming the parameters of the model are similar as those estimated with the IBSM data, except the baseline parasitemia which was set higher for the patients. The predictions were compared with Phase 2a data in uncomplicated P.*falciparum* patients. Modelling and simulation were performed in Monolix (version 4.3.3) using the IQM Tool (version 1.2) as an interface.

Results: A population PKPD model was obtained for each compound with a similar approach: first a population PK model was developed. Then, the PD parameters in a PKPD model were estimated whilst the individual PK parameters were fixed to the values estimated by the population PK model obtained in the first step. The PD model assumed the parasites dynamics resulted from a constant net growth rate estimated with the parasitemia measured prior to drug administration and from a concentration-dependent killing rate described by a sigmoidal Emax relationship. The population PKPD model described the challenge data quite well, although the DSM265 PKPD model had a greater uncertainty due to the reduced information avaialable – only two doses were tested and DSM265 being a slowly cleared compound, the range of concentrations investigated was more limited than for OZ439. Predictions of the parasitemia profiles in patients obtained with the combined PKPD models provided a reasonable indication of the clinical effect of the compounds and have been used to guide the dose selection of later stage trials.

Conclusion: IBSM challenge studies offer the opportunity to investigate sub-therapeutic doses in a well controlled and safe environment. Combined with PKPD modelling, they guide the selection of doses for the phase 2 trials in patients. The advantages and limitations of the approach will be discussed.

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Pharmacometric modelling of antimalarial drugs in development

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Aims: Determination of minimum inhibitory concentration (MIC) of antimalarial drugs in the clinical setting may provide a valuable alternative to empirical approaches to effective dose-finding. The aim was to estimate prospectively the *in vivo* MIC of cipargamin[1] in adults with uncomplicated *P. falciparum* malaria in an open-label, dose-ranging Phase IIa study.

Methods: Twenty-five Vietnamese adults with uncomplicated *P. falciparum* mono-infection confirmed by microscopy were allocated sequentially to treatment with a single sub-therapeutic dose of cipargamin (30, 20, 10, or 15 mg). The *in vivo* MIC of cipargamin was estimated using population pharmacokinetic-pharmacodynamic modelling of observed plasma cipargamin measurements and serial parasite densities assessed by microscopy and real-time quantitative polymerase chain reaction. Modelling and simulation were performed in NONMEM v7.3.

Results: The pharmacokinetic properties of cipargamin were well described by a flexible transit-absorption model followed by a one-compartment disposition model, resulting in a high predictive performance. Individual pharmacokinetic parameter estimates from the final model were imputed into the pharmacokinetic-pharmacodynamic model in order to evaluate the cipargamin-dependent parasite killing effect. No parasite growth data were available before drug administration and the parasite multiplication rate was therefore fixed to a 10-fold multiplication per parasite life-cycle (i.e. 48 hours). The initial implementation of the pharmacokinetic-pharmacodynamic model assumed a homogenous parasite population and drug-dependent killing of parasites (E_{MAX}-model). However, population and individual parasite clearance curves showed a clear biphasic pattern of parasitaemia decline. This could suggest presence of a non-sensitive (i.e. “dormant”) parasite population that is unaffected by the drug. The fraction of sensitive/dormant parasites was estimated but allowed for inter-individual variability in the same parameter. The activation (“awakening”) of dormant parasites was also estimated. Higher doses, and thus higher plasma cipargamin concentrations, were associated with a significantly faster maximum parasite killing. A total of 23 out of 25 patients were characterised accurately as cured, early treatment failure, or recrudescent infections using the final model. The resulting median (IQR) MIC was 0.126 ng/mL (0.0786–0.273 ng/mL), for patients correctly predicted as recrudescent (n=12). Time to MIC is a function of dose since a lower dose, and subsequently lower drug concentrations, will reach a putative MIC value faster than higher doses, assuming similar drug half-lives and parasite characteristics. Cured patients, correctly predicted as cured (n=7), showed a maximum median (IQR) MIC value of 0·236 ng/mL (0·0803–1·47 ng/mL), defined as the cipargamin concentration when predicted parasitemia fell below a total of 10 parasites.

Conclusion: The developed pharmacokinetic-pharmacodynamic model described the relationship between cipargamin exposure and drug-dependent parasite killing succesfully. Sub-therapeutic administration of drugs in development followed by a pharmacometric analysis demonstrated a highly informative approach for determining the *in vivo* MIC in patients. This provides a rational framework for dose-finding in antimalarial drug development.

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Introduction to human challenge models for respiratory viruses and the application of quantitative pharmacology to enhance drug development

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Adult volunteer challenge models are commonly used in a number of infectious diseases, to demonstrate proof of concept for vaccines and large and small molecules. For respiratory virus pathogens, infections are deliberately induced under carefully controlled and monitored conditions, involving attenuated virus strains. For respiratory virus drug candidates, human challenge models present opportunity to support dose selection for continued development with opportunity for lower operational, cost and scientific challenges imposed by patient studies involving natural infection. The application of quantitative pharmacology affords opportunity in the optimal design and application of human challenge models to enhance drug development for respiratory viruses. Case examples of the application of quantitative pharmacology approaches support the application of human challenge models will be presented for both influenza and respiratory syncytial virus.

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Challenges and pitfalls of building models for Flu/RSV and respiratory viruses

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Aims: Mechanistic viral kinetic (VK) models are increasingly being used to support drug development strategies in the treatment of respiratory virus infection [1]. We overview some of the challenges with these models, using influenza and Respiratory Syncytial Virus (RSV) as representative examples for respiratory viral infections.

Methods: The structure of mechanistic VK models is represented using known biology, typically characterizing the viral life-cycle, drug pharmacodynamics and clinical disease symptoms (Figure 1). Challenges associated with modelling each of these kinetic processes were investigated, including consideration of study design and data limitations.

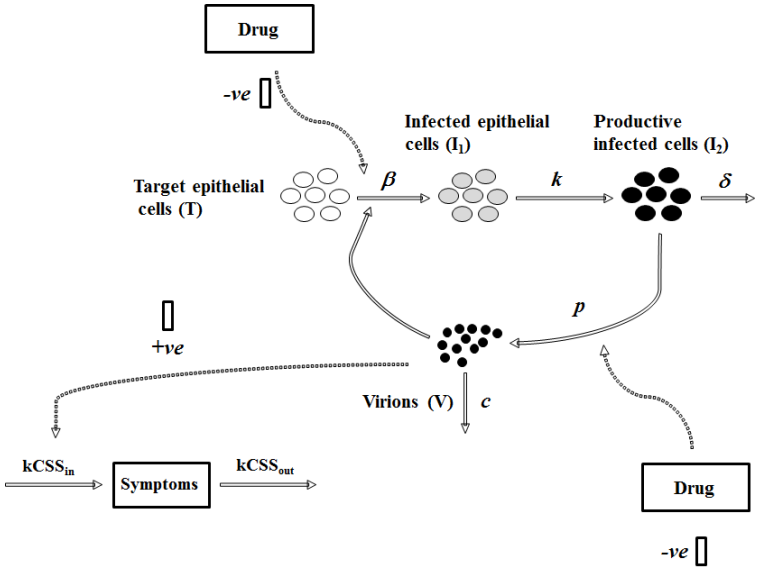

Figure 1 – Schematic representation of the structural model describing respiratory virus kinetics, pharmacodynamic effects and composite symptom scores.

Results: Parameter identifiability is a challenge during VK model development which is due to study design and measurement techniques. This can be overcome by utilising 'known' physiological estimates of RSV and influenza lifespans ($1/k + 1/\delta$) [2,3]. Improved model stability and individual predictions are obtained by eta correlation of infectivity and virion production. In addition, an "effective" antiviral treatment will often result in a large proportion (>50%) of the viral load data reported as BLQ, which can be appropriately handled with M3 implementation [4]. As the doses administered in challenge studies are often supra-therapeutic, this can present difficulties with EC50 estimation. Standard approaches to model evaluation can be challenging; possible solutions to help identify model robustness and mis-specification will be presented.

Conclusion: Mechanistic VK models can provide valuable insights in understanding the pathophysiology of respiratory virus infection and pharmacodynamic effects. However, several difficulties are presented during model development, and may require careful consideration when translationally simulating to target populations.

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A population model for respiratory syncytial virus (RSV) kinetics using transit compartments based on human challenge data

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Aims: Respiratory syncytial virus (RSV) causes acute respiratory tract infections, and is a major cause of hospital admissions and death in young children world-wide (1,2). Currently, no effective treatments exist in adults or children that can prevent or minimise the disease severity following exposure to the virus. The aims of this work were to develop a population model describing the viral kinetics of RSV in nasal lavage, and to describe how these kinetics were altered after treatment with an investigational RSV fusion inhibitor.

Methods: A target-cell limited viral kinetics model with delayed virus production developed by Baccam et al. for influenza A infections (3) is commonly used to describe RSV kinetics. However, the incubation period is considerably longer for RSV than influenza (4). As such, the model was adapted by increasing the number of transit compartments for the infected, non-producing and infected, producing cell populations to allow for a biologically more realistic description of the prolonged transition between the cell populations during the time course of the RSV infection. To ensure identifiability of the model, the virus elimination rate constant was fixed to a literature value of 0.125 hr^{-1}, and the elimination rate constant of the infected, producing cells was assumed to be equal to the transition rate constant for the infected, non-producing cells. The initial number of target cells was set to 410^8 according to the literature (3), while the bioavailability of the inoculum dose was estimated to obtain the initial number of virions in the system. The transit compartment model that best described the placebo data was carried forward into the PKPD model development for the investigational fusion inhibitor. Model development was conducted in NONMEM v7.3 (ICON Development Solutions, Hanover MD) using the SAEM estimation algorithm followed by importance sampling. Beal's M3 method was applied to account for data below the lower limit of quantification (5).

Results: The best placebo model included four transit compartments for infected, non-producing cells, and a single compartment for producing cells. This model fitted the placebo data significantly better than the prior (literature-based) model (3) and was able to capture peak viral load unlike the Baccam model. Between-subject variability was included on the infection rate constant and virus production rate constant, and was found to be high (>200%), with a significant negative correlation (Pearson's Correlation Coefficient = -0.97). The effect of treatment with the fusion inhibitor on RSV kinetics in nasal lavage was best described by a non-dose dependent transformation of the infectious virions into a non-infectious state.

Conclusion: An extended target-cell limited viral kinetics model with delayed virus production using a series of transit compartments was successfully applied to describe the viral kinetics of RSV in nasal lavage and the impact of treatment with a fusion inhibitor in a human challenge model.

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Evaluation of linezolid-induced thrombocytopenia based on hospital pharmacometrics

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Aims: Thrombocytopenia and anemia are among the most important adverse effects of linezolid treatment. Linezolid-induced thrombocytopenia incidence varies considerably but has been associated with impaired renal function. Two studies based on a myelosuppression model assuming non-immune mediated decreased production of platelets noted that the platelet count reached a nadir at day 15 to 20 post linezolid treatment [1, 2]. In contrast, several case reports propose a mechanism involving increased elimination of platelets by linezolid induced immune-mediated destruction [3, 4]. In light of the uncertainty about the mechanism of linezolid induced thrombocytopenia we have investigated the possibility that either myelosuppression or enhanced platelet destruction may be important in a individual patients using hospital data.

Methods: The pharmacokinetics of linezolid were described with a two-compartment distribution model with first-order absorption and elimination. Renal function (RF) was calculated using the Cockcroft & Gault formula with total body weight (TBW) of 70kg and a standard creatinine clearance of 6 L/h/70kg. The decrease of platelets by linezolid exposure was assumed to occur with one of two mechanisms in each patient. These mechanisms are inhibition of formation of platelets (PDI) or stimulation of the elimination (PDS) of platelets. We assumed all observed changes in PDI or PDI were related to plasma linezolid concentration. The pharmacodynamic model is composed of a compartment representing proliferating platelet precursor cells in the bone marrow, a compartment of systemic circulating platelets, and a link between them through three transit compartments reflecting platelet maturation.

Results: The pharmacokinetic parameters for linezolid CL, VC, VP and Q were:

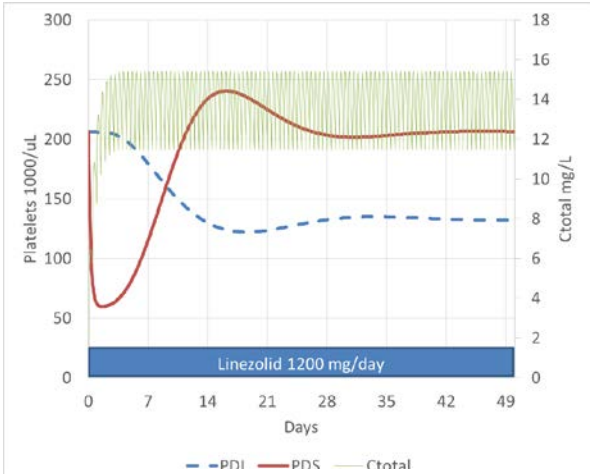
$CL\ (L/h) = (1.86\times e^{(-0.0205\times(AGE-69))}+1.44\times RF)\times(TBW/70)^{0.75}$

$VC\ (L) = 22.9\times(TBW/70)$

$VP\ (L) = 24.7\times(TBW/70)$

$Q\ (L/h) = 10.9\times(TBW/70)^{0.75}$

About half of linezolid elimination is explained by renal CL with normal RF. Impaired RF is common in patients requiring linezolid so RF is an important determinant of linezolid exposure. There was a small (2%/y) decrease of non-renal CL with age. The population mean estimated plasma protein binding of linezolid was 18% and independent of observed concentrations. The estimated mixture model fraction of patients with platelet count decreased due to PDI was 0.97 thus the fraction due to PDS was 0.03. RF had no significant influence on linezolid effect on PDI. Simulations of predicted platelet count of PDI and PDS models were performed with typical linezolid current dosage. When PDI is assumed then the predicted nadir of platelet count is at 14 days after linezolid administration. On the other hand, when PDS is assumed then the platelet count drops sharply to reach the predicted nadir after 2 days.



Time course of predicted platelets count inhibition and stimulation

Conclusion: We have described the influence of weight, renal function, age and plasma protein binding on the pharmacokinetics of linezolid. This combined pharmacokinetic, pharmacodynamic and turnover model has identified that the most common mechanism of thrombocytopenia associated with linezolid is inhibition of platelet formation. Target concentration intervention to reduce linezolid exposure is expected to reduce the risk of thrombocytopenia associated with impaired renal function.

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NextDose: a web-based collaborative tool for target concentration intervention

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Aims: The overarching aim of the NextDose project is to bring better dosing methods to the ward with target concentration intervention software. This includes two major steps of: providing a tool to allow pharmacometric model-based calculations useable by clinicians; and then actually getting them to use it. The goal is for doses to be determined by the best possible method, meaning real patients receiving doses that were determined (at least in part), by the most robust and accurate calculation method possible – not just the easiest to understand or most popular protocol.

Methods: The project started out with several iterations of a tool called FirstDose, beginning with a version written in Java, then an Adobe Flash version, followed by multiple rewrites in HTML and JavaScript until a useable and compatible calculator was fit for purpose for the wards. FirstDose was a fully client-side dose calculator used to recommend first and subsequent doses before concentration measurements became available for dose adjustment. It used published models for vancomycin, amikacin and gentamicin that took into account covariates such as height, weight, post-menstrual age, renal function and certain concurrent treatments. A small clinical trial in paediatric and neonatal intensive care units in Auckland was conducted that evaluated useability and improvements in serum concentrations compared to existing dosing protocols. Of significance, clinicians and lab scientists were more interested in learning how to improve dosing once concentration measurements became available, so work began on NextDose. NextDose would use Bayesian methodology to make the best use of information available for target concentration intervention. It would use a database to keep track of patients, and require a focus on security, stability and collaboration between team members from different locations. The initial release used published models of busulfan, methotrexate and tacrolimus and ran within a browser, communicating securely with a Windows server that performed Bayesian calculations using NONMEM. Output was parsed with Awk into text and csv files that were then processed by a PHP MySQL web server that interacted with a HTML5/JavaScript web app. As early release software, NextDose has been evaluated by audit, being used alongside existing departmental protocols to identify points of difference and opportunity for improvement.

Results: NextDose has been used in the care of over 90 patients receiving busulfan in Auckland. The majority were children under the age of 12. The median dose received has been close to that recommended by NextDose, being just 2% higher. Half of the dose changes made were within -6% and 10% of the NextDose recommended dose. However some doses were markedly different from the NextDose recommendation, in one case being 113% larger.

Conclusion: The NextDose project has met a number of practical challenges along the road to bring better dosing methods to the ward. Challenges include security of healthcare information, compatibility with ageing hospital computers, providing software support for an academic non-profit project, and trying to change routines in a clinical environment that is governed by multiple levels of management and policy. The limited data attained to date has been encouraging, supporting further research into software tools to improve target concentration intervention in hospitals.

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Modeling tumor size and survival in patients with metastatic gastric cancer

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Aims: The aim of this study is to 1) model the temporal course of tumor size of stage IV gastric cancer patients enrolled into 1st line chemotherapy trials, and 2) predict progression free survival (PFS) and post-progression survival (PPS) using tumor size model parameter estimates and patient covariates.

Methods: We analyzed 69 advanced gastric cancer patients enrolled into the ToGA study - a parallel, randomized, open-label, multi-center study - conducted in Severance Hospital, Seoul, Korea, who received one of the following 3 regimens - TXP, TFP and XP (T: Trastuzumab (Herceptin), X: xeloda (capecitabine), P: cisplatin, F: 5-FU) – beginning from December 2005. The time course of tumor size, recorded as a sum of longest diameter of all target lesions, was modeled using the following assumptions. First, kg, tumor growth rate constant, was assumed to increase with tumor size with its initial rate depending on the baseline tumor size ("density dependence"). To this end, logistic growth model was used. Second, from clonal selection theory, kg was assumed to increase with time ("time dependence"). Third, tumor cell populations were partitioned based on sensitivity profiles to different chemotherapeutic regimens, where population fractions sensitive to each drug were estimated as model parameters. Given no concentration data available, drug effect of each drug was modeled as a log-linear function of a hypothetical drug amount obtained from a KPD model linked with a delay compartment. In KPD modeling, a common rate constant was assumed for all drugs assuming X and F have the same drug effect. Total drug effect, which was assumed be a simple sum of drug effect to each drug, was then assumed to inhibit kg. In modeling tumor size, the baseline tumor size was treated as a covariate considering the nature of highly asymmetric distribution thereby being prone to introducing a bias in estimating other model parameters, and the carrying capacity of tumor growth was assumed to increase with the baseline tumor size. For survival modeling, PFS was predicted using the predicted depth of response (DoR) and patient covariates. The predicted DoR was obtained from the initial tumor shrinkage rate, which was either estimated from the baseline or observed from the tumor size measured at the first visit. Finally, a survival model of PPS was fitted using the predicted PFS and patient covariates. Internal validation of the model was performed using visual predictive checks.

Results: With kg increasing linearly with time due to selection pressure, the final tumor size model was parameterized using probability of sensitivity to each drug, rate of tumor progression (which is theoretically equal to tumor heterogeneity), rate constant of KPD model, scale factor of chemotherapeutic effect, and carrying capacity of tumor growth. The fraction of cells resistant to all three drugs was estimated to be about 63.99% for HER2 < 3+ and 49.41% for HER2 3+. Roughly, half of the total tumor cells in a typical patient are sensitive to at least one of the three drugs. The inter-individual variability associated with this probability, however, was large (CV% > 160%). The estimated rate of increase of kg is 11%/month/mm. There was a strong tendency of patients with lower posthoc probability of trastuzumab resistance to be associated with HER2 3+ status. The model well described the general time course of tumor size changes of most patients, and achieved a good fit with observed data. PFS was positively correlated with higher DoR and lower histologic grade. When survival analysis of PPS was done using the predicted PFS and patient covariates, longer predicted PFS and lower baseline tumor size seemed to confer a survival benefit, but only when histologic grade was either well- or moderately-differentiated. Patients with either poorly-differentiated or signet ring cell histology showed poor prognosis regardless of PFS or baseline tumor size. Visual predictive checks of the survival models suggested that our models well predicted the observations.

Conclusion: A new concept of tumor size progression, which is dependent on both tumor density and progression time, was presented. The main findings are: (1) tumor shrinkage rate is inversely proportional to tumor size (favoring Norton-Simon hypothesis over log-kill hypothesis) and thus higher baseline size is naturally associated with poorer prognosis. (2) Probability of trastuzumab sensitivity seems to positively correlate with the positivity of HER2 receptor status(3) With regards to PPS, histologic grade is the strongest determinant. Only when histologic grade is low does PFS and baseline tumor size useful for predicting PPS. This work demonstrates the feasibility of applying a model-based approach to predict tumor growth and patient survival.

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Road to individualising tacrolimus therapy in solid organ transplant recipients

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Aims: Tacrolimus is a pivotal immunosuppressant used to prevent and treat rejection in solid organ transplant recipients. Sub-optimal dosing of tacrolimus causes significant morbidity and mortality. Drug-induced toxicity (including hypertension, hyperglycaemia, nephrotoxicity and neurotoxicity), excessive immunosuppression (causing infections and malignancy) and rejection are frequent problems transplant recipients face. In the last decade several advances have been made to improve tacrolimus dosing. The aim of this talk is to highlight recent progress in this field.

Methods: A literature search was conduct and key study findings have been summarized.

Results: Tacrolimus has a narrow therapeutic index and displays large between subject pharmacokinetic variability. Several studies have demonstrated a relationship between drug exposure and patient outcomes (1). Currently 56 population models have been developed to describe the pharmacokinetics of tacrolimus in transplant recipients (2). Variability in tacrolimus pharmacokinetics amongst transplant recipients has most commonly been related to cytochrome P450 3A5 genotype; patient weight, haematocrit and hepatic function; and time post-transplant (2). The predictive performance of Bayesian forecasting methods to predict tacrolimus area under the concentration-time curve (AUC) based on a limited number of concentration-time measurements has been examined in 14 studies (2). Bias in prediction ranged from -15 to 10%, while imprecision is generally poorer overall, ranging from 0.8 to 40%. In a single-centre, prospective study involving 80 renal transplant recipients, subjects were randomised to receive either computerised or conventional manual dosage adjustment based on trough concentrations (3). Computerised dosing was associated with a significantly higher proportion of trough concentrations within the target range and significantly lower plasma glucose levels at 8 weeks after transplantation (3). Further work is required to promote the uptake of population pharmacokinetic models and Bayesian forecasting into the clinical setting (2). Programs are needed with comprehensive clinical capabilities which are flexible and user friendly. More research is also required to establish optimal tacrolimus exposure in transplant recipients. Since the SYMPHONY study (4) which demonstrated lower rates of acute rejection and improved graft function with low-dose tacrolimus in combination with mycophenolate mofetil and corticosteroids, many transplant centres are using tacrolimus minimisation protocols and lower target tacrolimus trough concentrations (3-7ng/mL). Further prospective studies are required, covering a range of post-transplant times to determine optimal AUC targets. In terms of its mechanism of action, tacrolimus blocks the calcineurin enzyme leading to inhibition of transcription of interleukin-2 and other cytokines normally generated during the late phase of T-cell activation (5). An increasing number of studies are starting to examine the biological efficacy of tacrolimus through immune parameters such as calcineurin enzyme activity, interleukin-2 mRNA expression and interleukin-2 production (5). Pharmacokinetic-pharmacodynamic models based on measurement of an appropriate biomarker may be helpful in adjusting the tacrolimus dose more precise to individual immunopharmacological profiles in the future.

Conclusion: Patient outcomes in solid organ transplant recipients are likely to be improved if dosing of tacrolimus is individualised, with concentration targeting based on rigorous pharmacokinetic and pharmacodynamics analyses.

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Understanding the influence of vitamin K on warfarin dosing requirements

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Aims: Warfarin acts by inhibiting the reduction of vitamin K (VK) to its active form, thereby decreasing the production of VK-dependent coagulation factors. The effects of warfarin can be overcome by administration of VK but this can lead to transient warfarin resistance. The overarching goal of this work is to quantify the influence of VK on warfarin dose requirements. To this end, the required first step is to understand the quantitative influence of warfarin on the time course of factors II, VII, IX, X, protein C (PC), and protein S (PS).

Methods: Data from 17 atrial fibrillation adults who were initiated with oral daily warfarin were analysed. One blood sample was collected at baseline, and at 1, 2, 3, 4, 5, 8, 15, and 29 days after warfarin initiation. Concentrations of clotting factors were quantified using relevant factor deficient plasma in prothrombin time assay (for factors II, VII, and X) and in activated partial thromboplastin time assay (for factor IX). Concentration of anticoagulation proteins, PC and PS, were quantified using chromogenic and ELISA assays, respectively. The data were modelled in a stepwise manner using NONMEM v.7.2. In the first stage, each of the six concentration-time profiles for the clotting factors and anticoagulation proteins were modelled independently using a kinetic-pharmacodynamic (K-PD) model. In the subsequent step, the six K-PD models were put into a single joint model whereby the six clotting factors and anticoagulation proteins were linked by the correlation in the parameter and residual error space. Structural identifiability issues were explored using the popt_i software.

Results: A K-PD turnover model was used for factors II, VII, IX, X, PC, and PS, respectively. The K-PD model consists of two parts: (a) a one-compartment model with linear absorption and elimination for describing the amount of warfarin in the biophase; and (b) an inhibitory Emax model linked to a turnover model for describing the delayed reduction in various clotting factors and anticoagulation proteins after warfarin initiation. Both the fixed effect and random effect of volume of distribution were fixed to obtain a structurally identifiable model. In the joint model, the estimated degradation half-life of VK-dependent clotting factors and anticoagulation proteins were in agreement with previous published values. Prediction-corrected visual predictive check showed that the joint model developed provided an adequate description of the observed data.

Conclusion: The warfarin exposure-response model developed represents the first work to model the influence of warfarin to all six VK-dependent clotting factors (factors II, VII, IX, X) and anticoagulation proteins (PC, PS) simultaneously. The current model provides an initial framework for subsequent incorporation of the VK cycle as an intermediary step between warfarin exposure and response. This will be useful for predicting the coagulation kinetics in response to exogenously administered VK in warfarinised patients.

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How can users benefit from the DDMoRe common language standard and interoperability framework?

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Aims: DDMoRe is a consortium of European Federation of Pharmaceutical Industries and Associations (EFPIA), Academic and Small Medium Enterprise (SME) partners founded in 2011 with the vision to improve quality, efficiency and cost effectiveness of model-informed drug discovery and development (MID3) (1) and therapeutic use (2). This can be achieved by creating standards, tools and a model sharing repository.

Methods: The core DDMoRe products are:

i) an open, pre-competitive drug and disease model repository allowing access to curated and shared knowledge;
ii) an open source interoperability framework providing a platform for bridging modelling tools and methodologies;
iii) training and education supporting adoption of the repository and the framework.

Results: The Model Description Language (MDL) and the Pharmacometrics Markup Language (PharmML) (3) standards have been developed to convey information about pharmacometric models and tasks. The goal of each language is to ensure models and tasks are described consistently between modellers (using MDL) and between software target tools (using PharmML). The model repository holds a diverse range of models encoded using the standards (MDL and/or PharmML) in a controlled environment. With scientific quality in mind, models submitted to the repository have to fulfil minimal requirements prior to their publication. The interoperability framework is an integrated infrastructure enabling use of MDL models across target software. The user interacts with the interoperability framework via the MDL Integrated Development Environment (MDL-IDE) graphical user interface, which includes an editor supporting MDL. During task execution, MDL is first translated to PharmML and then converted to the target software code, e.g. NMTRAN or MLXTRAN. Each task produces a standard output (SO) object which enables consistency in assessment, review and reporting of the modelling and simulation tasks across different target software. The user interacts with the MDL model and SO objects via R, allowing an interface with existing pharmacometrics packages such as Xpose and mlxR. Standards for describing provenance have been defined to capture the modelling context and provide knowledge management for the workflow tasks, to provide an audit trail, track assumptions and ensure reproducibility.

Conclusion: In support of MID3, the core DDMoRe products provide a vital improvement to transparency in model informed decision making, enhancing knowledge-sharing and scientific communication. An indexed, easily accessible and fully searchable drug and disease model repository enables sharing, comparison and integration of existing model knowledge to be applied to new projects/compounds. The use of a universal modelling language to describe models enhances a common understanding of purpose and hence facilitates model re-use. The interoperability framework provides a platform to streamline modelling, providing consistency and reproducible quantitative research. Altogether, the deliverables of the DDMoRe project provide a quantitative framework for prediction and extrapolation, centred on knowledge and inference generated from integrated models of compound, mechanism and disease level data, improving the quality, efficiency and cost effectiveness of decision making.

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What purpose is the DDMoRe library serving?

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DDMoRe, Drug Disease Model Resources, (http://www.ddmore.eu/) is an European project founded by the IMI and EFPIA, which aims to improve efficiency in the process of Model-informed Drug Discovery and Development (MID3). One of the key products is the DDMoRe model repository, an open, publicly-available and free-to-use cloud-based model library for drug and disease models currently under development and which will be further supported by the DDMoRe foundation.

Among the current bottlenecks in applying efficiently MID3 is the complexity of the structural and statistical sub-models and its coding, as well as dataset arrangement. In addition, drug and disease models as they are currently available in the scientific literature do not permit direct comparisons across models, and are often difficult to re-implement without code listings, which are uncommon. Therefore an efficient storage of models covering the majority of the needs in pharmacometrics practice is an urgent need, and has been one of priorities of the DDMoRe activities. To date no publicly-available drug and disease model libraries exist except for recent private initiatives.

To fulfil part of the daily requirements in pharmacometrics an efficient repository needs to be far beyond a simple warehouse. Under this philosophy the DDMoRe model repository provides a platform to: (i) store and share models in a secure and version control manner, (ii) friendly display key model features (e.g. structure, parameters, initial conditions), (iii) annotate models based on ontology standards and metadata, and (iv) connect to external databases opening opportunity for access from scientists of other life science domains. Those main characteristics together with a fully searchable engine can certainly increase the quality of communication and dissemination of results and advances among the pharmacometrics community.

The repository has been prepared to support models encoded in MDL and PharmML, the two standard languages developed by the DDMoRe consortium to enable interoperability across different modelling & simulation softwares and to facilitate communication of M&S models across different disciplines. Nevertheless models provided in original target code are also accepted.

In order to publish a model in the repository a set of minimal requirements, automatically checked when submitting a model, needs to be met. These requirements include the availability of an executable model code, an example of real or dummy dataset guiding data organization, a command text file illustrating how to execute the model, model output results and a set of annotations describing the modelling exercise and its context of use. The goal is to warrant the comprehension and re-usability of models. Currently, the repository contains models related to pharmacometrics in areas such as oncology, diabetes, central nervous system or infectious diseases. Models are supported by the corresponding publication in peer review journals or conference abstracts, but it is also open to models from other fields such as system pharmacology/biology.

In summary, the DDMoRe model repository provides the ground for a successful library which usefulness will ultimately depend on the community acceptance and adoption. It should be noted that currently the quality of the information available depends solely on the submitter. A certification process is currently under development to initially qualify published models from a technical point of view to ensure model correctness and re-usability; future extensions will consider establishment of a scientific validation.

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Would a certification process for models published on the DDMoRe repository serve the modelling community?

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Aims: The Drug Disease Model Resources (DDMoRe, http://www.ddmore.eu/) consortium was created to improve the quality, efficiency and cost effectiveness of Model-Informed Drug Discovery & Development (MID3) by delivering an open source, integrated framework to enable MID3. The DDMoRe Model Repository (http://repository.ddmore.eu/) is a platform for storage of models relevant for MID3 and includes specific features for models represented by the Pharmacometrics Markup Language, PharmML (1). Together with DDMoRe's unique Interoperability Framework, collaborative development of computational models can be facilitated. Models are accepted for publication in the DDMoRe Model Repository if they fulfil specified minimal requirements, which are automatically checked (no human intervention) when uploading the model. However, to ensure that models published in the DDMoRe Model Repository can be trustfully used, a Model Qualification Procedure (MQP) has been developed with the aim to assign qualified models with a DDMoRe model certification.

Methods: The MQP details a human-based review process performed by a body of qualified experts, the Modelling Review Group. The model being subject for review must be publicly available on the DDMoRe Model Repository and meet specified eligibility criteria. The certification is then requested by the model submitter. The review aims to ensure the technical validity of the model and its correspondence with the associated publication and, therefore, checks that i) information associated with the model is complete, makes sense and is sufficient to understand the model, ii) the submitted model code represents the original model in the associated publication without modifications, iii) the model can be executed using the DDMoRe Interoperability Framework, iv) additional validation information is sufficient to prove correspondence of the submitted model with the model in the associated publication. The model evaluation is concluded by a decision of granting or rejecting the certification and the DDMoRe model certification is displayed on the repository, with a short report of the model review outcome.

Results: When a model is granted the DDMoRe certification, the review confirms that the information provided by the submitter is sufficient for model interpretation, i.e. complete and comprehensible. Furthermore, successful execution of the model code by the reviewer endorses functioning of the code. Also, the review concludes that results of the model execution (e.g. parameter estimates and uncertainty, goodness of fit statistics) and other validation output generated from the model code (e.g. simulations, plots) are in agreement with the corresponding results and output generated from the original model code presented in the associated publication, thus confirming the adherence of the certified model with the associated publication. An example of the implementation of the MQP will be presented.
The benefits for the model community of such a technical validation procedure ensures that the certification guarantees that the documentation provided with the model is understandable and that the model can be downloaded from the repository and safely used for the purposes for which it was proposed. Furthermore, these models can then serve as useful examples for various modelling approaches.

Conclusion: The current MQP considers the validity of a model from a technical point of view, thus ensuring that a model is executable and corresponds to is the one reported in the associated publication.

This work is on behalf of the DDMoRe project (www.ddmore.eu).

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What advanced methods and algorithms are promoted through DDMoRe?

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Aims: With the development of common language standards, an interoperability framework and a library of (certified) models the DDMoRe project makes the use of model based drug development (MBDD) more feasible. These methods allow one to more easily investigate and evaluate current modeling methods as well as to develop new methods and algorithms in various real world settings. In light of this, one aim of DDMoRe was to develop new modeling methods and algorithms to improve MBDD.

Methods: Four areas of method and algorithm development were investigated: (1) clinical trial simulation (CTS), (2) model-based adaptive optimal design (MBAOD), (3) model diagnostics and model selection and (4) parameter estimation in complex models. The combination of these tools should allow for a more comprehensive approach to quantitative MBDD. Through simulations of virtual patients with relevant demographic and covariate data, CTS enables computation of the, for example, the anticipated success rate of a future trial. That trial can be designed through the use of MBAOD, to increase/optimize the information gleaned from the trial. With more information, more complex models that fit the current data well and are predictive of future outcomes can be more readily developed.

Results: For CTS, the Simulx R-package has been developed (simulx.webpopix.org), allowing one to simulate complex models for longitudinal data by interfacing the C++ MlxLibrary with R. For MBAOD, the MBAOD R-package has been developed (github.com/andrewhooker/MBAOD), and can be used to plan, simulate, evaluate and run adaptive experiments as your understanding of the system you are studying improves through intermediate analyses of the data. A wide variety of model evaluation and selection tools have been developed and implemented in a number of software packages including PsN (psn.sourceforge.net), Xpose (xpose.sourceforge.net), and npde (www.npde.biostat.fr). Finally, a number of tools for estimation in complex models has been developed and implemented in Monolix (lixoft.com). These tools and the methodolgy behind them have been investigated in a number of pharmacometrics case studies, some of which will be presented.

Conclusion: A number of new methods and algorithms have been developed and implemented in new or existing software tools. These tools can work together to improve quantitative MBDD.

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Why MIC is poison for the mind

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The cost of drug development has exploded in recent years and risen to a level that soon will no longer be affordable to society. One reason for the high cost of drug development are many unnecessary studies where the results could have been predicted with reasonable certainty. PK/PD modeling is a tool that can be used to collect and integrate all the available information about a drug candidate and its class in order to make rational decisions on studies that will decrease the uncertainty of the compound. It is based on quantitative data on drug exposure and response and particularly well suited to address the question of dose finding and optimization. In the drug development process, it bridges the complete cycle from discovery to clinical use. The advantage of this approach is to define objective go/no-go decision criteria for the development process rather than relying on subjective empirical decisions. There is no way that today all developing questions can be answered by experimental evidence, and modeling and simulation is a powerful alternative approach. This modeling and simulation approach is of particular need in the field of new anti-infective agents where the rise of resistance has become an international threat to society. However, very few drug companies are currently developing new antibiotics due to the poor perspective of return on investment. However, the cost of anti-infective drug development can be dramatically lowered by applying pharmacometric concepts and selection of some key experiments based on pharmacokinetic/pharmacodynamic (PK/PD) concepts. Using microdialysis, it is today possible to measure the local exposure at the infection site in both animals and humans. This PK information is much more useful than traditional serum pharmacokinetics. Furthermore, pharmacodynamic activities can be much better captured by analyzing time-kill curves rather than simple minimum inhibitory concentrations (MICs). The use of the MIC has been a major obstacle for fully using all available data in anti-infective pharmacology. MIC is imprecise as it is measured in tewofold increments. It is monodimensional and only assessed at one time-point. MIC does not disclose any information about the maximum kill rate since it is defined by reaching visible growth, independent of maximum kill rate. This is a fundamental difference to EC50 which is defined as the concentration that produces half-maximum effects. There are many situations where the use of MIC is grossly inadequate but the field has been creative in inventing 'patches' (post-antibiotic effect, sub-MIC effect) that are widely accepted without rationale. Kill curve measurement can be shown to provide much more detailed information about the quantitative concentration-effect relationships and is a much more powerful tool to identify optimum dosing regimens both in drug development as well as in patient care. Examples from various classes of antibiotic drugs will be presented where these concepts are applied and illustrated. Application of these concepts will help to develop new anti-infective treatments at low cost to combat resistance development with optimum efficacy and safety. MIC is seen as a threshold value that results from the inability of our brains to integrate multiple simultaneous quantitative relationships. In the old days these situations were often resolved by gut-level decisions. If it gets too complicated we like to draw a line to visualize 'how much we need'. Fortunately, we do now have computers that can aide us in making better and explicit decisions. Appropriate computer software and apps are currently being developed that will make the applications of these PK-PD concepts user friendly and easy to implement.

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Pharmacometricians and statisticians in drug development: can't we all just get along?

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Using some light-hearted 'stereotypes' and informal examples, we will explore some fundamental differences between biostatisticians and pharmacometricians in drug development roles. These include visibility and familiarity to clinical teams, history in the pharmaceutical industry, types of models, and communication of results. Kowalski (1) identified several points of tension and skepticism that has in the past hindered successful collaboration between these two quantitative disciplines. Some of these sources of conflict include the distinction between having a good fitting model versus a model with demonstrated predictive performance, the use of multiple comparisons (stats) versus dose- or exposure-response (pharmacometrics) to make dosing decisions, and pharmacometricians' frequent use of exploratory data analyses to draw confirmatory conclusions. While many of these issues do indeed cause friction, it is important to recognize that pharmacometricians and biostatisticians are both, at their core, modelers; partnering together as a quantitative team is critical. We will make some recommendations on how these two disciplines can cooperate and leverage their complementary assets and skillsets to strengthen the quality of drug development decision making.

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Regulatory-endorsed M&S platforms: the case of Alzheimer Disease CTS

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Aims: Describe the regulatory sciences pathway used by the Modeling and Simulation Work Group of Critical Path Institute's (C-Path) Coalition Against Major Diseases (CAMD), to achieve the first-ever regulatory endorsement for a quantitative drug development platform (a clinical trial simulation platform for mild and moderate Alzheimer's Disease) by FDA and EMA.

Methods: A drug-disease-trial model for mild and moderate AD was developed by integrating patient-level data from clinical trials (CAMD AD database) and a large observational study (the Alzheimer's Disease Neuroimaging Initiative), with summary-level data from the literature, using a Beta-regression approach. With FDA, the regulatory review process was based on the Qualification Process for Drug Development Tools Guidance Document, for which the formal regulatory decision for endorsement took the form of a "fit-for-purpose" designation. With EMA, the regulatory review process was based on the Guidance for Applicants on Qualification of Novel Methodologies for Drug Development, with the ultimate goal of an EMA qualification opinion.

Results: The Context of Use (COU) Statement endorsed by FDA (fit-for-purpose designation) and EMA (qualification opinion), is summarized as follows: What the quantitative drug development platform is: A clinical trial simulation tool to help optimize clinical trial design for mild and moderate AD, using ADAS-cog as the primary cognitive endpoint
What it is based on: A drug-disease-trial model that describes disease progression, drug effects, dropout rates, placebo effect, and relevant sources of variability
What it is NOT intended for: Approve medical products without the actual execution of well conducted trials in real patients.

Conclusion: Both FDA and EMA concluded that this model adequately captures relevant information regarding disease progression, drug effects and clinical trial aspects (placebo effect and dropouts), and that clinical trial simulations based on this tool allows the objective, prospective and realistic evaluation of the operating characteristics of different trial designs.

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Pharmacometrics, biostatistics and computational biology postgraduate training: how can we integrate courses?

Assoc Prof Julie Simpson[1]

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Aims: A career in pharmacometrics, biostatistics and computational biology attracts individuals who enjoy working with mathematical equations, data and writing computer programmes, but at the same time are interested in collaborating with clinicians and laboratory scientists on problems in medicine and biology. There is a lot of overlap in the knowledge and skill set required for each of these careers, highlighting the importance of integrating postgraduate training. The aim of this presentation is to review current course offerings worldwide to see what cross-disciplinary courses are being offered to students.

Methods: As part of the redevelopment of the University of Melbourne Master of Biostatistics, I recently reviewed postgraduate biostatistics courses at leading Universities in the US and UK (e.g. Harvard University, and London School of Hygiene and Tropical Medicine). This was carried out to ensure the core and elective subjects offered at the University of Melbourne, were benchmarked against market leaders. Furthermore, to offer multiple career pathways for graduates, I reviewed other postgraduate degrees in disciplines that also attract students with an aptitude for mathematical sciences and an interest in biomedical research (in particular, the emerging discipline, Computational Biology) to expand the offering of elective subjects.

Results: A pharmacometrics subject was not offered as an elective in any of the Master of Biostatistics courses reviewed. All courses offered a core or elective subject on the analysis of longitudinal (repeated measures) data, however, these subjects only covered linear mixed-effects modelling and generalised linear mixed-effects modelling (e.g. where there is a nonlinear link function for binary outcomes that is linearly associated with the regression model parameters). Non-linear mixed-effects modelling, the main statistical method applied in population pharmacokinetic-pharmaocdynamic modelling, requires knowledge of specialist programmes which are tailored for solving ordinary differential equations (e.g. NONMEM) and have flexible algorithms (e.g. MONOLIX) to circumvent convergence issues. With regards to other discipline Master degrees, a google search only revealed a Master of Science in Pharmacometrics at the University of Maryland, US. The Master of Computational Biology emerged as a growing market with degrees now offered at many Universities worldwide. The inter-disciplinary nature of computational biology was highlighted with students required to complete compulsory biostatistics, biology and computer science subjects.

Conclusions: Currently there is very little cross-over in postgraduate training of biostatisticians and pharmacometricians, with pharmacometrics training primarily offered as a short course taught by Pharmacometrics groups (e.g. PAGANZ offer annual short courses). Postgraduate coursework degrees in biostatistics and computational biology share core and elective subjects to ensure students have the necessary depth and breadth for their future careers. Why is pharmacometrics absent from many of the programmes, when clearly pharmacometricians need adequate statistical knowledge and computational skills as well as an understanding of clinical pharmacology? Is the current training model for pharmacometricians sufficient, or should there be more bridging with postgraduate courses in biostatistics and computational biology? I welcome a lively debate.

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Assessment of pharmacometric and statistical analysis methods in dose-finding trial design: application in diabetes drug development

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Aims: To evaluate the performance of different pharmacometric and statistical methods of analysis when evaluating power of dose-finding trial designs for treatment of type 2 diabetes, with differing levels of model uncertainty (due to limited prior data in patients).

Methods: A population PK/PD model was used to simulate exposure-response relationships for HbA1c and glucose in a typical Phase 2 patient population with diabetes. Although the true underlying model is assumed to be known (an indirect response model of fasting blood glucose linked to HbA1c), different levels of uncertainty are simulated as scenarios with varying confidence in the model parameters. The uncertainty in estimates of Emax and EC_{50}, ranging from 0 to 200% CV, reflect the amount of prior knowledge in patients. Doses for the simulations were selected based on the current parameter estimates. 1,000 trial replicates were simulated for each combination of sample size and number of dose levels. The simulated data were then used for longitudinal and dose/exposure-response modeling by both pharmacometrics and statistics to calculate power. Power was calculated for various metrics, including ability to estimate model parameters and the target dose, using the different models. Simulations are visualized using Shiny, an R package.

Results: In general, power increased with sample size and number of dose levels, and decreased with increasing uncertainty. For example, using an exposure-response model for a 5-dose design, the sample size required for at least 80% power to estimate a target dose whose true typical HbA1c response is within 0.15% of the desired response was 39/arm for the lowest uncertainty, and 53/arm for the highest uncertainty (Figure 1). For Emax models, exposure-response models typically provided slightly greater power than dose-response models. When using the linear model, power was significantly lower due to model misspecification. Results from other analyses are forthcoming.

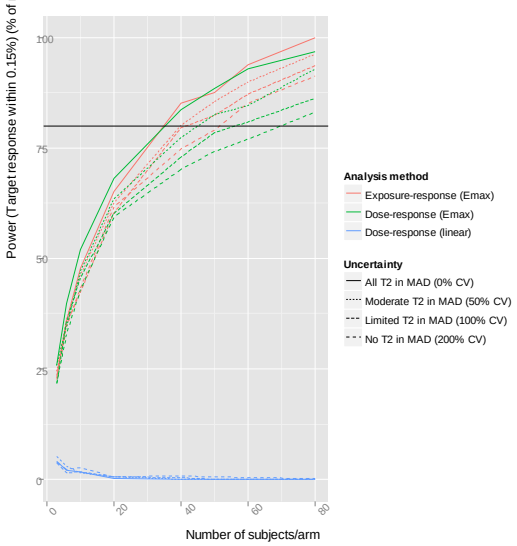

Figure 2

Conclusion: Emax models based on exposure and dose performed comparably, although exposure-response models offer greater advantage when uncertainty is high. Simple linear regression was extremely poor, suggesting that power is low when using a model that does not well describe the underlying dose-response relationship. Further, model uncertainty has significant impact on the design of a dose-finding Phase 2 study. Thus, leveraging prior data in T2DM patients may have significant cost-saving benefits.

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Leaping from plasma and saliva PK to optimize dose selection for optimal drug use

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Aims: Caffeine is the preferred treatment over methylxanthine to treat apnea of prematurity in neonates. There are limited use of therapeutic drug monitoring (TDM), however the possibility of having toxicity and sub-therapeutic concentrations remains in extremely premature neonates. TDM typically requires taking a blood sample, which is difficult in this patient population. There is a trend towards the use of salivary sampling, which is non-invasive. Since neonates have a higher salivary secretion pattern than adults, it is feasible to obtain much richer samples from salivary sampling. The objective of this study is to develop a population PK model to describe the kinetic association of plasma and salivary caffeine concentrations after dosing in preterm neonates.

Methods: Enrolled preterm subjects (n=29) received a daily oral dose of caffeine at 10 mg/kg/day [1]. A pair of plasma and salivary samples was obtained less than 1 hour prior to the next dose and subjected to HPLC analysis for caffeine concentrations. The concentration and dosing data were fitted with a population PK model. NONMEM 7.3 (ICON plc) and PsN 4.4.8 were used to develop the model.

Results: We developed an innovative circulation model that simultaneously describe the plasma and salivary PK of caffeine in neonates. This model links the plasma and saliva PK of caffeine and describes the kinetic association of caffeine concentrations in between plasma and saliva depot after dosing. Based on this model, salivary caffeine measurements can be used to calculate and predict plasma concentrations for the purpose of in situ drug monitoring and dosing regimen adjustments.
The proposal is to use M&S techniques to show approaches to optimize dose selection in this situation. We are working to develop a method and an interactive software package to implement the optimization. The software is designed to function based on predefined population caffeine plasma/saliva PK model. It will use a few in situ measurements of salivary caffeine levels as inputs, and calculate Bayesian estimates of PK parameters for each individual patient. With this, it can provide the prediction of current plasma concentrations with statistical confidence and suggest next optimal dose(s) to aim for targeted therapeutic windows. We are building a demo version of the software in an R Shiny application to showcase the concept. After this, we are looking to transfer the application to other platforms that are more accessible to clinicians in hospital use.

Conclusion: We have developed an innovative circulation model that links the plasma and salivary PK of caffeine in neonates. Based on this model, we are developing an application that would not only be used to predict between plasma and saliva concentrations but also for dose determination, and predict if dosing is sufficient in the neonates when measuring only saliva PK concentrations.

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Application of a multi-criteria decision analysis model in the dose selection of combination therapy for overactive bladder

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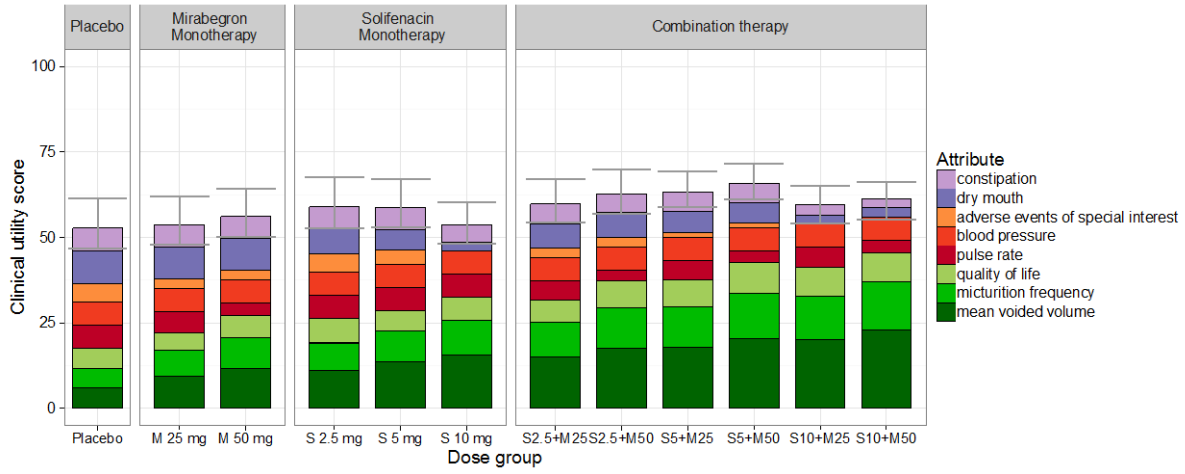
Aims: To support the selection of dose combination(s) of solifenacin and mirabegron for further development using a transparent and standardized approach, and to characterize the added value of the combination compared to the respective monotherapies. This was accomplished by performing a multi-criteria decision analysis (MCDA) evaluating the clinical utility of the combination use of solifenacin and mirabegron.

Methods: MCDA is used to optimize decision making in situations requiring simultaneous evaluation and trade-off of multiple, qualitatively different criteria. Building on the expert knowledge required for complex decision making, MCDA provides a transparent framework in which to interpret and compare the relevant benefits and risks in a quantitative fashion.

Efficacy and key safety data obtained in a phase II study (study 178-CL-100) were used for the MCDA. Reported surveys and informal discussions with European and US urologists, as well as patient opinions, were used to identify crucial attributes and their relative importance. A component utility function was defined for each attribute, describing the contribution to the overall utility of the combination of solifenacin and mirabegron. The utility functions were based on historical results from monotherapy trials. Factors associated with efficacy, safety and tolerability were balanced, using the MCDA, to determine the clinical utility of different dose combinations. Improvements in efficacy (e.g. increased mean voided volume) and improvements in safety and tolerability (e.g. reduced dry mouth) resulted in a higher clinical utility. Sensitivity analyses were performed to assess the effect of varying the relative attribute weights, thus testing the robustness of the results.

Results: The clinical utility of different dose combinations of solifenacin and mirabegron is presented in the figure below. In this figure, the relative contribution for each attribute is shown and the sum represents the clinical utility score. The error bars represent the 95% confidence interval of the total clinical utility score.



Conclusion: The combinations of solifenacin 5 mg and mirabegron 25 mg and mirabegron 50 mg had the highest clinical utility score in the primary analysis and supported combination therapy development of solifenacin and mirabegron for phase III clinical development at these dose regimens. This case study illustrates how a MCDA approached can integrate the benefit risk assessments of clinical experts as well as patient opinions to support a clinical drug development program in a transparent and standardized manner.

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Modeling and simulation with evolving cancer therapies: combinations, cancer immunotherapy, and more

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Aims: Recent break-through and success in oncology including immuno-oncology and combination therapies has generated many excitement. With newer medicines being more effective to prolong patient's life, finding the optimal dose regimens that best balance efficacy and safety profile is critical for chronic anti-cancer treatment. The aim of this presentation is to illustrate the impact of multiple modeling and simulation (M&S) approaches for dosing optimization in oncology with case examples including combinations and cancer immunotherapy.

Methods: M&S approaches to be highlighted include preclinical-to-clinical translational modeling, early-to-late translational modeling, exposure-response and longitudinal Pharmacokinetics/Pharmacodynamics (PK/PD) for efficacy and safety endpoints, literature meta-analysis, and Physiologically-Based Pharmacokinetics (PBPK) modeling.

Results: Combination therapy has become common practice in oncology with multiple mechanisms of action and/or simultaneous inhibition of multiple targets to enhance activity in broader population with less resistance. Typical combo strategy includes combination of an investigational agent with Standard of Care (SOC) or combination of 2 investigational agents, each has their unique considerations in dosing optimization. Recent immune-oncology therapies have shifted the oncology development paradigm with their unique mechanism of actions and pronounced efficacy in many cancer types. These drug development challenges offer special opportunities for innovative study design, mechanism related effective measurements (pathway and disease biomarkers, imaging), and broad application of M&S throughout the development cycle. Case examples will include application of PBPK and population PK approaches to evaluate PK drug-drug interaction (DDI) and inform trial design for small molecule combinations, application of translational and clinical PK/PD to evaluate PD DDI and optimize dosing based on therapeutic windows, with highlight of special considerations for cancer immunotherapy. Meta-analysis of literature summary-level data and internal individual-level data offer unique insights regarding SOC benchmarking, decision making based on early trial endpoints, and the underlying response mechanisms to ensure right patient selection.

Conclusion: Modeling and Simulation has shown growing impact with evolving cancer therapies to provide data driven quantitative analyses and projection to guide study design and decisionmaking in drug development.

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Bench-to-bedside translation of antibody drug conjugates (ADCs) using a multiscale mechanistic PK/PD model

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This presentation will highlight the importance of understanding and quantitatively integrating the preclinical PK of antibody-drug conjugates (ADCs) to enable their preclinical-to-clinical translation. Two different case studies will be presented using the two clinically approved ADCs, trastuzumab emtansine (T-DM1) and brentuximab vedotin (SGN-35). Importance of understanding the tumor disposition of ADCs to enable the prediction of their clinical efficacy will be highlighted using SGN-35. In addition, the importance of understanding the whole body disposition of ADCs to enable the prediction of their clinical PK (and hence the toxicity) will be highlighted using T-DM1.

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Optimization of trial design and dose selection based on the quantitative assessment of the efficacy of TAK-385, an investigational, oral GnRH antagonist, in patients with prostate cancer

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Aims: To select a dose for confirmatory trials using prospective simulations based on a PK/PD model of testosterone (T) suppression with the non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist TAK-385, resulting in >90% of patients with Testosterone ≤ 50 ng/dL (medical castration) for 48 weeks.

Methods: Pharmacokinetic (PK) and Testosterone (T) data were obtained from 3 phase I/II clinical trials. In total, 104 healthy males and 174 prostate cancer patients contributed 2465 PK and 3445 T observations, after treatment with various TAK-385 maintenance doses (40-160 mg daily) for up to max 48 weeks. A PK/PD model was developed using non-linear mixed-effects modelling in NONMEM V7.2.0 [1]. Simulations were performed to construct the exposure-effect curve, and predict the fraction of subjects with sustained T ≤ 50 ng/dL over a 48-week treatment period (80-120 mg OD, after a loading dose on day 1).

Results: A three-compartment model with first-order delayed absorption and first-order elimination and an exponential error model adequately described TAK-385 PK. T levels were described using a semi-mechanistic PK/PD model, which combined indirect response-based modelling of production and degradation processes (GnRH, testosterone) with competitive and reversible inhibition of endogenous GnRH binding by TAK-385, and down-regulation mechanisms of GnRH receptors. Age was included as a covariate for the endogenous agonist (GnRH) concentration at baseline to account for different baseline T between healthy men and prostate cancer patients. Simulations showed that the proportion of patients with sustained medical castration reached a maximum at doses of 100 mg OD and above, with minimal added benefit beyond 120 mg OD. Higher doses were associated with a more robust T lowering response vs lower dose regimens, taking the 95% CI of expected responders into account. Large variability in PK and PD responses required a sufficiently high maintenance dose to ensure that >90% pts achieve and maintain T ≤ 50 ng/dL.

Conclusion: This analysis provided an integrated understanding of the relationships between TAK-385 dose, exposure and efficacy to inform trial design and decision-making in oncology drug development. A clinical trial of 610 patients receiving TAK-385 120 mg OD, which can produce a larger and consistent treatment effect, has a prospective power of >90%, even when allowing for a 15% dropout.

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An analysis of patient-reported outcomes (PRO) in breast cancer patients through item-response theory (IRT) pharmacometric modeling

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Aims: Patient-reported outcomes (PRO) provide a valuable means to assess the subjective impact of a disease and treatment on patients' symptoms, adverse effects, functional status and quality of life. An item response theory (IRT) pharmacometric (PM) approach (1) is proposed herein to facilitate PRO interpretation, accounting for their multi-scale nature and frequent missing data. This IRT PM analysis aims to characterize Functional Assessment of Cancer Therapy-Breast (FACT-B) data in breast cancer patients following treatment with trastuzumab emtansine (T-DM1), investigate potential exposure-response relationships, and compare the response of TDM-1 to a reference (capecitabine and lapatinib) treatment.

Methods: The FACT-B questionnaire consists of 36 items with ordered categorical answers, divided into 5 subscales: physical, social, emotional and functional well-being, and a breast-cancer subscale (BCS). Item-level FACT-B data were collected at multiple visits from locally-advanced or metastatic breast cancer patients involved in a phase 3 trial (2) and treated with TDM-1 (N=484) or capecitabine and lapatinib (reference arm, N=478). The IRT longitudinal model was developed in three steps using TDM-1 arm data. In step 1, a base IRT model was fitted to naively pooled data from all visits. Proportional-odds models described the probability of each item's score as a function of item-specific parameters and a latent variable (well-being, Ψ) specific to each patient, visit and subscale. Ψ was assumed to be standard normally distributed at baseline. The empirical Bayes estimates of Ψ were subsequently used as dependent variable in step 2 where a longitudinal well-being model was developed to describe Ψ individual time-courses. Linear and non-linear functions of time were considered. A stepwise covariate search evaluated the effect of baseline characteristics (demographics, disease state and prior therapies) on model parameters. TDM-1 exposure (AUC_{cycle1} and $C_{min,cycle1}$)(3) effect on model parameters was also investigated. In step 3, models developed in steps 1 and 2 were combined into a final longitudinal IRT model. A similar 3-step approach was applied to the reference arm data, fixing the item-specific parameters and keeping the longitudinal model and covariate model structures as in TDM-1 model.

Results: In the base IRT model, 180 item-specific parameters were estimated using TDM-1 data. The BCS being heterogeneous, its items may thus not relate to the same underlying variable and could not be adequately fitted using a separate Ψ variable; their reassignment to one of the four other subscales based on log-likelihood ratio tests resulted in an improved fit (dOFV=-1138). Correlations at the individual level between Ψ from different subscales ranged 34-68%. The time course of Ψs was best described by an asymptotic function of time. A large additive inter-individual and moderate inter-subscale variability on the asymptote parameter Ψ_{ss} allowed patients to improve ($\Psi_{ss}>0$), stay stable ($\Psi_{ss}=0$) or worsen ($\Psi_{ss}<0$) in a subscale-specific manner. A common progression half-life for all subscales was estimated to 52 days. The typical emotional well-being improved over time whereas social well-being worsened. No statistically significant typical change in well-being was identified for the physical and functional subscales. A statistically significant ($p>0.001$) effect of race was found on the baseline social and functional well-being. No relation was identified between progression and TDM-1 exposure. When applied to reference arm data, the IRT longitudinal model showed a statistically significant typical worsening in the physical subscale resulting in lower typical expected scores for the physical subscale items in the reference arm compared to the TDM-1 arm. The typical asymptote was also slightly lower for the other subscales.

Conclusion: The developed framework adequately described longitudinal FACT-B data following TDM-1 or reference treatment. It could characterize the multidimensional nature of FACT-B and handled missing scores with no need for imputation. No exposure-response relationship was found in the TDM-1 arm for either of the subscales. There was a worsening of physical well-being identified in the chemotherapy containing reference arm, whereas in the TDM-1 arm patients typically stayed stable. When combined with traditional efficacy and safety analyses, PRO offer health care professionals, patients and payers an additional assessment of overall health care value from a patient-centered perspective at the approved dose.

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From transformative to disruptive - pharmacometrics' crucial role for inferring treatment effectiveness

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Background: Employment of pharmacometric concepts and techniques (PM), including modeling and simulation, in drug development have been transformative via integration into regulatory guidance, review, and approved drug labels[1 2 3]. Although application of PM can yield quasi-causal evidence of effectiveness and safety, such findings have been limited to a "supportive" role in drug approval [4 5].

The traditional statistical framework employed by regulatory agencies for inferring "substantial evidence" of effectivness for marketing approval has employed empirical frequentist null-hypothesis tests, demonstrating a *low probability ($p<0.05$), assuming non-effectiveness*, based solely on outcomes of two phase III randomized controlled clnical trials, ignoring evidence from other sources[4]. The frequentist approach involves estimating the probability of the trial data, given the assumption of non-effectiveness. Exceptionally, PM derived, supportive evidence of effectiveness has informed approval decisions, as in the 505(b)(2) and single trial FDA approval pathways [5 6 7].

Thesis: Disruptively, but beneficially, "substantial evidence" of effectiveness can be based on acceptance of a *high probability of effectiveness*, from accumulating evidence from all reliable sources of effectiveness data, especially using quasi-causal evidence derived using PM. This statistical framework, differs from the frequentist approach by directly estimating the *probability of effectiveness, combining prior information with new data*, and bears the signatures of Bayes and Laplace.

Progress: Population distributions of Exposure (dose or concentration) - Response data using parmacometrically modeled trial data, have provided valuable support for labeling elements such as individualization of dosage (to minimize toxic exposures, drug-drug interactions and other adverse demographic influences), evaluation of QT prolongation, and occasionally to support evidence of effectiveness[3]. The latter use has been ad hoc and variably employed to expedite approval of drugs for unmet medical needs, such as for cancer and rare diseases. Two public workshops on Bayesian methods in drug development and regulation (2004[8] - 2016[9]) have encouraged employment of this approach in adaptive trials[10], construction of historical controls, and regulatory decisions. The DIA Bayesian Scientific Working Group (BSWG) has worked to facilitate the appropriate use of Bayesian methods for design, analysis, and interpretation of clinical trials[11]. At the same time, widespread misuse of frequentist methods in evaluation of clinical trials has increasinigly come under intense, critical scrutiny[12].

Conclusion: The statisical framework for regulatory evaluation of substantial evidence is approaching a tipping point, potentially transitioning from strict reliance on frequentist null-hypothesis testing to employment of Bayesian/Laplacean inference. Rigorously employed, the transformative effect of pharmacometrics can become a powerful vehicle for the disruptive incorporation of PM derived, quasi-causal evidence in drug approval decisions.

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Using normal fat mass to account for body size and composition

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Aims: Allometry is the study of how body size is related to body function. In clinical medicine, size related differences in biological functions such as heart function (cardiac output, CO) and kidney function (glomerular filtration rate, GFR) are routinely scaled by body surface area (BSA). In contrast, a more fundamental theory (1) relates body mass to function, based on the energetic needs of cells and the structural overhead associated with larger mass. This biologically based allometric theory is consistent with previous "scaling laws" and has been confirmed by extensive cross-species observations in all domains of biology. Total body mass (TBM) can be thought of as being composed of fat mass (FAT) and (fat free mass (FFM). However, current allometric theory does not distinguish between these two components of body mass. The aim of this presentation is to show how allometric theory can be extended to describe body size and composition using the concept of normal fat mass (NFM).

Methods: Normal fat mass is defined by $NFM = FFM + Ffat \times FAT$.
Ffat is the fraction of FAT kg that contributes to **functional body size** relative to FFM kg.

Results: For a wide variety of drugs, elimination and distribution are well described using theory based allometry and normal fat mass. NFM becomes FFM when Ffat=0 and TBM when Ffat=1.

Drug	*Ffat* elimination	*Ffat distribution*	Subject population
Warfarin	0	0	264 adults (2)
Gemcitabine	0	0	56 adults (3)
Dexmedetomidine	0	0	40 adults (4)
Busulfan	0.509	0.203	1610 neonates-adults (5)
Ethanol	1	0.390	108 adults (6)
Paracetamol	1	0.778	189 adults (7)
Propofol	1	1	70 adults (8)

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Prediction of fat free mass in children

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Aims: Fat free mass (FFM) describes the non-fat component of the body. It has been advocated as an appropriate size descriptor to scale drug clearance (CL) and hence drug doses in adults and children. When compared to other size descriptors such as total body weight, FFM has been shown to correlate well with CL. Models for predicting FFM have been developed in adults but there is currently a paucity of mechanism-based models developed to predict FFM in children. The aim of this work was to develop and evaluate a model to predict FFM in children.

Methods: A large dataset (496 females and 515 males) was available for model building. Subjects had a relatively wide range of age (3 to 29 years) and body mass index values (12 to 44.9 kg/m^2). Two types of models (M1 and M2) were developed to describe FFM in children. M1 was fully empirical and based on a linear model that contained all statistically significant covariates and their interactions. M2 was a simpler model that incorporated a maturation process. M1 was developed to provide the best possible description of the data (i.e. a positive control). In addition, a published adult model (M3) was applied directly as a reference description of the data (Janmahasatian et al, 2005). The predictive performances of the three models were assessed by visual predictive checks and by using mean error (ME) and root mean squared error (RMSE). A test dataset (90 females and 86 males) was available for external evaluation.

Results: M1 consisted of 9 terms with up to 2nd level interactions. M2 was a sigmoid hyperbolic model based on post-natal age with an asymptote at the adult prediction (M3). For the test data set, the ME and 95% CI for M1, M2 and, M3 were - 0.16 (- 0.32 to - 0.01), - 0.56 (- 0.87 to - 0.29) and - 1.49 (- 2.1 to - 0.91) kg, respectively and RMSE were 1.14 (0.98 to 1.33), 2.02 (1.5 to 2.49), and 4.32 (3.52 to 5.19) kg.

Conclusion: A maturation model that asymptoted to an established adult model was developed for prediction of FFM in children. This model was found to perform well in both male and female children. Interestingly, the adult model (M3) performed similarly to the maturation model to describe FFM in females. The ability to predict FFM in children from simple demographic measurements is expected to improve understanding of human body structure and function with an application in drug dosing.

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The importance of body size for bridging studies

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Clinical development standard in Japan has changed over the last decades along with ICH E5 and Japan guidelines (JP GLs; by MHLW, PMDA) that support use of non-Japanese data as part of clinidacal data package for NDA in Japan, which is practically implemented as "bridging study" or "global study". After ICH-E5[1] and JP GLs for multi regional clinical trial[2-3], timeline to develop drugs in Japan had also been synchronized with Western countries and we no more hear the word "drug lag" in Japan. In current Japan standard development, participation to international phase 3 clinical trials is encouraged, which avoids repeating stand-alone trials in Japanese patients that are often underpowered. In recent JP GL[4] referring to phase I and multi regional clinical trial, J-Ph1 studies are stated as not necessarily required prior to Japan's participation to global studies ifforeign clinical data ensure safety in Japanese patient population. In order to optimize development scenario in Japan, not only to take advantage of recent regulation in Japan, inter-ethnicity comparison for PK and safety (and efficacy) is increasingly important both in early and late phase of clinical studies. For example, PMDA is often concerned about the consistency of outcomes in the subset of Japanese patients and the total trial population.

Body size is ruitinely considered, and in most cases account for signifincant part of PK difference between Japanes and non-Japanese patient population. However, it is not always sufficient factor to explain the inter-ethnicity difference depending on drug's characters.

We would like to present overview of body size effects based on our experiences in drug development and to discuss how pharmacometric appproach can support our development.

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3. JP GL: Basic principles on global clinical trials (reference cases) 2012
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A simple mechanistic pharmacometric model for HIV in children and adults

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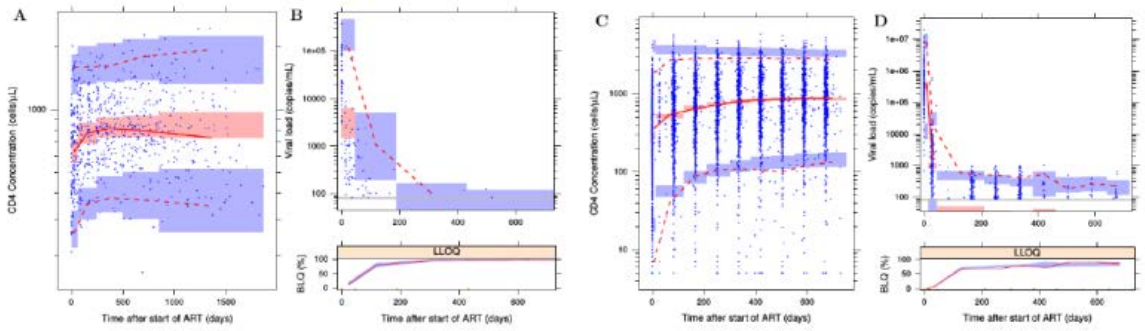
Aims: Models for CD4 count and viral load have long been crucial in antiretroviral drug development [1], and have increasingly been used in long-term pharmacometric studies [2,3]. However, the basic model has the following problems when fitting long-term data: mathematical instability and oscillatory behavior; not accounting for CD4 T-cells division in the periphery; no clear method to scale for size and age (normal CD4 T cell count drops 3-fold over the first 5 years of life); incorrect attribution of multi-phasic viral decline due to very rapid free virion clearance and insufficient circulating latent reservoir to give multiple phases (<1% of circulating cells are infected [4]); assumption of steady-state so cannot account for disease progression. These problems extend to more complex models with latently and quiescently infected compartments. We aimed to develop a new model which is mathematically simple but incorporates biological prior knowledge to address these problems. Focus in this work will be scaling for size and age.

Methods: Starting with the basic model we removed the infected CD4 T cell compartment, adding a viral-dependent CD4 loss term. The zero order CD4 production rate was assumed to come directly from thymic output, and density-dependent proliferation and loss terms were added. Considering scaling for size, Ki67 (a marker for proliferation) expression decreases with age [5] suggesting proliferation (and loss assuming homeostasis) is higher in younger patients. Upon reanalysis we show size is a more plausible explanation, the proliferation and loss allometric exponent estimate being 0.77. Thymic output inferred from thymic epithelial space volume, or more accurately by T cell receptor excision circle expression, falls with age according to a well characterised relationship [5]: this scaled our thymic output term. Virion production and loss were set equal, with loss assumed to slow with decreasing viral load using a logistic Michaelis-Menten-like term. We have fitted this model to adult and paediatric data but confine this work to two paediatric studies ARROW and PENTA11. Briefly, ARROW was an open-label RCT in 1206 antiretroviral naive children followed up for 3-5 years. PENTA11 randomised 109 children already on antiretrovirals, to either continue treatment or have periods of treatment interruption. Importance sampling implemented in NONMEM 7.3 was used for parameter estimation; the M3 method was used for viral load datapoints below the detection limit.

Results: System-related parameters were similar for both ARROW and PENTA studies indicating mechanistic parameters have been captured: for example the proportion of expected thymic output being 0.10 and 0.18 respectively, which is in agreement with recent work suggesting the Bains estimate [5] to be high. Various extensions have been explored including a model for viral rebound in the ARROW data (time to rebound 408 days, IIV 89%CV).

Figure 1: VPC for CD4 T cell count and viral load in PENTA (treatment interruption) (A,B) and ARROW (responders) (C,D)



Conclusion: A new HIV model has been developed with a priori scaling for size and age. Future work will involve inclusion of PK data and adding genetic determinants of viral resistance.

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Population pharmacokinetics and pharmacodynamics of an oral glucagon receptor antagonist (LY2409021) and implications of patient dropout

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Aims: Study protocols for antidiabetic drugs often include withdrawing study participants due to elevated fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) above clinically acceptable limits, or withdrawing participants for safety reasons. Furthermore, patients can voluntarily dropout from the study for any reason at any point during the study. We sought to quantify the exposure-response relationships for efficacy (FPG and HbA1c) and safety (alanine aminotransaminase [ALT]) for an investigational glucagon receptor antagonist (LY2409021) in patients with type 2 diabetes mellitus (T2DM). In addition, we included information on dropout and evaluated the impact of this information on the estimated exposure-response relationship. Lastly, we carried out clinical trial simulations to investigate the impact of dropout on study power and tested alternative study designs.

Methods: Data from a total of 373 healthy subjects and patients with T2DM (7 studies) were combined to develop the population pharmacokinetics (PK) model and investigate the effect of predefined covariates. Pharmacodynamic data (FPG, HbA1c and ALT) were available from a 24 week phase 2 dose ranging study in which patients with T2DM were equally randomized to 3 LY2409021 dose levels and placebo (N = 254). PK and exposure-response modeling were performed using NONMEM 7.3.0. Clinical trial simulations were carried out using R 3.2.2.

Results: A one-compartment model with first order absorption and elimination adequately described the PK of LY2409021. Body weight was the only significant predictor of clearance and volume. A linked indirect response model was used to describe the time course of FPG and HbA1c simultaneously. Time course of ALT was also modeled simultaneously with the FPG and HbA1c using an indirect response model. Treatment with LY2409021 decreased FPG, consequently leading to a long term reduction in HbA1c. Through an Emax model, the glucose-lowering effect of LY2409021 was constrained such that the HbA1c could not be reduced below a physiological threshold. A time-dependent placebo effect on FPG and HbA1c was included in the model. There was a trend towards higher ALT concentrations with increased LY2409021 exposure, which was adequately captured through a non-linear relationship. A time to event modeling approach was used to describe the dropout, and FPG was a significant predictor of the hazard. Patients with higher FPG values (those in the placebo arm and those with lower LY2409021 exposure) were at higher risk of dropping out of the study, resulting in patients randomized to higher LY2409021 doses being more likely to complete the study, potentially biasing the estimation of drug effect.

Conclusion: The exposure-response relationships for LY2409021 were described through a simultaneous modeling approach that included a model for the dropout. Simulations revealed that daily doses of 10mg to 20mg of LY2409021 would be effective in achieving clinically significant FPG and HbA1c reductions in patients with T2DM. The model incorporating dropout was also used to determine the study power for various study designs taking into account the impact that dropout would have on the number of patients completing a 24 week study period. Adaptive designs that increase drug exposure in patients with elevated FPG may result in a more efficient and optimized clinical trial designs.

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Recommended doses of Levobupivacaine for TAP Blocks: Development of a pharmacokinetic model and estimation of the risk of symptoms of local anesthetic systemic toxicity

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Aims: Tranversus Abdominal Plane (TAP) blocks are widely used for postoperative analgesia following abdominal surgery. In this block, the local anaesthetic (LA) solution is injected between the internal oblique and transverse abdominis muscles. Ultrasound guidance has facilitated anatomical plane identification, increasing TAP block popularity. Despite higher precision using ultrasound guidance, high plasma levels of local anaesthetic and systemic toxicity (LAST) cases have been reported with standard doses of ropivacaine and levobupivacaine. Currently, there are no population pharmacokinetic (PK) models describing levobupivacaine absorption during TAP blocks. Our aim is to characterize levobupivacaine absorption pharmacokinetics with and without epinephrine using a population modeling approach, and estimating the risk of LAST of different dose schemes, based on simulation analysis.

Methods: This secondary PK analysis of levobupivacaine uses data from a previously published study[1]. Eleven volunteers underwent ultrasound-guided TAP blocks in two independent occasions; the first one, receiving 20 ml of plain 0.25% levobupivacaine, and the second one, adding epinephrine (5mcg*ml-1) to the anaesthetic solution. Serial venous concentrations were measured for 90 minutes. Plasma concentrations of levobupivacaine were used to estimate PK population parameters, using Nonlinear Mixed Effects Models. Analysis of covariates included the use of epinephrine. Estimated pharmacokinetic parameters of levobupivacaine with and without epinephrine and their variability were used to test different dose schemes in a simulated population of 1000 patients. The associate risk of LAST symptoms was calculated, for two commonly recommended dose schemes of 3.0 mg*kg-1 levobupivacaine with epinephrine and 2.5 mg*kg-1 levobupivacaine without epinephrine.

Results: A 1-compartment first order input and elimination model adequately fit levobupivacaine data. The inclusion of epinephrine effect on Tabs produced a significant decrease in OFV of -20.659 points. An additional effect of epinephrine on levobupivacaine bioavailability was tested producing a further improvement in model fit (ΔOFV of -62.834). The derived model predicts that levobupivacaine dose schemes should be halved from 3 mg*kg-1 with epinephrine to 1.5 mg*kg-1 without epinephrine, to obtain a comparable risk of anaesthetic toxicity symptoms of approximately 0.1%. The distribution of levobupivacaine Cmax values obtained using two commonly recommended dose schemes of 3mg*kg-1 levobupivacaine with epinephrine and 2.5mg*kg-1 levobupivacaine without epinephrine is shown in figure 1.

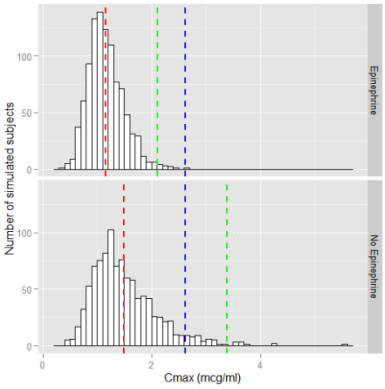

Figure 1. The red dashed line is the mean Cmax. The green dashed line is the 99th percentile of Cmax distribution. The dashed blue line represents the levobupivacaine toxic threshold (2.62 mcg*mL-1)).

Conclusion: Our results strongly support the addition of epinephrine to the local anaesthetic solution, especially when doses of levobupivacaine > 1.5 mg*kg-1 are required. Recommendations regarding the maximum allowable doses of local anaesthetics should consider population analysis to determine safer dosage ranges.

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A Framework for quantifying the influence of adherence and dose individualization

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Aims: The property of a drug that signifies the likelihood of therapeutic success to imperfect adherence is termed forgiveness. Recently forgiveness has been quantified as relative forgiveness (RF) [1] which describes the times more likely a drug is forgiving under imperfect adherence compared to perfect adherence (typically RF < 1). RF does not account, however, for the underlying probability of therapeutic success. The aims of this work were to (1) introduce an extension to this concept that accounts for the underlying probability of therapeutic success both without individualization *a priori* relative forgiveness and after dose individualizaiton *a posteriori* relative forgiveness and (2) illustrate cases for interpreting these measures.

Methods: (1) Defining *a priori* and *a posteriori* RF. In both cases is scaled by the probability of therapeutic success based on using the standard dose, *a priori* (, or after doses have been individualized, *a posteriori* (. (2) Application of *a priori* and *a posteriori* forgiveness to examples of atorvastatin and omeprazole. We consider atorvastatin in the presence or absence of physician-led individualization of the dosing regimen; and omeprazole in the presence and absence of patient-led symptom control of gastroesophageal reflux disease. For both cases, a population pharmacokinetic-pharmacodynamic (PKPD) model was identified. Subsequently, the clinical utility of *a priori* forgiveness and *a posteriori* forgiveness were explored using three dose levels of each drug. Five thousand sets of individual PKPD parameters were simulated under perfect adherence and imperfect adherence. For both cases a series of imperfect adherence scenarios constructed were 1, 10, 20, 30, 40, 50, 60, 70, 80, and 89 missed doses out of 90. Because missed doses were generated randomly, each virtual patient would have had a different profile of imperfect adherence. *A priori* RF and *a posteriori* RF were then plotted against the series of imperfect adherence scenarios to evaluate the influence of missed doses compared to individualization.

Results: Atorvastatin Three doses considered were 10 mg, 40 mg, and 80 mg. For atorvastatin we see that *a posteriori* RF is always greater than *a priori* RF for all levels of missing doses (up to 80 missing doses out of 90). In addition higher doses were always more forgiving. For instance at 45 missed doses (half of the total number of doses) the *a priori* RF of the 10 mg dose is approximately half that of *a posteriori* RF. This indicates that dose individualization is important irrespective of the underlying adherence in terms of the relative forgiveness. Hence dose individualization provides both a higher probability of therapeutic success as well as inherently making atorvastatin more forgiving. Omeprazole Three doses considered were 10 mg, 20 mg, and 40 mg. The influence of individualization in adherent patients makes a marked difference in *a posteriori* forgiveness compared to *a priori* forgiveness for up to about 30 missed doses (per 90 days of treatment). After this level of missed doses the RF for both *a priori* and *a posteriori* RF declines rapidly to close to zero and overlap. It is clear for omeprazole, that adherence is the primary factor of interest for those who are likely to be poorly adherent and should be the primary goal.

Conclusion: The concept of *a priori* forgiveness and *a posteriori* forgiveness provides a quantitative measure that allows the influence of adherence to be disentangled from dose individualization and could be used to provide clear guidelines about the relative importance of each in clinical practice.

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