PAGE Program 2019

Tuesday 11 June		
14:00-18:00	**Registration at the Conference Venue**	
18:00-19:30	**Welcome reception with drinks and light snacks (no dinner)**	

Wednesday 12 June		
08:00-08:45	**Registration**	
08:45-09:00	**Welcome and Introduction**	
09:00-09:45	**Keynote lecture**	*Chair: Dinesh De Alwis*
09:00-09:45	*Jeff Sachs*	Pharmacometrics: A shot in the arm for vaccine discovery and development ~or~ Vaccines are not immune to the charms of pharmacometrics
09:45-09:50	**PAGE scientific program**	*Siv Jönsson*
09:50-11:15	**Coffee break, Poster and Software session I**	
	Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter	
11:15-12:15	**Infectious diseases**	*Chair: France Mentré*
11:15-11:35	*Marjorie Imperial*	Stratified medicine approaches for drug susceptible tuberculosis patients
11:35-11:55	*Stefanie Hennig*	Repeated time-to-event models support that Pseudomonas aeruginosa infection increase the risk of acquiring Aspergillus in young children with cystic fibrosis
11:55-12:15	*María García-Cremades*	Individual level data meta-analysis from HIV pre-exposure prophylaxis (PrEP) clinical trials
12:15-13:45	**Lunch**	
13:45-14:30	**Tutorial**	*Chair: Mats Karlsson*
13:45-14:30	*Nicky Best*	Use of informative priors in model-informed drug development

14:30-15:10	**Machine learning in oncology**		*Chairs: Mats Karlsson, Paolo Magni*
14:30-14:50	*Chiara Nicolò*	Machine learning combined to mechanistic modeling of differential effects of neoadjuvant sunitinib on primary tumor and metastatic growth	
14:50-15:10	*Sebastien Benzekry*	Machine learning versus mechanistic modeling for prediction of metastatic relapse in breast cancer	
15:10-16:40	**Tea break, Poster and Software session II**		
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter		
16:40-16:45	**Clinical pharmacometrics - ISoP special interest group**		*Mirjam Trame and Eva Germovsek*
16:45-17:25	**Clinical applications**		*Chair: Oscar Della Pasqua*
16:45-17:05	*João Abrantes*	Bayesian forecasting utilizing bleeding information to support dose individualization of factor VIII	
17:05-17:25	*Belén Pérez Solans*	Model-based characterization of neutrophil dynamics in children receiving busulfan or treosulfan for hematopoietic stem cell transplant conditioning	
17:25-18:05	**Rare (and other) diseases**		*Chair: Panos Macheras*
17:25-17:45	*Zinnia Parra-Guillen*	Disease pharmacokinetic-pharmacodynamic (PKPD) modelling to support the development of gene therapy treatments for rare diseases	
17:45-18:05	*Pascal Chanu*	A disease progression model for geographic atrophy	

Thursday 13 June			
08:30-09:50	**Lewis Sheiner Student Session**		*Chair: Andrew Hooker, Emilie Hénin, Thomas Dorlo*
08:30-08:55	*Moustafa Mahmoud Abdellatif Ibrahim*	Competing risks analysis of the Finnish diabetes prevention study	
08:55-09:20	*Sebastiaan Goulooze*	Novel pharmacometric techniques to quantify and prevent iatrogenic withdrawal in children	
09:20-09:45	*Elena Tosca*	Dynamic Energy Budget (DEB) based models of tumor-in-host growth inhibition and cachexia onset	
09:45-09:50	**Presentation of Lewis Sheiner student session awards**		
09:50-09:55	**Special announcement**		
09:55-11:20	**Coffee break, Poster and Software session III**		
	Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter		
11:20-12:25	**Regulatory model-informed drug discovery and development**		*Chair: Aris Dokoumetzidis*
11:20-12:05	*Kristin Karlsson and Flora Musuamba Tshinanu*	Regulatory model-informed drug discovery and development in EU – News flash and examples	
12:05-12:25	*Sylvie Retout*	A model-based extrapolation enabled labelling of emicizumab in haemophilia A paediatric patients	
12:25-12:30	**Announcement for ACoP9 2019**		*Mirjam Trame*
12:30-14:00	**Lunch**		
12:30-14:00	**ISoP Student Community meet-and-greet during lunch**		
14:00-15:20	**Stuart Beal methodology session**		*Chair: Emmanuelle Comets and Siv Jönsson*
14:00-14:20	*Theodoros Papathanasiou*	Model based optimization of dose-finding studies for drug-combinations	
14:20-14:40	*Antonio Goncalves*	Model averaging in viral dynamic models	

14:40-15:00	*Mohammed Cherkaoui Rbati*	A liver model for chemoprotection against malaria
15:00-15:20	*Xiao Zhu*	A cohesive model framework of receptor pharmacology: beyond the Emax model
15:20-15:25	**Announcement for WCoP 2020**	
15:25-16:50	**Tea break, Poster and Software session IV**	
	Posters in Group IV (with poster numbers starting with IV-) are accompanied by their presenter	
16:50-17:30	**Stuart Beal methodology session, continued**	*Chair: Justin Wilkins*
16:50-17:10	*Alison Margolskee*	Exploratory graphics (xGx): promoting the purposeful exploration of PKPD data
17:10-17:30	*Marc Cerou*	Performance of npde for the evaluation of joint model with time to event data
18:30-01:00	**Social event**	

Friday 14 June			
09:20-10:20	**Oncology**		*Chair: Ana Ruiz, Siv Jönsson*
09:20-09:40	*Aurelia de Vries Schultink*	Prospective evaluation of therapeutic drug monitoring of endoxifen: feasibility of observational and randomized trials	
09:40-10:00	*Coralie Tardivon*	Association between tumor size kinetics and survival in advanced urothelial carcinoma patients treated with atezolizumab: implication for patient's follow-up	
10:00-10:20	*Jiajie Yu*	A new approach to predict PFS in ovarian cancer based on tumor growth dynamics	
10.20-10.25	**Preview of PAGE 2020**		
10:25-11:00	**Coffee break**		
11:00-11:40	**Oncology, continued**		*Chair: Marylore Chenel*
11:00-11:20	*Julie Janssen*	A semi-physiological framework to predict changes in pharmacokinetics of cytotoxic drugs in pregnant women	
11:20-11:40	*James Lu*	Integrated efficacy-safety QSP model of acute myeloid leukemia (AML) generates insights into the role of clinical dose schedules on cytopenia	
11.40-11.50	**Closing remarks**		
11:50-12:10	**Audience input for potential PAGE 2020 topics**		

PAGE2019 Oral Abstracts

B-03: *Jeff Sachs* Pharmacometrics: A shot in the arm for vaccine discovery and development ~or~ Vaccines are not immune to the charms of pharmacometrics

Jeffrey R. Sachs
Pharmacokinetics, Pharmacodynamics, and Drug Metabolism – Quantitative Pharmacology and Pharmacometrics, MSD., Inc., Kenilworth, NJ, USA

Objectives:

The objective is to (1) inform the audience about pharmacometrics (PMX) opportunities in vaccine discovery and development (D&D), and (2) to motivate, by examples, PMX practitioners to impact vaccine D&D.

Overview/Description of presentation:

Prophylactic vaccines are safe and effective and have made an immense contribution to human and animal health [1]. Pharmacometrics (PMX) has only recently been introduced to vaccine discovery and development, and is now becoming fully integrated into, and impactful on decision-making. This has resulted in better scientific understanding, increased POS, substantial savings, and other benefits that have been seen in the other therapeutic areas that have adopted PMX. The impact of this work has included go and no-go decisions, design of efficient pre-clinical and clinical trials, integration of preclinical and clinical data, quantitative prediction for go/no-go and dose-level decisions, and integration of data across multiple trials for more informed decision-making. The methods used include QSP modelling, trial simulation, Bayesian inference, and model-based meta-analyses (“comparator modelling”).

The presentation will start with a background on vaccine discovery and development (contrasting with other therapeutic areas) including a brief overview of: the risk/benefit considerations in vaccines, the choices and uses of biomarkers to mitigate risk, vaccine terminology, the immune system, and vaccine platforms (DNA, protein, VLP, etc.). This will be followed by examples across the spectrum of applications from discovery through development and across the many kinds of decisions impacted and methods used. These will include

- An application of M&S that supported both Go and No-Go decisions
- An application of M&S that increased power in trial design while saving considerable cost by optimizing sampling of subjects’ disease state.
- An application of M&S providing a novel phase 3 endpoint substantially increasing power of a proposed trial design

Conclusions/Take home message:

Application of PMX to vaccine D&D has developed into an opportunity to impact human health and to develop innovative PMX methods applicable to other areas.

References:

[1] Brian Greenwood, *The contribution of vaccination to global health: past, present and future*, Philos Trans R Soc Lond B Biol Sci. **369**(1645), 2014. doi: 10.1098/rstb.2013.0433.

B-06: *Marjorie Imperial* Stratified medicine approaches for drug susceptible tuberculosis patients

Marjorie Z. Imperial (1), Payam Nahid (1), Patrick P. J. Phillips (1), Geraint R. Davies (2), Katherine Fielding (3), Debra Hanna (4,5), David Hermann (5), Robert S. Wallis (6), John L. Johnson (7,8), Christian Lienhardt (9,10) and Rada M. Savic (1)

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Objectives:

Tuberculosis (TB) kills more people than any other infectious disease. All current approaches to TB treatment are based on a one-size-fits-all approach, which leads to under-treatment of patients with severe forms of disease and entails unnecessarily long treatment with potential toxicities for many patients in whom the disease is less severe.[1] Currently, all TB drug development efforts are aimed at shortening treatment duration using the same one-size-fits-all paradigm.[2] However, all recent Phase 3 clinical trials (OFLOTUB[3], REMoxTB[4], and RIFAQUIN[5]) failed to show non-inferiority between 4-month fluoroquinolone-containing regimens and 6-month standard of care. Nonetheless, the 4-month treatments achieved 80% cure rates, confirming that a significant proportion of global TB burden is eligible for short duration, only if major characteristics of these patients are identified. To that end, we pooled individual patient data from these three trials to 1.) identify populations eligible for short course therapy, and conversely, hard-to-treat populations requiring longer courses, 2.) assess the value of sputum culture conversion biomarker, common Phase 2B endpoint, as a predictor of outcomes, 3.) evaluate the impact of adherence and dosing strategies on outcomes, and 4.) develop data-driven clinical tools that can be used to provide recommendations for treatment interventions in stratified groups.

Methods:

Standardized individual patient data were obtained from a public repository.[6] Each trial evaluated later-generation fluoroquinolones as substitutions for ethambutol or isoniazid with the objective of shortening treatment duration from the standard six months to four months. A fourth trial, DMID 01-009[7], in patients with non-cavitary disease treated with a 4-month standard regimen was used for external validation.

The primary efficacy endpoint was time to an unfavorable outcome up to 24 months after start of treatment. We performed multivariate Cox proportional hazard analysis to identify risk factors of unfavorable outcomes. Baseline predictors that were common across trials were included in the analysis: age, race, body mass index, sex, HIV status, presence of cavitation and smear status (measure of bacterial burden). Month 2 culture status and patient adherence were considered as on-treatment predictors.

Non-inferiority analyses were performed in patient subgroups according to identified risk factors in the Cox analysis. The difference in proportion of unfavorable outcomes was calculated using inverse probability Kaplan-Meier (KM) estimates at 24 months after start of treatment. Non-inferiority was assessed using the upper bound of the two-sided 90% confidence interval (CI), determined by bootstrapping (n=500), and a non-inferiority margin of 6 percentage points.

A parametric survival model was developed next to obtain a clinical trial simulation tool and patient stratification algorithm. A competing risks model was developed for two types of unfavorable outcomes: a.) TB related events (i.e. relapse) and b.) non-TB related events (i.e. dropout). Gompertz, Weibull, and surge hazard models were explored. Baseline characteristics, treatment exposure (treatment duration, cumulative number of treatment days, and regimen composition), and on treatment culture positivity were evaluated as predictors of outcomes using a stepwise model selection approach with forward inclusion ($p<0.05$) and backward deletion ($p>0.01$) steps.

The final parametric model was used to evaluate in silico novel clinical trial designs and novel strategies to TB treatment based on stratified medicine principles – in which individualized treatment duration is based on patient phenotypes.

All analyses were performed in R 3.4 and NONMEM 7.4. Clinical simulation and clinical management tools were developed using the 'shiny' package in R 3.4.

Results:

Of 3405 patients, 1404 were randomized to a 6-month control regimen and 2001 to 4-month experimental regimens. In patients assigned to experimental regimens, baseline smear 3+ relative to smear negative or 1+ and HIV seropositive were the two major clinical risk factors for unfavorable outcomes with an adjusted hazard ratio (HR) of 1.6 (95% CI,1.2-2.3) and 1.5 (95% CI 1.1-2.0), respectively. HIV seropositive was also a major clinical risk factor in patients assigned to the control regimen (HR 3.1; 95% CI 2.0-4.6). Non-adherence was the most significant risk factor of unfavorable outcome irrespective of regimen with HR of 5.7 (95% CI, 3.3-9.9) and 5.9 (95% CI, 3.3-10.5) for patients who miss 10% or more doses relative to fully adherent patients following a 4- and 6-month regimen, respectively.[8]

In an easy-to-treat phenotype, the proportion of unfavorable outcomes for patients with a baseline smear <2+ grade or non-cavitary disease, representing 47% of the population, was non-inferior in 4- vs 6-month groups (difference in KM estimate, 3.4; 90% CI, 1.5 to 5.4), indicating that these patients can receive short course therapy. Patients with smear 3+ and cavitary disease, consisting of 34% of the study population, were inferior with the 4-month regimens (difference of 8.8; 90% CI, 6.4-11.3). The easy-to-treat population was externally validated in an independent dataset from the DMID 01-009 trial.[8]

The parametric model confirmed results of the Cox analysis and showed that high baseline smear, HIV seropositive, increased number of missed treatment days, and month 2 culture positivity increases the risk of TB related events. Additionally, older patients are at increased risk of non-TB related events.

Three stratified virtual populations were investigated in clinical trial simulations: a.) easy-to-treat defined as smear <2+ or non-cavitary disease, b.) moderate-to-treat defined as smear 2+ and cavitary disease, and c.) hard-to-treat defined as smear 3+ and cavitary disease. Clinical trial simulations indicated that stratified medicine approaches to TB care, where treatment duration is selected with precision based on patient risk, can result in high cure rates and enable implementation of superiority trial designs in TB drug development.

Conclusion:

In this pooled analysis of three recent Phase 3 treatment shortening trials, we have identified easy- and hard-to-treat phenotypes in drug susceptible TB patients. The rifampin-containing regimens tested in these

trials are unforgiving with minimal non-adherence resulting in significantly increased risk for unfavorable outcomes. Based on these results, we have developed a risk stratification algorithm and clinical trial simulation tool that was used to investigate optimal treatment interventions for stratified populations. Our results have led to two novel Phase 3 trials currently being designed and developed to evaluate principles of stratified medicine for treatment of drug susceptible and multi-drug resistant TB, which is a paradigm-shifting approach to tackling the TB epidemic.

References:

[1] P. Nahid *et al.*, "Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis," *Clin. Infect. Dis.*, vol. 63, no. 7, pp. e147–e195, 2016.

[2] S. Goldberg, "TBTC Study 31: Rifapentine-containing Tuberculosis Treatment Shortening Regimens (S31/A5349)." [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT02410772.

[3] C. S. Merle *et al.*, "A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis," *N. Engl. J. Med*, vol. 371, no. 23, pp. 1588–1598, 2014.

[4] S. H. Gillespie *et al.*, "Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis," *N. Engl. J. Med.*, vol. 371, no. 17, pp. 1577–1587, 2014.

[5] A. Jindani *et al.*, "High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis," *N. Engl. J. Med.*, vol. 371, no. 17, pp. 1599–1608, 2014.

[6] "Platform for Aggregation of Clinical TB Studies, TB-PACTS," *Critical Path Institute*. .

[7] J. L. Johnson *et al.*, "Shortening Treatment in Adults with Noncavitary Tuberculosis and 2-Month Culture Conversion," *Am J Respir Crit Care Med*, vol. 180, pp. 558–563, 2009.

[8] M. Z. Imperial *et al.*, "A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis," *Nat. Med.*, vol. 24, no. 11, pp. 1708–1715, Nov. 2018.

B-07: *Stefanie Hennig* Repeated time-to-event models support that Pseudomonas aeruginosa infection increase the risk of acquiring Aspergillus in young children with cystic fibrosis

Sabariah Noor Harun,(1,2) Nicholas H. G. Holford,(2,3) Keith Grimwood,(4,5) Claire E. Wainwright,(6,7) Stefanie Hennig,(2) on behalf of the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study group

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Objectives: Chronic *P. aeruginosa* infection is usually treated with long-term, inhaled antibiotic therapy in patients with cystic fibrosis (CF). However, such treatment has been associated with airway dysbiosis and acquisition of other potential pathogens, including filamentous fungi from the *Aspergillus* genus. While *Aspergillus* detection rates in adults, adolescents and older children with CF have increased, the risk of acquiring this fungal pathogen in young children is unknown.

This study aimed to determine the risk and explanatory factors of acquiring *Aspergillus* in children with CF within the first 5-years of life.

Methods: Clinical, bronchoalveolar lavage (BAL) and treatment data from the Australasian Cystic Fibrosis Bronchoalveolar Lavage study [1] was used to identify predictive factors for detecting *Aspergillus*. Infants detected by a new born screening programme and with features of classic CF (two or more of the following: two CF gene mutations, sweat chloride >60mmol/L, pancreatic insufficiency or meconium ileus) were randomised to either BAL-directed therapy or standard care where clinical judgement and oropharyngeal (OP) swabs guided treatment of pulmonary exacerbations in the first 5-years of life. When a child in either study arm had a pulmonary exacerbation, a specimen (either via BAL or OP) was obtained. Children in the BAL-directed arm had a BAL at baseline (before age 6-months), at the study end (at age 5-years), and after completion of any *P. aeruginosa* eradication therapy. A confirmed *P. aeruginosa* infection was treated identically with a course of anti-pseudomonal eradication therapy, which involving 2-weeks of intravenous antibiotics, followed by 8-weeks of tobramycin solution for inhalation. OP specimens are commonly associated with increased false positive results, therefore only BAL culture data was analysed.

A longitudinal parametric survival analysis was performed using interval-censored repeated time-to-event (RTTE) models to determine the risk of acquiring recurrent positive *Aspergillus* BAL cultures in the first 5-years of life. Specifically, a RTTE model for positive *P. aeruginosa* BAL cultures was built concurrently with an *Aspergillus* RTTE model from birth until age 5-years. The joint model allows for the influence of the *P. aeruginosa* eradication therapy on the risk of having *Aspergillus* positive cultures to be evaluated.

Results: The median (interquartile range) age for the first *P. aeruginosa* positive culture was 2.38 (1.32-3.79) years and 3.69 (1.68-4.74) years for the first *Aspergillus* positive culture.

In the child's first year of entering the study, the risk of acquiring P. aeruginosa had a hazard ratio of 0.399 (95% CI 0.181 to 0.599). After the first and second P. aeruginosa events, the risk of acquiring the subsequent P. aeruginosa infection increased with a hazard ratio of 138 (95%CI 50.6, 1236). As predicted by a Gompertz hazard model, the risk of acquiring *Aspergillus* event was very low during the first year of the study period. However, the risk then increased influenced by factors other than time alone. Having had the first *Aspergillus* event increased the risk of a second or third *Aspergillus* event as shown by hazard ratios of $7.29x10^5$ (95%CI $1.99x10^5$, $1.83x10^6$) and $5.97x10^5$ (95%CI $1.21x10^5$, $2.05x10^6$), respectively. After completing *P. aeruginosa* eradication therapy, the *Aspergillus* risk increased with a hazard ratio of 2.75 (95%CI 1.45, 5,41). Kaplan Meier visual predictive checks for *P. aeruginosa* events show good predictions and for *Aspergillus* events also indicate that the final model describes the observed data generally adequately, with some discrepancies at 4 years of age.

Conclusions: A joint RTTE model for two non-competing but interacting interval censored events was developed. Young children with CF, completing intensive *Pseudomonas aeruginosa* eradication treatment and having experienced a previous *Aspergillus* event are associated with substantially increased risk of acquiring further *Aspergillus* events.

References:

[1] Wainwright CE, Vidmar S, Armstrong DS*, et al.* Effect of bronchoalveolar lavage-directed therapy on *Pseudomonas aeruginosa* infection and structural lung injury in children with cystic fibrosis: a randomized trial. *JAMA* 2011;306:163-71.

B-08: *María García-Cremades* Individual level data meta-analysis from HIV pre-exposure prophylaxis (PrEP) clinical trials

Maria Garcia-Cremades (1), Katarina Vučićević (1,2), Craig Hendrix (3), Leah Jarlsberg (1), Robert Grant (4), Connie L. Celum (5) , Michael Martin (6,7), Jared Baeten (5), Jeanne Marazzo (8), Peter Anderson (9), David Glidden (10), Radojka M. Savic (1)

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Introduction: Daily tenofovir has proven efficacy in preventing HIV infection in high-risk populations, when patients are compliant. However, effective preventive concentration has not been determined using HIV infection as outcome, due to lack of power in a single clinical trial and large cofounding with non-adherence. Furthermore, infection risk in target populations is poorly defined, making it difficult to properly identify key patients who would benefit the most from PrEP therapy. To address those pertinent questions, we have constructed the largest individual data base up to date from the 5 latest Phase 3 HIV prevention clinical trials.

Our aims were (i) to identify patient subgroups at the highest risk of HIV infection in target populations, (ii) to estimate preventive tenofovir concentrations in target populations based on pharmacokinetic (PK)-HIV outcome modeling and (iii) to evaluate the target site tenofovir diphosphate PK in peripheral blood mononuclear cells (PBMC) vs plasma tenofovir as a marker of HIV prevention.

Methods:(i) Longitudinal PK data of tenofovir in plasma and tenofovir metabolite in PBMC, (ii) HIV outcome and (iii) individual's demographics and risk factors data from 13,727 individuals obtained from 5 phase 3 randomized controlled trials were integrated and analyzed with NONMEM 7.4 using population approaches. Those trials evaluated tenofovir-based PrEP therapy efficacy in different HIV risk groups: injection drug users (Bangkok[1]), men or transgender women who have sex with men (iPrEX[2]), women at high risk of infection (VOICE[3]), HIV serodiscordant heterosexual couples (Partners[4]), and high risk heterosexual men and women (TDF2[5]). The analyses were done sequentially:

- The probability of HIV infection over time was analyzed through parametric survival analysis using data from the placebo arms of the 5 PrEP trials (n=5313). Studies were analyzed separately due to availability of baseline covariates specific for target populations. Baseline survival models were evaluated and covariate analysis was performed by stepwise covariate modelling. Patient-specific risk stratification algorithm was developed.
- The PK analysis of tenofovir (2 compartment model) and its metabolite (effect compartment model) was done sequentially pooling the available data from iPrEX, VOICE and Partners (n=2360). Longitudinal adherence to the treatment was assessed by applying mixture modeling approaches

on the relative bioavailability fraction. Data below limit of quantification were handled with the M3 method.

- PK exposure metrics for tenofovir in plasma were linked to the probability of HIV infection in parametric survival analysis. The effect of tenofovir diphosphate in PBMC as predictor of HIV prevention was explored.

Results: Exponential hazard distribution best fitted the time to HIV infection data from the control arms of the PrEP studies. The analysis identified set of risk factors which are common (e.g. female sex, age) or unique to each population (e.g non-condom receptive anal intercourse, and syphilis seroreactivity in iPrEX study). Most surprisingly, women appear to be at greater risk of HIV infection compared to men. In population PK model, 2 patient subpopulations were identified, adherent F=100% and non-adherent F=<1%) through the application of a mixture model on relative bioavailability, with an estimated probability of being in adherent group of 55%. Longitudinal adherence and PK profiles were reconstructed for each patient based on the established mixture model and PK data. These were then linked to HIV infection (characterized by a survival model with Surge hazard distribution) using a sigmoidal Emax model. Underlying individuals risk hazard was found to be important factor in determining accurate PKPD. The EC_{50} identified in high risk group was found to be 10.21 ng/mL. Tenofovir diphosphate, appeared to be a better marker of HIV prevention compared to the plasma tenofovir, with an estimated EC_{50} of 6.91 fmol/10^6cells.

Conclusions: We have quantified tenofovir preventive concentration based on the largest database up to date which includes HIV outcome. We have established patient-specific risk stratification algorithm for HIV infection. These models and tools will further be used for: (i) optimization of novel PrEP clinical trial designs, enrollment and follow up strategies, (ii) the development of novel tenofovir formulations and (iii) implementation of patient management strategies in the clinic.

References:

[1]Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013;381:2083–90.
[2]Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363:2587–99.
[3]Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. N Engl J Med. 2015;372:509–18.
[4]Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. N Engl J Med. 2012;367:399–410.
[5]Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. N Engl J Med. 2012;367:423–34.

B-10: *Nicky Best* Use of informative priors in model-informed drug development

Nicky Best
GlaxoSmithKline

Objectives:

- To introduce methods for constructing informative priors from historical data or by elicitation from experts
- To discuss different methods for weighting priors in relation to data and for assessing and handling conflicts between prior and data
- To share examples of how such priors are implemented in models to inform different stages of drug development

Overview/Description of presentation:

This presentation will provide a brief overview of some of approaches for combining prior information and data for model-based inference and decision-making for drug development. I will discuss the use of expert elicitation methods to "bridge the gap" between existing in vitro/pre-clinical data and expected treatment effects in patient populations, and show how the elicited priors can be used to calculate expected probability of success of clinical development plans. I will also discuss "dynamic borrowing" methods for constructing robust priors directly from historical data and using these in a Bayesian model which adaptively down-weighs the prior according to the observed conflict between prior and new data. This approach will be illustrated with case studies using historical control data to supplement the control arm in a new clinical trial, and extrapolation of clinical efficacy from adult to paediatric populations.

Conclusions/Take home message:

The methods and examples presented in this tutorial illustrate the possibility to enable robust inclusion of prior information into model-based drug development.

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B-11: *Chiara Nicolò* Machine learning combined to mechanistic modeling of differential effects of neoadjuvant sunitinib on primary tumor and metastatic growth

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Introduction:

Despite proven clinical action of angiogenic inhibitors [1], recent experimental evidence also suggests differential effects of these drugs on primary and secondary tumors [2]–[4]. In this work we extended our previous mechanistic model [5] to describe the effect of neoadjuvant sunitinib therapy in an ortho-surgical mouse model of spontaneous metastatic breast cancer. Model development was guided by a large experimental data set of 104 mice treated with multiple scheduling strategies. The experimental data comprised longitudinal measurements of primary tumor (PT) size and metastatic burden (MB), as well as survival data and pre-surgical biomarkers (circulating tumor cells (CTCs) and myeloid-derived suppressor cells (MDSCs) counts and proliferation and endothelial immunohistochemical markers).

Objectives:

- Understand the differential effects of Suntinib on primary tumor and metastatic growth
- Establish a minimal kinetics-pharmacodynamics (K-PD) model of neoadjuvat suntinib therapy
- Assess the predictive power of biomarkers on the model parameters

Methods:

We adapted a previously established mathematical model [5] to include the effect of neoadjuvant sunitinib therapy by assuming that the drug reduces the primary tumor growth rate by a term proportional to its concentration. As no pharmacokinetic data were collected in our study, we used a K-PD approach (one compartment model with elimination rate from the literature [6]).

PT and MB data were fitted simultaneously for vehicle and sunitinib-treated animals using a nonlinear-mixed effects modeling approach [7]. Maximum likelihood estimates of the population parameters were obtained using the Stochastic Approximation of Expectation-Maximization (SAEM) algorithm implemented in the nlmefitsa Matlab function [8].

Effects of covariates on the model parameters were assessed using linear regression and a number of machine learning regression techniques (artificial neural networks, support vector machines, random forest models) [9] using the train function of the R caret package [10], [11].

Survival times were analyzed using the Monolix software [12]. A log-logistic distribution was used. We utilized the COSSAC (Conditional Sampling for Stepwise Approach based on Correlation tests) covariate selection algorithm for automatic building of the covariate model [13].

Results:

We used parameter values estimated from a previous study on control groups [5] to generate model predictions under the assumptions of effect (A) or no effect of therapy on metastatic growth (B). Population distributions obtained under the hypothesis A failed to describe the data, whereas simulations under hypothesis B reproduced the behavior of the experimental data notably well. This was observed in all the treated groups and suggested rejection of the assumption A, with B being a valid possible alternative.

Based on these results, the K-PD model we developed considered that the antiangiogenic agent affects only primary tumor growth. The calibrated K-PD model was able to describe both the structural dynamics and inter-subject variability of the experimental data in both vehicle and treated animals. The model parameters were identified with good precision (relative standard error ≤ 17%) thanks to the large number of animals (n=104). Confirming previous results [5], interanimal variability was mainly characterized by a model parameter μ expressing the metastatic potential of the tumor, which was also found to be significant for predicting survival. However, the biomarkers included in all tested machine learning algorithms demonstrated only limited predictive power on the mathematical parameters (R2 = 0.13 – 0.2, best relative error on 9.83 10.70 %).

Conclusions:

We developed a K-PD model for describing the effects of neoadjuvant antiangiogenic treatment on primary and metastatic growth dynamics. Analysis of a large data set revealed a highly heterogeneous population in terms of the metastatic potential parameter μ. Identifying biological predictors of μ would be of critical clinical interest by providing more individualized. According to our analysis of the biomarkers as covariates in the model, expression of Ki67 and CD31 in the primary tumor, and pre-surgical CTC and MDSC levels are not significant predictors of metastatic potential and survival. Although likely to depend on the animal model of cancer, these results highlight the need to investigate other molecular and cellular markers.

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B-12: *Sebastien Benzekry* Machine learning versus mechanistic modeling for prediction of metastatic relapse in breast cancer

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Introduction:
Predicting the probability of metastatic relapse for patients diagnosed with early-stage breast cancer is critical for decision of adjuvant therapy [1]. Current predictive models usually rely on proportional hazard Cox regression models [2]. Using the breast cancer database from the Bordeaux Bergonié Institute (n=1057 patients), we investigated the potential use of machine learning (ML) algorithms for predicting 5-years metastatic relapse (MR) or metastatic-free survival. Both Cox regression and ML algorithms are purely statistical methods and do not integrate any biological knowledge. To address this and provide personalized, data-informed simulations of the natural history of the disease, we developed a mechanistic model of the time to relapse based on the biology of metastatic spread.

Objectives:

- Investigate the applicability of machine learning algorithms for prediction of MR
- Develop a mechanistic model of time to MR
- Compare both approaches to classical survival models

Methods:
Classification algorithms for prediction of probability of MR at 5-years included logistic regression, support vector classification, k-neighbors, naïve bayes, random forest, gradient boosting and multi-layer perceptron. They were trained using the python package *scikit-learn* [3]. Due to the small probability of MR (<10% at 5 years) possibly impairing the results of classification algorithms, we restricted ourselves to a balanced data set with 50% of relapse for this task. To deal with time-to-event data and censoring (not handled with classical ML regression algorithms), survival random forests were also investigated [4]. The mechanistic model of time to MR was built based on a model using a size-structured population dynamics framework (transport partial differential equation) for description of metastasis [5]. This model was previously validated against longitudinal experimental data of spontaneous metastatic development after surgery in a clinically relevant animal model of breast cancer [6]. A nonlinear mixed-effects model was added to the structural model for description of inter-individual variability in the two parameters (growth and dissemination), as well as assessment of the impact of covariates, pivotal in the development of the model as a personalized predictive tool. Population parameter estimation was performed using the R package *saemix* [7]. To prevent using the same set for training the models and prediction, 10-fold cross-validation was used to assess the predictive power of the various models.

Results:
For the classification task (prediction of 5-years MR probability), the best performances were achieved by the random forest algorithm with an accuracy on test sets of 60%, area under the ROC curve of 0.7 and positive and predictive values of 60% each. A calibration plot also indicated good predictive power. The random survival forest algorithm had similar performances with a concordance index [8] of 0.68, which was also the score obtained by a proportional hazard Cox regression model. The mechanistic model was able to

provide accurate fits of the survival data with random effects in two key parameters of dissemination and growth. Critically, these parameters allowed for integration of biological covariates in a physiologically meaningful way. The primary tumor size at diagnosis for instance is a direct variable of the model. In addition, significance of covariates (assessed by means of Wald tests) suggested other covariates to be either biomarkers of growth (such as the level of the proliferation marker Ki67) or dissemination (such as the vimentin level). At the time of writing of this abstract, we can only report on the concordance index on the calibration set (0.66) due to the large computational cost (8 hours to fit the population parameters on the entire data set on a 24 CPU server).

Conclusion:
These findings provide the first step towards the development of a mechanistic model for prediction of metastasis. It could yield a personalized prediction tool of help for routine management of breast cancer patients. Not only would it provide estimates of the metastasis-free survival probability, but it would also generate informative estimates of the invisible metastatic burden at the time of diagnosis and forward simulations of future dissemination and growth. To achieve concrete clinical transfer, the model should be further refined and validated on external data sets.

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B-15: *João Abrantes* Bayesian forecasting utilizing bleeding information to support dose individualization of factor VIII

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Objectives:
Model-based PK-guided dose individualization of factor VIII (FVIII) replacement therapy has been increasingly encouraged [1,2]. Yet, mounting evidence shows large phenotypic differences in bleeding between patients due to multiple components besides plasma FVIII activity [3,4].

The aim of this work was to employ a pharmacokinetic-repeated time-to-event (PK-RTTE) model to contrast different sources of patient information in their ability to predict future occurrence of bleeds in severe haemophilia A patients receiving prophylactic FVIII replacement therapy.

Methods:
Data and model
Dose, covariate, observed plasma FVIII activity and bleeding time data collected over 6 to 12 months during the *Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease* (LEOPOLD) clinical trials were used in this evaluation [5-7].

A previously developed integrated population PK-RTTE-FREM model for FVIII was used for Bayesian forecasting [3].

Bayesian forecasting and bleeding probabilistic forecast
Empirical Bayes estimates (EBEs) of PK and hazard parameters were estimated based on the information observed from the start of the LEOPOLD study up to the end of each consecutive 24-hour period, i.e. repeatedly for each patient up to the end of study. The estimation was performed using three *information scenarios*:

1. *PK* - plasma FVIII activity observations;
2. *Bleed* - time of bleed, or lack of bleed, during each day;
3. *All* - plasma FVIII activity observations, time of bleeds and covariate information.

Subsequently, the longitudinally estimated individual bleeding hazard was used to derive the individual forecasted probability of having a bleed in the upcoming 24-hour period (P_i(bleeding)).

The effect of the duration of the Bayesian observation period was also assessed by estimation based on the past 15 days, 1, 2, 3 or 6 months, to investigate the trade-off between longer periods and the most up-to-date information.

Bleeding predictive performance assessment
The predictive performance of the different *information scenarios* was assessed by comparing P_i(bleeding) with the individual observed occurrence of a bleed on the forecasted day, using separation plots, receiver

operating characteristic (ROC) and precision-recall analyses [8-10]. The optimal threshold of P_i(bleeding) in the ROC analyses was determined by the Youden's *J* statistics.

Results:
In total, 101 bleeds were observed in 51 patients aged *<12 years*, and 530 bleeds in 121 patients aged *≥12 years,* and days with observed bleeds were ~1% of the forecasted days.

For the group *<12 years*, the expected number of bleeds over the study period was 66 (*PK*), 96 (*Bleed*), and 90 (*All*), and for *≥12 years* it was 218 (*PK)*, 461 (*Bleed*) and 500 (*All*). Separation plots showed a sharper increase in P_i(bleeding) associated to days when bleeds occurred for *Bleed* and *All* compared to *PK*, for both age groups. The ROC curves showed that *Bleed* had a predictive power comparable to *All*, and both were superior to *PK* (**Table 1**).

Table 1 - Summary statistics of the ROC analyses for the different *information scenarios* in patients *≥12 years*.

	PK	*Bleed*	*All*
ROC AUC (95% CI)	0.67 (0.65-0.69)	0.78 (0.76-0.80)	0.79 (0.77-0.81)
Sensitivity (95% CI)	0.59 (0.47-0.68)	0.69 (0.62-0.78)	0.69 (0.65-0.77)
Specificity (95% CI)	0.68 (0.59-0.80)	0.73 (0.65-0.81)	0.76 (0.69-0.78)
J	0.26	0.43	0.45

The differences between scenarios in the group *<12 years* followed the same trends, with an AUC of 0.67 (0.61-0.72) for *PK*, 0.74 (0.69-0.79) for *Bleed* and 0.77 (0.73-0.81) for *All*. The results of ROC analyses were confirmed by the precision-recall analyses, with *PK* closer to the performance of a random classifier.

Using *Bleed*, patients with a high bleeding risk required shorter observation periods to inform the EBEs, namely, between 60 and 90 days prior to the EBEs estimation. No advantage was found to use only the most up-to-date information to estimate the EBEs.

Conclusions:
A PK-RTTE-FREM model-based forecasting approach considering the efficacy endpoint of interest (bleeds) under prophylactic treatment has been developed. Using observed data to contrast sources of information to be used in Bayesian forecasting, this work suggests that individual bleed information adds value to the optimization of prophylactic therapy in severe haemophilia A. Further steps to optimize the proposed tool for FVIII dose adaptation in the clinic are required.

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B-16: *Belén Pérez Solans* Model-based characterization of neutrophil dynamics in children receiving busulfan or treosulfan for hematopoietic stem cell transplant conditioning

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Objectives:

Busulfan (Bu) and treosulfan (Treo) are used in the conditioning prior to paediatric haematopoietic stem cell transplantation (HSCT). Myeloid cell suppression leaves patients severely immunocompromised [1,2], increasing mortality.

Bu pharmacokinetics (PK) has been studied [3,4], requiring therapeutic drug monitoring (TDM) and the same therapeutic range in malignant and non-malignant disorders. For Treo less is known about the therapeutic range [5,6].

The objectives of this project were to establish: (i) a PKPD model for the treatment and engraftment effects on neutrophil counts comparing Bu and Treo, (ii) the relationship between neutropenia and overall survival (OS), (iii) optimised dosing schedules with respect to time to HSCT, and (iv) optimised PK sampling for Bu TDM.

Methods:

Electronic records from 72 children receiving Bu (7 m-18 y, 5.1–47.0 Kg) and 54 Treo (4 m–17 y, 3.8–35.8 Kg), were collected. Neutrophil count observations (8,935) were recorded from 1 month prior to 2 months post HSCT. Patients suffered from malignant (48 patients) and non-malignant diseases (78 patients).

Bu concentrations (534) from 72 patients were obtained. Treo samples were obtained in 20 children. Population parameters were used for patients without PK samples. NONMEM 7.3 and the FOCE-I estimation method were used. The Friberg model [7] was extended to account for HSCT effects. EMAX and linear models were tested for drug effect.

Patient, disease and treatment-related covariates were explored with stepwise covariate modelling (SCM) with forward inclusion ($p<0.05$) and backward deletion ($p<0.01$).

The model was used to evaluate dosing schedules of both drugs through simulations. In addition, the optimal Bu PK sampling collection times were determined using the R package PopED [8].

A survival analysis performed in R with the package survminer [9] explored the relationship between OS and possible predictors (patient, disease and model-derived metrics).

Results:

A 2-compartment model best described the concentration vs time profiles of Bu and Treo. A maturation function was included affecting clearance (CL) - time to reach half of the adults' maturation (PM50), and the Hill coefficient, fixed to 45.7 weeks and 2.3 for Bu [10], and 42.2 weeks and 2.3 for Treo.

The final model included separate steady-state neutrophil count (CIRC0) before and after transplant ($p<0.01$). The HSCT was represented by an amount of cells entering the proliferation compartment. HSCT enhanced cell proliferation and maturation increasing by 2-fold the related parameters ($p<0.01$), with a latency period of 9 days (99% IIV). Additionally, HSCT elicited a slight but significant ($p<0.001$) 5% increase in the proliferation constant and the feedback parameter γ.

System parameters (CIRC0, mean transit time (MTT) and γ) were consistent across drugs, estimated as $0.79 \cdot 10^9$ cells/L (75.9% IIV), 8.02 days (35.4% IIV) and 0.10 (77.1% IIV).

The neutrophil decline was modelled with a linear model for Bu (KKILL=0.7) and an EMAX model for Treo (EMAX=1.2). The SCM showed that the presence of alemtuzumab enhanced the HSCT effect, resulting in a 2.9 fold increase in proliferation, transit and circulating constants.

Results from a multi-variable analysis showed that the area under the neutrophil vs time curve was a predictor of OS independent of Bu or Treo AUC. A univariate analysis shown that patients with malignancies with an area under the neutrophil vs time curve lower than the median values (125·109cells day/L) had significantly increased OS in a 1-year ($p=0.045$, Hazard ratio (HR)=0.26, 95%CI, 0.06-0.97) and a 3-year follow-up ($p=0.013$, HR=0.27, 95%CI, 0.09-0.81).

The dosing schedule evaluation showed that a 2-day delay in Treo administration would leave the patient less time immunocompromised without damaging the HSCT.

The optimal design exercise suggested a reduced sampling schedule (4 samples compared to 6), obtaining similar parameter precision (maximum bias <10%).

Conclusions:

The semi-mechanistic PKPD model developed predicts neutrophil reconstitution trajectories from children after HSCT, being a useful tool to improve their clinical management. New dosing (for Treo) and sampling schedules (for Bu) are proposed, and increased neutropenia appears to be beneficial for patients with malignant disease.

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B-17: *Zinnia Parra-Guillen* Disease pharmacokinetic-pharmacodynamic (PKPD) modelling to support the development of gene therapy treatments for rare diseases

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Introduction: Acute intermittent porphyria (AIP) is a metabolic rare disease caused by the hepatic deficiency of the enzyme porphobilinogen deaminase (PBGD), third enzyme in the heme biosynthesis pathway. In this context, therapies that restore enzyme levels in the liver are an appealing option [1]. Different mRNA sequences encoding for the PBGD enzyme and encapsulated in different lipid nanoparticle formulations have been developed by Moderna, Inc [2].

Objectives: The goal of this analysis was to build a mechanistic computational model describing longitudinal pharmacokinetic (i.e. liver PBGD activity, PK) and pharmacodynamic (i.e. 24-h urinary heme precursors, PD) data obtained in the porphyric pre-clinical arena across different species and using different PBGD mRNA compounds in order to project the results to humans.

Methods: To mimic porphyric acute attacks, porphyrogenic drugs (e.g. phenobarbital) were daily administered for 2-5 days over one or more challenges. Then, treated animals received mainly one or up to 3 doses of different PBGD mRNA compounds -i.e., PBGD mRNA sequence & lipid formulation- on day 2 or day 3. In total, 8 different sequences encoding for the PBGD enzyme and encapsulated in 3 different lipid nanoparticle systems were available for the analysis.

The disease PKPD model for AIP C57BL mice is comprised of the following main processes: (i) the PBGD PK model describing mRNA release from the formulation, degradation and translation to the encoded PBGD protein in the liver, (ii) the disease model characterising the urinary excretion of heme precursors (ALA, PBG and porphyrins [POR]) during phorphyric acute attacks in the absence of treatment, and (iii) the PBGD activity model accounting for the normalisation of heme precursor in urine in the presence of PBGD enzyme.

To account for the additional liver PBGD activity data from wild type animals (C57BL mice, Sprague Dawley rats, New Zealand rabbits and cyno), and the PD data collected in wild type rats and rabbits, species-specific parameters were estimated without modifying the structure of the AIP mouse model. Finally, baseline PBGD activity levels of AIP patients were used to extrapolate preclinical results to clinical scenarios.

Results: Assuming formulation-specific release parameters and mRNA sequence-specific degradation parameters, the proposed disease PKPD AIP mouse model successfully described all available experimental scenarios for the different mRNA compounds using a common model structure. More than two-fold differences were observed between formulation release parameters, whereas larger variations were obtained across sequences with degradation values ranging between $2.56x10^{-4}$ to $8.9x10^{-3}$ h^{-1}. Differences in the response (i.e. reduction of urinary precursor accumulation) were thus explained at the PK level, since PBGD efficacy was preserved across mRNA compounds. PBGD activity levels achieved during the initial acute attack were sufficient to inhibit more than 90 % of the drug-induced accumulation of precursors (compared to baseline) with the majority of the mRNA compounds except for one mRNA sequence.

An adequate data characterization was obtained when using the AIP mice model, but adjusting the PBGD activity at baseline for the different species (dose was adjusted per animal weight) and estimating species-specific excretion rate constants of the heme precursor. The final model was used to predict *in silico* the inhibition that the different mRNA compounds would offer in case of a theoretical acute attack in humans assuming a PBGD activity model similar to that of AIP mice. Under these assumptions, predicted liver PBGD activity levels in AIP patients would remain above the normal PBGD activity levels -quantified in healthy untreated donors- for up to two months after the administration of the standard dose of 1mg/kg of some evaluated mRNA compounds to AIP patients.

Conclusions: In summary, an integrative quantitative framework capable to describe the effects of novel mRNA compounds on the accumulation of heme precursors in urine during-induced acute attack across different animal species has been proposed. This framework has been used to project the time course of the different mRNA compounds to humans. Moreover, it has the potential to be expanded with additional information characterizing the time course of urine heme precursors in humans during acute attacks to predict *in silico* the pharmacodynamic response during PBGD mRNA treatment.

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B-18: *Pascal Chanu* A disease progression model for geographic atrophy

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Objectives:

Geographic atrophy (GA) is a non-exudative form of age-related macular degeneration (AMD), also called dry AMD. Lampalizumab, an antigen-binding fragment of a humanized monoclonal antibody directed against complement Factor D, was developed to prevent activation of the alternative complement pathway and thus impede the progression of GA and vision loss. Positive results were observed with lampalizumab 10 mg administered intravitreally every month in the Mahalo study (CFD4870g) which met its primary endpoint: the mean difference in GA growth between the monthly group compared to the sham group at Month 18 was 0.595 mm^2 (80% CI: 0.109, 1.081). In addition, a statistically significant relationship was found between cumulative AUC in both serum and aqueous humor and change from baseline in GA area in patients positive to complement factor I biomarker. Two Phase 3 studies of more than 900 patients each: Chroma (GX29176) and Spectri (GX29185) were run to assess the efficacy and safety of lampalizumab versus sham. Both Phase 3 studies failed to demonstrate the efficacy of lampalizumab 10 mg given monthly, the highest drug exposure tested.[1] The objective of this work was to develop and validate a disease progression model for GA using Chroma and Spectri data and propose a model-based approach to assess treatment effect in GA to aid drug candidate selection at an early stage of clinical drug development.

Methods:

Both Spectri and Chroma data were used as well as data from Omaspect (GX30191), the long-term safety extension study which patients who completed parents studies i.e. Spectri or Chroma could enrol to. GA area was assessed by at 24, 36, 48, 72 and 96 weeks in Spectri and Chroma and every 24 weeks in Omaspect up to 96 weeks. As lampalizumab development was interrupted prematurely, the longest GA area follow-up reached 3.3 years. Spectri data was used to develop the disease progression model, comprising 970 patients (including patients receiving lampalizumab), among those 411 were enrolled into Omaspect, 6755 GA areas were used. The model structure was similar to the one published by Delor et al. based on the disease onset time concept.[2] The individual GA areas at the start of Spectri ranged from 2.54 to 30.56 mm2; indeed, patients were not at the same disease stage at the time of enrolment in the study. Therefore, there was a need to accurately reconstruct the full disease progression trajectory. The disease onset time approach leverages data from each subject itself informing a portion of the trajectory. The rate of increase in GA area was modelled as the sum of a linear increase with time and a first order term adjusting for individual contribution to disease progression. A first model qualification was performed on Spectri (including Omaspect portion) data using visual and posterior predictive checks. Then, Chroma (including Omaspect portion) data was used for external validation of the model.

Results:

The disease progression model structure using the disease onset time concept enabled the reconstruction of the disease trajectory over more than 12 years. While disease progression appeared to be linear with time over the clinical trial duration of 2 years, GA seemed to progress in a non-linear way (faster than linearity with time) over 12 years. The disease progression model showed that on average patients started

their disease 5.2 years before Spectri enrolment but with large inter-patient variability (1.3 to 18.5 years prior to enrolment). The GA area at study entry was a structural covariate in the model. Disease progression was faster for patients with GA area at study entry >6 mm^2, in patients with multifocal lesions (+16% versus unifocal) and in patients with non-subfoveal lesions (+15% versus subfoveal). The model was qualified based on Spectri data and a successful external validation was performed versus Chroma data on 901 patients.

Conclusions:

A disease progression model for GA was developed and externally validated. It can be used to assess treatment effect for future drug candidate in GA. Indeed a model-based approach comparing the model-predicted GA area (only due to disease progression) to the corresponding observations (due to disease progression and potential treatment effect) can represent a complementary analysis to classical statistical analyses based on change from baseline and improve future drug development decisions.

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C-01: *Moustafa Ibrahim* Competing risks analysis of the Finnish diabetes prevention study

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Objectives:
Clinical studies are often performed to assess a certain primary endpoint or event (e.g. manifestation of diabetes), in the presence of other competing risk events [1], i.e. the occurrence of an event that prevents the primary event from being observed, e.g. dropout. If these competing risk events are dependent on the primary event e.g. if dropout of a patient reflects a greater risk of diabetes manifestation, then predicting the primary event in a patient with the competing risk event is impossible. Marginal survival functions, when risks are dependent, are inestimable from the data and Kaplan-Meier estimators or standard survival models in such case result in profoundly biased estimates of the cumulative probabilities of the competing risks. When treatment groups are compared, the relative differences between treatment groups may be biased [2,3]. These are consequences of the underlying assumption that censoring is independent of the primary event and that the survival probability is constant over the occurrence of competing events. Also, if subjects are observed only at finite clinical visits, i.e. interval-censored data, there is an additional uncertainty of whether the patients experienced one or more of the competing events between the last event-free visit and the diagnostic visit. In this work, we considered model-based analysis of competing and semi-competing risks to describe data from the Finnish diabetes prevention study (FDPS) [4]. Afterward, we explored potential covariates on the different risks and investigated the predictiveness of various assessment methods of insulin sensitivity (S_I) for the onset of development of type 2 diabetes (T2D).

Methods:
The FDPS is a randomized controlled study carried out in Finland 1993-2001 with follow-up until 2010. Data was collected from 522 overweight middle-aged subjects with impaired glucose tolerance, randomly assigned to control and lifestyle intervention. The aim of the FDPS was to investigate the effect of lifestyle changes among subjects with impaired glucose tolerance on the development of T2D. Oral glucose tolerance test (OGTT) for all subjects was performed yearly for assessment of subjects' clinical status, and subjects with 2 hr postprandial glucose concentrations > 200 mg/dL were diagnosed with T2D and excluded from the study. From the yearly OGTT, S_I could be measured by nine surrogate methods [5].
During the FDPS, subjects failed by one of the three possible and mutually exclusive events: developing T2D, dropping out (DO), or death. Here, DO refer to stopping treatment, and does not mean lost to follow up as all subjects were followed until 2010. Once the subject had failed, his follow-up was started. During the follow-up, subjects cannot drop out and T2D cannot censor death (semi-competing process). There are five states that subjects could experience during the study and its follow-up: healthy (state 1), T2D (state 2), DO (state 3), DO-T2D (state 4; subjects developing T2D after DO), and death (state 5). All subjects were healthy at enrolment (state 1), and during the study, they could stay healthy (state 1), develop T2D (state 2), drop out (state 3), or die (state 5). The study ended once a subject moved from state 1 to any other state. After the study (during follow-up), subjects with T2D could stay in state 2 or die (state 5), subjects who dropped out could remain healthy in state 3, develop T2D (state 4) or die (state 5) and subjects who dropped out and then developed T2D could stay in state 4 or die (state 5). These restrictions defined the

nature of the different risks and the model's system of differential equations. Different hazard distributions and predictors were investigated for the transition intensities (λ_{ij}) from state *i* to state *j*. We tested three hypotheses: the risk of death for healthy subjects is independent of DO (i.e. $\lambda_{15}=\lambda_{35}$), the risk of death for subjects with T2D is independent of DO (i.e. $\lambda_{25}=\lambda_{45}$) and dropout out is non-informative for developing T2D (i.e. $\lambda_{12}=\lambda_{34}$). Yearly measured covariates including the nine indices for measurement of S_I were tested one by one prospectively on the different λs.

Results:
The model could jointly describe the semi-competing terminal process of death and the two competing non-terminal processes of developing T2D and DO while accounting for the interval-censoring. The model was non-stationary in λ_{12} and λ_{15} and homogenous in λ_{13} and λ_{34}. Transition intensities to death were indeed independent of DO and were described by scaling Gompertz-Makeham formula estimated from the Swedish population, to adapt for the different death incidences observed in the FDPS data. The estimated scaling parameters reflected a 20% higher risk of death among subjects with T2D than others, that was not significant when the data was analyzed by the standard survival cox models [6]. The model showed that informative DO is present and subjects are more likely to drop out if they were healthier and thus, after DO they were at ~ 3.5 lower risk for developing T2D than subjects who stayed in state 1. The model identified age and sex as predictors on dying, intervention and baseline BMI on λ_{13}, and intervention, baseline BMI, time-dependent HbA_{1c} and time-dependent S_I measurements to be the significant covariates on λ_{12}. QUICKI, HOMA and Avignon indices as time-varying measurements of S_I surpassed the other investigated indices, while baseline QUICKI and HOMA were the best to predict the future onset of T2D. The effects of the significant covariates on the competing risks at different combinations can be easily assessed by plugging the desired covariates' values in the model's system of equations. Visual predictive checks of the model stratified by subjects' treatment group showed a nice agreement between the simulated and observed proportion of subjects in the different states at different times.

Conclusions:
We successfully developed a multi-state model for competing risks analysis of data from the FDPS. The model described the data, characterized mechanisms leading to incomplete observations and accounted for the occurrence probability of the non-terminal processes in the interval between visits as only death dates can be retrieved exactly. The model allowed simultaneous estimation of covariate effects on all λs. Though with a different methodology, we successfully identified the same covariates recently used for stratifying patients with T2D into subgroups with differing disease progression and risk of diabetic complications [7]. Finally, our model is naturally extendable for PK/PD joint modeling of drugs, biomarkers and competing clinical outcomes. This framework, with suitable adaptions, may find widespread applicability for competing risks interval-censored longitudinal data instead of the currently used misspecififed standard survival models.

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C-02: *Sebastiaan Goulooze* Novel pharmacometric techniques to quantify and prevent iatrogenic withdrawal in children

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Introduction:

Prolonged treatment with analgesics and sedatives can cause iatrogenic withdrawal syndrome (IWS) in children being weaned from these drugs (1). Reported incidences of IWS in the pediatric ICU are high and variable (5–87%), suggesting a need for both individualized weaning strategies and monitoring of IWS.

In the pediatric ICU of the Dutch Sophia Children's Hospital, IWS monitoring relies on the $SOS_{withdrawal}$, a validated, objective scale that scores the presence of 15 withdrawal-associated symptoms (1,2). Some symptoms may however also be caused by pain, undersedation or delirium, complicating IWS monitoring. In addition to the $SOS_{withdrawal}$, the nurse also forms an expert opinion of withdrawal severity (2). In this study, the expert opinion was scored on a numeric rating scale ($NRS_{withdrawal}$) ranging from 0 (no withdrawal) to 10 (worst withdrawal), taking contextual factors such as the possibility of co-occurring pain, undersedation or delirium into account.

As a first objective, we aimed for a model-based quantification of the dynamics of drug dependence and withdrawal severity to ultimately individualize weaning strategies based on a child's prior use of analgesics and sedatives. For this application, we developed a novel mechanism-based iatrogenic withdrawal model. This model was based on the $NRS_{withdrawal}$ scores, as they provide more global albeit subjective information regarding withdrawal severity.

The second objective was to increase information obtained from the $SOS_{withdrawal}$ scale by performing an item response theory (IRT) analysis on its item-level data. As the unidimensionality assumption is violated by the impact of pain, undersedation and delirium, regular IRT modelling was not be applicable (3) and we therefore developed two extensions of regular IRT: the supervised IRT (sIRT) (4), and supervised multi-dimensional IRT (smIRT). The rationale of these supervised IRT methods is to leverage the expert opinion contained in the $NRS_{withdrawal}$ score to improve the quantification of withdrawal severity from the objective symptom data.

Methods:

Clinical study

In 81 children (aged 1 month to 17 years), 1782 paired IWS assessments were performed with the $SOS_{withdrawal}$ and $NRS_{withdrawal}$ scales, during an observational clinical study (2). $NRS_{withdrawal}$ scores range from 0 (no withdrawal) to 10 (worst withdrawal possible).

Characterizing the dynamics of $NRS_{withdrawal}$

A novel mechanism-based withdrawal model structure was developed to characterize the development and disappearance of drug dependence over time. The model contains hypothetical 'dependence compartments', which equilibrate with the central pharmacokinetic compartment at an estimated rate. Published population pharmacokinetic models were used in combination with individual dosing information to generate population predicted plasma concentration-time profiles in each patient of all key analgesics and sedatives (i.e. morphine, fentanyl, methadone, midazolam, lorazepam, propofol, esketamine and clonidine). Withdrawal severity was modelled using a linear relation with the drug deficiency, defined as the difference between the concentration in the 'dependence compartment' and the predicted concentration in the central compartment. A generalized truncated Poisson model with Markovian transition probability inflation was used to respect the bounded integer nature of the $NRS_{withdrawal}$ (5). Using simulations, different weaning strategies were compared for different drugs.

Supervised IRT modelling of $SOS_{withdrawal}$ items

Pharmacometric models based on item-level data of the $SOS_{withdrawal}$ were developed using three IRT-based modelling techniques, i.e. regular IRT, sIRT and smIRT. For the sIRT and smIRT, the nurse's $NRS_{withdrawal}$ score was used as a 'supervising variable' to guide the latent variable of the model towards withdrawal (3). For the smIRT, one or two unsupervised latent variables were added to the sIRT model to limit violations of the local independence assumption, by accounting for the impact of conditions other than IWS that affect the $SOS_{withdrawal}$ items.

To allow for a comparison of linear association between the $NRS_{withdrawal}$ score and the latent variables of the regular IRT, sIRT and smIRT models, the parameters of the sIRT and smIRT models were fixed to their estimated values, and refitted to the data in the absence of the $NRS_{withdrawal}$ scores, re-estimating only the distribution of a logit-normally distributed latent variable on the same 0–10 scale as the $NRS_{withdrawal}$ scores. The AIC of linear models in which the total composite score of the $SOS_{withdrawal}$ or the latent variable of a particular IRT model was the predictor, and the $NRS_{withdrawal}$ score the dependent variable.

Results:

Using the mechanism-based withdrawal model, the dynamics of withdrawal and dependence could be established with statistical significance for fentanyl ($p< 10^{-6}$), morphine (p=0.043) and esketamine (p=0.002). The estimated rate constant of the drug dependence compartment was higher for fentanyl (0.265 h^{-1}) compared with esketamine (0.018 h^{-1}) and morphine (0.008 h^{-1}). As a result the dynamics of dependence for fentanyl are also affected by its clearance. For all drugs, the weaning period should be increased with increasing drug levels prior to weaning.

Compared with the total $SOS_{withdrawal}$ score, the latent variable of the regular IRT model showed a weaker association with the $NRS_{withdrawal}$ score (ΔAIC = +180.5). The re-estimated latent variables of the two supervised IRT models had a stronger association than the total $SOS_{withdrawal}$ score, even when removing the $NRS_{withdrawal}$ after estimation of the supervised IRT models, with the strongest association being observed with the smIRT with two latent variables (ΔAIC = -223.7). Interestingly, the residual item-pair correlations in the sIRT model corresponded with clinical knowledge regarding the $SOS_{withdrawal}$ items that are associated with pain and undersedation, and these correlations were attenuated in the smIRT models.

Conclusion:

The mechanism-based withdrawal model dynamically predicts IWS from fentanyl, morphine and esketamine and showed that the optimal strategy for weaning of drug-dependent children depends on both the type of drug and the drug levels prior to weaning.

For the $SOS_{withdrawal}$, where individual items are not only affected by withdrawal, regular IRT modelling was worse in terms of quantifying withdrawal, than analysis based on total $SOS_{withdrawal}$ score. The quantification of withdrawal severity was improved when using sIRT and smIRT, in which the subjective $NRS_{withdrawal}$ score was used to 'guide' the latent variable towards withdrawal. Using the supervised IRT models developed here to estimate the IWS severity from symptoms alone, can be useful when $NRS_{withdrawal}$ scores are lacking, or as a supplement to the subjective $NRS_{withdrawal}$ score.

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C-03: *Elena Tosca* Dynamic Energy Budget (DEB) based models of tumor-in-host growth inhibition and cachexia onset

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Objectives: The great contribution of PK-PD tumor growth inhibition (TGI) models in the anticancer drug development process is already well-established. However, models currently available are always focused only on the drug efficacy assessment and, completely neglecting the host organism, overlook the drug/tumor-related toxic effects [1, 2][PM1] . Actually, host conditions significantly influence tumor growth that, in turn, has a relevant impact on the host. Severe body weight (BW) loss (cachexia) and reduced food intake (anorexia) are among the main causes of cancer death and, also, relevant endpoints in the preclinical studies. Finding the best compromise between efficacy and toxicity is the goal of any anticancer therapy. In absence of appropriate models that consider both the tumor and host body interactions (tumor-in-host models) and the anticancer drug effects, this efficacy/toxicity evaluation is based on heavy and time-consuming trial-and-error procedures. Here, a new modeling approach able to describe tumor-in-host growth dynamics and cachexia onset during an anticancer treatment is proposed to better exploit data routinely generated in the preclinical phase of an oncological drug development process.

Methods: *Tumor-in-host DEB-based model:* Following the van Leeuwen work [3], the Dynamic Energy Budget (DEB) theory [4] is adopted as general framework to describe the host organism. The dynamics of host body, composed by the structural biomass and the energy reserve, follow from an energy balance. Tumor is conceived as an additional component able to subtract a fraction k_u of the host energy for its maintenance and growth. As tumor exploits host resources, in certain conditions, the organism can even degrade its structural biomass to survive and, at the same time, to satisfy the tumor energy demand (tumor-related cachexia). This condition can be further worsened by the negative impact of tumor progression on host energy intake (tumor-related anorexia).

Tumor-in-host DEB-TGI models: The tumor-in-host DEB-based model is extended and adapted to describe the effects of different anticancer treatments. 1) *Cytotoxic agents*: Drug exerts a direct killing effect on tumor cells, modeled as in the Simeoni model [5], and an inhibitory effect on the host assimilation. The latter accounts for the temporary decreased energy intake (drug-related anorexia) due to drug side effects and followed by host BW loss (drug-related cachexia). 2) *Anti-angiogenic agents*: An inhibitory effect, linked to the drug concentration, is added on k_u fraction to account for the modification of the energy partition between tumor and host that follows the reduction of tumor vascularization due to the anti-angiogenic therapy. 3) *Combination of anti-angiogenics with chemotherapy*: A joint model, incorporating both the anti-angiogenic and cytotoxic DEB-TGI models, is used to predict tumor and host response to a combination therapy under a 'no-interaction' assumption [6]. The nature of combination (additivity/synergisms/ antagonisms) can be evaluated comparing model predicted and observed tumor weight (TW) and host BW.

Experimental data refer to TW and net host BW of 16 xenograft mice studies involving 6 tumor cell lines and 14 anticancer agents administered at several doses and schedules [7,8,9]. Furthermore, a study assessing etoposide (ETO) effects on both tumor-free and tumor-bearing Wistar rats is considered [10]. Average and individual data are analysed in Monolix 2016R1, by a naïve average and a non-linear-mixed-effect approach, respectively.

Results: *Tumor-in-host DEB-based model:* The model, identified on control animals, successfully describes TW and host BW, predicting a S-shape tumor growth profile that directly follows from physiological hypothesis on tumor-host energetic interactions. *Cytotoxic agents:* For 8 xenograft studies involving 3 tumor lines, the model is able to simultaneously describe and predict TW and host BW growth in control and treated mice with both novel anticancer compounds and well-known drugs (paclitaxel, 5-FU, cisplatin, vincristine, vinblastine and gemcitabine) [7]. A slightly revised model formulation, combined with the use of intratumoral concentration as driver of tumor kinetics, successfully describes the ETO effects on Wistar rats accounting also for its schedule-dependence [10]. This well-design experiment, including treated and untreated tumor-free animals, allows to fully exploit model capabilities in describing and discerning all the *in vivo* growth dynamics. *Anti-angiogenic agents:* The tumor-in-host DEB-based TGI model, adapted for cytostatic therapy, is successfully applied to 7 xenograft mice experiments assessing the Bevacizumab (BVZ) effect on 3 tumor cell lines [8]. In this case, in addition to the drug potency estimates, quantitative measurements of tumor-related cachexia are provided. Finally, a hypoxia-triggered resistance model allows to describe the decreased BVZ efficacy observed after prolonged treatments [9]. *Combination of anti-angiogenics with chemotherapy*: A combination study on xenograft mice treated with BVZ, 2 doses of NMS-937H or a combination of both is successfully analysed [8]. Model parameters estimated on the single-agent arms are used to predict the expected tumor and host response in the combination groups. Comparing the predicted curves with the observed data, no significant departures from additivity are found for both efficacy (TGI) and safety (cachexia) profiles. However, an increment in the TGI due to BVZ and NMS-937H coadministration highlights the advantage of the combination strategy.

Conclusions: A simultaneous modeling of tumor and host organism interactions during anticancer treatments is proposed on the basis of the DEB theory. This approach, suitably adapted to several preclinical experimental contexts, is able to integrate all the different aspects characterizing the *in vivo* TGI studies: drug cytotoxic or cytostatic activity on tumor, onset of drug/tumor-related cachexia and anorexia and influence of host condition on tumor growth. This allows for the first time to investigate separately BW loss due to tumor progression and to treatment, providing in addition better estimates of anticancer drug efficacy that is disentangled from TGI due to depletion of host energy. These findings strongly suggest the adoption of the tumor-in-host approach in the preclinical oncological setting for a joint assessment of drug efficacy and toxicity on animal BW and for a better protocol design of the experiments. Finally, the successfully application of the DEB-approach to different host species, several anticancer agents based on different mechanisms of action and experimental settings, including combination therapies, encourages further investigations. Specific modeling efforts are focusing on taking advantages of the DEB-based paradigm as preclinical to clinical translational approach. Preliminary results are encouraging.

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C-07: *Kristin Karlsson* Regulatory model-informed drug discovery and development in EU – News flash and examples

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Objectives: To provide an update on modelling and simulation involvement in the EU regulatory activities and procedures and highlight the latest news regarding MIDD in EU regulatory framework and to present examples of procedures where model-based approaches were essential for decision making.

Overview/Description of presentation: The presentation will provide some key statistics on M&S related regulatory activities and highlight some regulatory documents where model-based approaches are described and promoted. Examples of documents that have been published within the last year are Extrapolation Reflection Paper[1], Modelling and Simulation Working Party Paediatric Q&A[2], and Guideline on the reporting of physiologically based pharmacokinetic modelling and simulation[3]. Furthermore, there is ongoing work within various aspects of paediatric drug development, and the strategy document EMA Regulatory Science to 2025.

The second part of the presentation will focus on EU regulatory examples where model-based approaches played a vital role in the development and authorization of medicinal products. There are numerous examples of where model-based approaches have proven to be pivotal for the benefit/risk assessment in a market authorization application. Other regulatory interactions with increasing visibility of model-based drug development are central scientific advices (through the Scientific Advice Working Party) and paediatric investigation plans (through the Paediatric Committee) will be highlighted.

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C-08: *Sylvie Retout* A model-based extrapolation enabled labelling of emicizumab in haemophilia A paediatric patients <1 year old despite lack of clinical data

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Objectives: Emicizumab is a bispecific humanised monoclonal antibody (mAb) that binds activated factor (F) IXa and FX to activate FX, mimicking the function of missing or defective FVIIIa in patients with haemophilia A (PwHA) [1]. European Medicine Agency (EMA) among others approved a maintenance dose of 1.5 mg/kg/week from birth to adulthood in PwHA with inhibitors against FVIII. No data in PwHA

Methods: A popPK model was available for emicizumab, developed on a dataset of 191 PwHA, including 17 PwHA aged 2 to < 6 y, and only 4 PwHA aged 1 to < 2 y. The model included a body weight (BW) effect on the apparent clearance (CL/F) and volume, with estimated exponents of 0.891 (RSE=4.0%) and 1.02 (RSE=3.5%) respectively; CL/F was also impacted by albumin concentrations, increasing with decreasing albumin levels. For the PK extrapolation to PwHA < 1 y old, a known albumin variation with age [2] was implemented in the popPK model and the increase in BW with age was accounted for by using an actual covariate database from 693 infants tau$_{,SS}$) at the dose of 1.5 mg/kg/week in PwHA 1 y old could be used to extrapolate CL/F to PwHA < 1 y old; (2) or assuming that CL/F follows an age-based maturation function combined with the classical fixed allometric exponent of 0.75 for BW effect as described in [4]. Simulated $AUC_{tau,SS}$ were then translated into bleeding event risk using an existing exposure–efficacy model [5].

PBPK simulations using SimCyp Version 15 [6] were also carried out to investigate whether a more mechanistic description of age-related differences could further improve the confidence in PK projections, especially in PwHA

Finally, the emicizumab popPK model was compared with published popPK models of other mAbs in children and infants.

Results: The popPK simulations with the maturation function predicted the lowest reduction of $AUC_{tau,SS}$ (27%) compared to PwHA >1 y old. At those levels, the efficacy of emicizumab is expected to be maintained, with exposures still at the plateau of effect.

Predicted CL/F with PBPK approach were 15%-20% higher than the ones predicted by the emicizumab popPK model for patients aged 3 months to 1 y and twofold higher for neonates. However, those predictions remained highly uncertain due to the lack of validation of the PBPK approach for mAbs in paediatrics, the absence of data for the ontogeny of key mechanisms (e.g., FcRn), and also the fact that the PBPK model over-predicted CL/F (up to +40%) in age ranges where patient data were available. Those PBPK predictions were however provided to the EMA, highlighting that the methodology was not robust enough yet to confidently extrapolate PK in infants.

Lastly, of the very few published popPK models of mAbs [8], only the palivizumab model [4] included an explicit age-based maturation function, whereas the others included only allometric scaling approach using BW. The palivizumab model was developed on a dataset of 1684 patients from birth to 2 y of age, and its use of a maturation function was therefore considered as the most robust extrapolation approach. The

emicizumab CL/F was found very comparable to the current knowledge regarding CL/F of mAbs in paediatrics, especially to palivizumab's, even for PwHA

Conclusions: By leveraging emicizumab models (i.e: popPK, PBPK and exposure-response), together with literature data, the proposed dosing of emicizumab for young infants was deemed appropriate although no data in PwHA < 1 y old were available. That full model-based extrapolation, together with a high unmet medical need and assumptions for disease and PK-pharmacodynamics similarities compared to PwHA >1 y old, was considered acceptable and led to the approval of emicizumab in PwHA with FVIII inhibitors in all age groups in the European Union countries.

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C-12: *Theodoros Papathanasiou* Model based optimization of dose-finding studies for drug-combinations.

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Objectives:

Combinations of pharmacological treatments are increasingly being investigated for potentially higher clinical benefit, especially when the combined drugs are expected to act via synergistic drug interactions [1,2]. The clinical development of combination treatments is particularly challenging, especially during the dose selection phase, where a vast range of possible combination doses exist [3]. Traditionally, dose-finding drug-combination studies are conducted based on factorial designs and variations thereof [3]. While simple in their conception and construction, the choice of the investigated dose levels is often empirical.

Model-Based Drug Development (MBDD) has been proposed by regulatory agencies, academia and pharmaceutical industry as an efficient approach to mitigate the risks of dose selection and improve confidence in decision-making [4, 5]. As part of MBDD, exposure-response (E-R) analyses that associate an exposure metric, such as average concentration in steady state, and a continuous response variable measured at a single time point, have become a critical component for supporting dose selection for phase III [6]. It has previously been shown that dose selection can be improved though the modeling of exposure-response (E-R) relationships of combinatory drug effects and that the study design is important in correctly characterizing these models used for dosing decisions [3].

In this work we investigate how dose selection can be optimized in drug-combination studies through the use of optimal design methodology in tandem with E-R analyses. The optimized designs are compared to a typical drug-combination dose-finding design (3x3 factorial) [3] in regard to overall parameter accuracy and precision, precision of pre-specified effect level predictions and their ability to correctly identify the minimum effective combination dose ($MED_{A,B}$) to be brought forward to a confirmatory clinical trial.

Methods:

Model based optimizations were performed using the R package PopED [7]. The true combination model was assumed to be an effect addition model with one interaction term [2,3], where the pharmacodynamic effect is driven by steady state concentrations of both drugs (C_{ss}). The E-R relationships of the individual mono-components were assumed to be described by E_{max} models with different maximal effects and their pharmacodynamic interaction was assumed to be synergistic [3].

Optimizations of the allocations of the investigated dose levels were performed using a local optimality criterion (D-optimality) to maximize the precision of all model parameters in a simulated exposure-response (E-R) surface [2,3]. ED-optimality with a uniform distribution around the effect parameters was also used to obtain a generalizable design for situations where uncertainty around the effect parameters is present.

Since the objective of dose-finding studies is to identify the best doses to be brought forward to confirmatory trials, good precision around a target effect level is highly desirable. In the case of single-drug therapies, where the treatment response is driven by the exposure of a single drug, trial optimization towards this goal can be achieved by either approaching the target exposure level as a model parameter with uncertainty that should be minimized or by constructing designs that minimize the asymptotic variance of the target concentration estimates [9]. For drug combinations, such approaches are complicated by the fact that the treatment effect is driven by the combination of two variables (i.e. exposures of Drug A and Drug B). The approach used here was to utilize an optimality criterion that aims to reduce the average prediction variance in a specific region of the three-dimensional E-R surface (V-Optimality) [10]. V-Optimal designs can be hard to construct and generally lead to poor parameter estimation [10], which is undesirable when performing a model-based analysis. To mitigate this, we considered a compound criterion incorporating D- and V- optimality characteristics (D/V-optimality), with equal contribution from both criteria.

Stochastic simulation and estimation (n=1000) was performed to determine the parameter precision resulting from the reference and optimized study designs. Overall parameter precision was defined as the average %RSE of all the parameters in the model for each competing design, which was compared to the same value calculated for the reference study design. All simulations and estimations were performed in NONMEM version 7.3 [11] using PsN [12].

Lastly, all designs were evaluated regarding their ability to correctly identify the correct minimum effective combination dose ($MED_{A,B}$), defined as the dose leading to a wanted pre-specified effect level that simultaneously minimizes the needed dose from both mono-components. The $MED_{A,B}$ was calculated using the true and SSE derived model parameters and the probabilities of identifying the correct dose A alone (MED_A), correct dose B alone (MED_B) and the true combination dose ($MED_{A,B}$) were derived (where correct is assumed to be a dose that is within 20% of the true $MED_{A,B}$).

Results:

The D-efficiency of the D-optimal design as compared to the reference design was 141%. When the D/V-optimality criterion was used, the D-efficiency was slightly lower (107.5%). A slight loss in the D-efficiency of the globally optimal design was observed 98.7%.

The overall parameter precision was improved in the optimized designs. The average %RSE for the D-optimal design was 13.6%, followed by the D/V- and ED-optimal designs (16.1% and 17.9% respectively). The %RSE for the reference design was 17.3%.

Regarding correct $MED_{A,B}$ identification, the highest probabilities were observed for the D/V-Optimal design (88.2%), followed by the D- and ED-optimal design (76.7% and 73.7% respectively). The lowest probability for identifying the correct $MED_{A,B}$ was seen when the reference design was used (67.7%).

Conclusions:

Our study results indicate that using optimal design in tandem with E-R analyses can be an attractive method for dose allocation in drug-combination dose-finding studies. Optimized studies significantly improved the extracted amount of information, allowing for the same information from as little as 60% of the subjects as compared to a typical drug-combination design. Additionally, the flexibility in defining the optimality criteria can help improve the probability of identifying the optimal combination dose to be brought forward in late stage development.

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C-13: *Antonio Goncalves* Model Averaging in viral dynamic models

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Objectives: Nonlinear mixed effect models (NLMEM) are now becoming a central tool in viral dynamic models to estimate parameters of viral pathogenesis and identify relevant factors limiting viral replication [1–3]. However data fitting and model building remain challenging due to the fact that i) models often involves poorly identifiable parameters and/or ii) several structural models with different biological assumptions may provide nearly similar fits to the data. To overcome these issues, the most standard way is to fit the data using a set of candidate models and then to retain the model providing the best fit to the data using standard tools of model selection (such as AIC). However, this approach of Model Selection (MS) ignores the uncertainty due to multiple tested models and thus is subject to overoptimistic conclusions [4]. Here we assess the benefit of using of model averaging (MA) to provide better parameter estimates and more robust predictions, an approach that weighs predictions of different candidate models [4][5].

Methods: We evaluated MA by simulations in two different settings, both in the context of an acute viral infection, using parameters estimated during Ebola virus infection [6]. In the first setting, we focused on estimation step and provided confidence intervals of estimated parameters when some model parameters are fixed to arbitrary values. Data were simulated according to a target cell limited model [7] where both the eclipse phase rate and the initial viral load inoculum cannot be identified and were fixed to different plausible values [8]. Parameters and confidence intervals were then estimated and we compared the coverage rate of the estimated parameters, in particular the reproductive ratio number, R_0, under MA, MS and the true model used for simulation.

In the second setting we focused on the predictions derived from MS and MA and considered, in addition to the target cell limited model, 4 models describing the putative role of the innate and adaptive immune system in clearing infection. The magnitude of immune response was comparable between models and they provided similar fits to the data. For each trial replicate, we predicted the median AUC under increasing treatment effects (from 10% to 99.9%) for MA, MS and the true model used for simulations. Relative root mean square errors (RRMSE), relative bias (RB) were calculated to compare prediction precision. Finally, the Kullback-Liebler divergence of the median AUC (KLD_{AUC}) were computed to evaluate MA and MS predictive performances. KLD_{AUC} represents the divergence between the true and estimated probability distributions.

Each simulated trial included 30 individuals drawn every 3 days from day 3 to day 18. Under each setting and for each trial replicate, parameters were estimated by maximum likelihood using the SAEM algorithm implemented in Monolix2018R2 and standard errors were obtained by stochastic approximation.

Results: Regarding the first simulation setting, the true model was selected in the different scenario in less than 63% of the cases. This, therefore, led to a poor coverage of R_0 was comprised between 0.37 and 0.62. This was corrected using MA, where the coverage rates increased above 0.90 in all cases. In the second setting, MA was associated with a better prediction of the median AUC compared to MS. When simulating with efficacy of 99%, both RRMSE and RB lowered from 52.9% to 36.7% and 12.3% to 6.7% respectively. Using MA, the mean KLD_{AUC} was reduced by 50% compared to MS. Finally, the true model used to simulate

the data was not selected up to 49% of the cases leading then to wrong conclusion about the mechanism of the immune response.

Conclusions: This work shows how model selection, by ignoring the model uncertainty, can lead to biased estimates and/or predictions of the median AUC under treatment. Furthermore, this work illustrates that model averaging may be useful in the context of viral dynamic models to take into account the fact that several candidate models can provide equally good fits to the data.

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C-14: *Mohammed Cherkaoui Rbati* A liver model for chemoprotection against malaria

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Introduction: Chemoprotective drugs are developed to protect people from being infected by plasmodium, and in particular by *P. falciparum*, the most prevalent and deadly malaria strain in Africa. MMV's stretched goal is to develop a treatment able to protect people for one month after a single dose. It is thus important to understand how a drug kills parasites not only in the blood stage, which causes symptoms, but also in the liver stage, where the infection starts whilst remaining asymptomatic.

Whilst PKPD models have been developed to understand the blood-stage activity of antimalarial candidates to cure patients, little modelling has been proposed for liver-stage activity. What makes modelling liver-stage challenging is that the liver-stage parasites, unlike blood-stage parasites, cannot be counted.

Objective: Develop a PKPD model to describe the drug killing effect on both the liver and blood-stage parasites. The example of DSM265, a plasmodial dihydroorotate dehydrogenase (DHODH) inhibitor, is chosen to illustrate the approach.

Methods: A mathematical model was developed and consists of two ordinary differential equations which describes the dynamic of the liver and blood-stage parasites, respectively. Each equation includes a net growth rate and a drug killing rate specific to each stage. One term accounted for the release of the parasites from liver to blood-stage. Since liver-stage parasitemia cannot be monitored, the activity on liver-stage had to be deconvoluted from the knowledge of the blood-stage activity. Therefore, the estimation of the PKPD parameters was conducted in four steps; (i) parasite growth in the blood, (ii) parasite growth in the liver, (iii) drug activity in the blood and (iv) drug activity in the liver.

Two studies in which volunteers were injected infected red blood cells then administered DSM265 at 150mg and 400mg, respectively, were used to determine (iii) [1]. Then two studies, in which volunteers were administered a dose of 400 mg DSM265 administered 1, 3 or 7 days prior to infecting them with an *i.v.* injection of 3200 sporozoites or 5 mosquito bites, were used to deduce (i), (ii) and (iv) [2]. In these studies, the parasites invade first the liver, then the red blood cells. In all four Volunteer Infected Studies (VIS), PK concentrations and blood-stage parasitemia were measured in each individual.

All parameter estimations were conducted with Monolix (v2018R2), an NLME modelling software. When the number of subjects was limited, some of the inter-individual variability parameters were fixed. First, the blood-stage parameters were estimated with the blood-stage VIS data; then they were fixed, and the liver-stage parameters were estimated with the liver-stage VIS data.

Finally, a sensitivity analysis was conducted to identify which parameters are key in protecting people with DSM265. Moreover, to validate the model, simulations of the liver-stage VIS were conducted to compare the predicted fraction of subjects with breakthrough with the observations.

Results: The growth of the parasite in blood was better described by a cyclic model, with a growth rate estimated at 0.064 hr^{-1} and a period at 44.9 hours. For the liver-stage parasites, the growth rate was calculated to be 0.063 hr^{-1} and the fraction of viable sporozoites estimated to be 0.2% corresponding to 6 sporozoites invading hepatocytes. In comparison, it was estimated that about 35% of the 50-100 sporozoites injected after a mosquito bite reached the blood stream and could potentially invade hepatocytes [3]. The blood-activity analysis led to the estimation of a Minimum Inhibiting Concentration (MIC) of 1180ng/mL against blood infection, whereas the liver-activity analysis led to a MIC against liver infection of 2440ng/mL. The sensitivity analysis showed that the chemo- protectiveness of DSM265 is sensible to its liver-activity, and to a lesser extent to its blood-activity. Finally, the simulations showed that the chemoprotection PKPD model could reproduce the liver-stage VIS results, despite the limited number of volunteers.

Conclusion: In conclusion, combining liver and blood-stage VIS made it possible to develop a promising PKPD model that can describe the activity of an antimalarial drug on both liver and blood-stages. Nevertheless, further analyses and more studies are needed to validate the model. Hopefully, this will help select better dosing regimen for chemoprotection to be tested in phase II studies.

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C-15: *Xiao Zhu* A cohesive model framework of receptor pharmacology: beyond the Emax model

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Background: Just over 150 years ago, the Norwegian mathematician Cato Guldberg and the chemist Peter Waage, propounded the law of mass action [1]. A.V.Hill was the first to apply this mathematic principle to physiology [2]. In his studies on nicotine and curari, on the basis of the law of mass action and mass balance, he derived what was later known as "Emax model". In pharmacological nomenclature, it is conventionally written as: E = Emax*A/(KA+A), where A is the concentration of a ligand and KA the equilibrium binding of the agonist. The Emax model is probably the most widely used model to describe drug-receptor interactions whether at the level of binding or a bioassay of a response variable. By linking pharmacokinetics (PK) to pharmacodynamics (PD), the Emax model (now driven by the concentration-time profile) provides a practical tool to describe concentration-effect relationship [3]. However, Emax model is so ingrained in PD modelling that the assumptions attached to it are often overlooked. This may cause difficulties in the interpretation of estimated parameters and extrapolation of the findings across different contexts (e.g., cell, tissue, animal and human). Hence, it is useful to have a framework that underpins our understanding and use of the Emax model.

Objectives: The overall goal of this work is to develop a cohesive model framework for the Emax model that allows generalisation of its application to meet a diverse range of experimental conditions. This encompasses three specific objectives:
(1) to systematically assess the assumptions underpinning the Emax model,
(2) to relax these assumptions to accommodate different experimental conditions and physiological behaviours of systems,
(3) to develop a user-friendly interface of the framework for scientific communication.

Methods: The assumptions underpinning the Emax model were identified based on an evaluation of its historical origins, subsequent mathematic derivations, expert opinion, and logical reasoning. PubMed, Scopus and Google Scholar were searched for the features of receptor pharmacology that were not in line with the assumptions of the Emax model. Subsequently, the publications that cited these papers were screened to identify necessary model components for describing these features. At the end, by assembling all the necessary model components together the Emax model was generalised into a cohesive model framework of receptor pharmacology. In addition, a Shiny website was developed for interactive presentation of the cohesive model framework.

Results: Seven assumptions underpinning the Emax model were identified:
Assumption 0: The ligand-receptor interaction follows the law of mass action.
Assumption 1: There is linear relationship between receptor occupancy and response.
Assumption 2: There is no ligand-independent receptor activity.
Assumption 3: One receptor only produces one type of response.
Assumption 4: The total amount of receptor is constant.
Assumption 5: The binding of ligand to receptor is at equilibrium.
Assumption 6: There is an excess of ligand.

Assumption 0: The law of mass action ensures that the reaction rate depends on the concentrations of the reactants or products and the stoichiometry, forming the foundation of drug action. This assumption seems to be valid for most cases.

Assumption 1: The Emax model cannot explain the phenomenon of receptor reserve (i.e., the ability of a ligand to elicit a maximal response with only a fraction of the whole receptor population occupied) [4], indicating a possible nonlinear relationship between receptor occupancy and response. Relaxation of Assumption 1 leads to the development of the operational model [5]. The operational model incorporates an arbitrary transduction function to transform receptor occupancy into response. Most of the time, it would be the rectangular hyperbolic function.

Assumption 2: The Emax model cannot explain the phenomenon of constitutive activity (i.e., ligand-independent receptor activity) or inverse agonist [6]. Relaxation of Assumption 2 leads to the two-state model [7]. In the two-state model, receptor could spontaneously form the active state and there exists dynamic equilibrium between active state and resting state even without any ligand present. In addition, the ligand could alter the equilibrium between resting state and active state. Note an empirical generalisation often includes a baseline effect as an approximation to the two-state model.

Assumption 3: The Emax model cannot explain the phenomenon of biased agonism (i.e., a ligand can act on one receptor to differentially regulate multiple signalling pathways) [8]. Relaxation of Assumption 3 leads to the three-state model (i.e., the simplest version of multi-state model) [9]. In three-state model, receptor has two mutually competing active states and therefore can have two distinct signalling profiles.

Assumptions 4-6: These Assumptions are related to the equilibrium conditions of the Emax model. The loss of surface receptor overtime has been observed in some receptors (e.g., cannabinoid 1 receptor and mu-Opioid receptor), suggesting the need to relax Assumption 4 and consider receptor turnover and internalisation [10,11]. The validity of Assumption 5 is largely depended on the relative magnitude between the drug-target residence time and the observation period. Because of the potential advantages on duration of pharmacological effect, there is an increasing interest in lead optimisation of long residence time [12]. The Emax model is not applicable for these ligands and ligand binding kinetic is warranted. As a pharmacometrician, we are more aware of the violation of Assumption 6. Due to ADME processes, the relative magnitude between the amount of receptor and the amount of ligand changes over time. Hence, a PK model of ligand is incorporated in most of modelling work. The relaxation of Assumptions 4-6 leads to target-mediated drug disposition model [13]. This model consists of receptor turnover, ligand binding kinetic, ligand-mediated receptor internalisation and ligand PK.

Generalising Assumptions 1-6 and integrating all the necessary model components provide a cohesive model framework of receptor pharmacology. Subsequently, a Shiny website was implemented for interactive presentation of this cohesive model framework (https://xiaozhu.shinyapps.io/GPCRmodel).

Conclusion: A single framework of receptor pharmacology is proposed as a series of generalisations of the standard Emax model which can accommodate different experimental conditions and physiological behaviours of systems. This framework allows modellers to examine their current use of the Emax model and facilitates the interpretation of modelling results. The next step of this work is to assess the identifiability of different sub-models from the cohesive model framework based on available input output data.

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C-18: *Alison Margolskee* Exploratory graphics (xGx): promoting the purposeful exploration of PKPD data

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Introduction: As pharmacometricians, we sometimes jump into complex modeling before thoroughly exploring our data. This can happen due to tight timelines, lack of ready-to-use graphic tools or enthusiasm for complex models. Exploratory plots can help to uncover useful insights in the data and identify aspects to be explored further through modeling or in future studies. Exploratory plots can even quickly answer questions without the need of a complex model, improving our efficiency and providing timely impact on project strategy. The Exploratory Graphics (xGx) tool is an open-source R-based tool, freely available on GitHub [1]. Intuitively organized by datatype and driven by analysis questions, the tool aims to encourage a question-based approach to data exploration focusing on the key questions relevant to dose-exposure-response analyses.

Objectives:

- Facilitate the purposeful exploration of PKPD data
- Encourage a question-based approach to data exploration, focusing on dose-exposure-response relationships
- Provide a teaching tool for people new to PKPD analysis

Methods: PK (single and multiple ascending dose), and PD (continuous, time-to-event, categorical, count, and ordinal) data were simulated and formatted according to a typical PKPD modeling dataset format. Lists of key questions relevant to dose-exposure-response exploration were compiled, and exploratory plots were generated to answer each question. The graphs were created following good graphics principles to ensure quality and consistency in our graphical communications [2].

Results: Examples of the key analysis questions include:

- Provide an overview of the data:
    - What type of data is it (e.g. continuous, binary, categorical)?
    - How many doses?
    - What is the range of doses explored?
    - For PK data, how many potential compartments are observed?
    - Is the exposure dose-proportional?
    - Is there evidence of nonlinearity in clearance?
- Assess the variability:
    - How large is the between subject variability compared to between dose separation?
    - Can any of the between subject variability be attributed to any covariates?
    - Are there any patterns in the within subject variability (e.g. circadian rhythms, seasonal effects, food effects, underlying disease progression)?
- Assess the dose/exposure-response relationship:
    - Is there evidence of a correlation between dose/exposure and response?
    - Is the relationship positive or negative?

- Is there a plateau or maximal effect in the observed dose/exposure range?
- Is there evidence of a delay between exposure and response?

For each datatype in the simulated dataset, plots were generated to answer these key questions. The plots along with the codes to produce them were compiled into a user friendly interface. The tool is intuitively organized by datatype and driven by the analysis questions. Since the graphs were generated based on a typical modeling dataset format and hosted online, they can be easily accessed and applied to new projects.

Conclusion: Exploratory plots were generated, built around typical key questions particularly relevant to dose-exposure-response exploration and compiled into a user friendly interface. The Exploratory Graphics (xGx) tool can help underscore the role of purposeful data exploration for quantitative scientists. Through a question-based approach, xGx helps uncover useful insights that can be revealed without complex modeling and identify aspects of the data that may be explored further.

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C-19: *Marc Cerou* Performance of npde for the evaluation of joint model with time to event data

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Objectives:

Joint models are increasingly used in clinical trials. An important part of model building is to properly assess the descriptive and predictive ability of these models. Normalised prediction discrepancies (npd) and normalised prediction distribution errors (npde) have been developed to evaluate graphically and statistically non-linear mixed effect models for continuous responses [1]. In the present work, we extend npd to time-to-event (TTE) models [2].

The aims of this work were to:

- develop npd for TTE data and evaluate their performance on a simulated example
- evaluate the performance of the combined test for joint longitudinal and TTE models

Methods:

Let V denote a dataset. In this work we first consider a dataset with only TTE observations and then a dataset with both longitudinal and TTE observations. The null hypothesis H_0 is that observations in V can be described by a model. Prediction discrepancies (pd) are defined as the quantile of the observation within its predictive distribution. In nonlinear mixed effect models (NLME), the predictive distribution is approximated by Monte-Carlo simulations (MCs). The pd for unobserved (censored) event times are imputed in a uniform distribution based on the model prediction of the probability of censoring [2], using a similar method as the one developed to handle data under the lower quantification limit (LOQ) [3].
[1] Under H_0, the pd follow a uniform U(0,1). They can be transformed back to a normal N(0,1) distribution using the inverse normal cumulative function, and we test their distribution either through a Kolmogorov-Smirnov test or a combined test of normality, mean and variance [1].

In joint models, we compute separately the pd for TTE data and the prediction distribution error (pde) for the longitudinal data, which are obtained after decorrelating simulated and observed data [1]. We then propose to use a combined test, combining the p-values of the tests on longitudinal data and on TTE data, adjusted with a Bonferroni correction.

We evaluated the performance of npd/npde through two simulation studies inspired by [4]. Desmée et al. characterised the relationship between the prostate specific antigen biomarker (PSA) and survival in 500 prostate cancer patients via joint modelling. We simulated event times and PSA trajectories from the joint model, for different sample sizes (50, 100, and 200) and evaluated the type I error and power of npd/npde to detect different types of model misspecifications. In the first simulation study, we assumed that the PSA model is correct and consider only TTE data. We tested two types of misspecification on the TTE model: PSA impact on survival and on the baseline hazard model. In the second simulation study, we considered both longitudinal and TTE data. We assumed that the TTE model was correct and tested misspecifications on PSA model's parameters.

Results:

In the first simulation study and in both cases of deviations for the TTE component, we found that the type I error associated with the npd-TTE was close to the expected 5% for all sample sizes. They were able to detect a model and parameter misspecification. In both cases of deviations, censoring the TTE data led to a decrease of the power. This is expected because in that case pd are imputed under the model being tested.

In the second simulation study, the npde-PSA were able to detect misspecifications in the PSA model, with a type I error close to 5%. A misspecification on an influential parameter of the PSA model was captured by both npde-PSA and npd-TTE. This suggests that, if a test rejects the survival model, we have to look at whether the problem may not come from the longitudinal model.

For all types of misspecifications, the type I error of the combined test was found to be close to the expected 5%. The power of the combined test to detect model misspecifications increased with the difference from the true model and as expected, with sample size. Graphically the power increase can be related to larger differences in the shape of the survival function or PSA evolution.

Conclusions: npd can be readily extended for event data by imputing the pd for censored event under the model [1]. The combined test for multiple responses performed well with an adequate type I error, and was quite sensitive to alternative models tested.

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D-01: *Aurelia de Vries Schultink* Prospective evaluation of Therapeutic Drug Monitoring of endoxifen: feasibility of observational and randomized trials.

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Objectives Tamoxifen is an anti-estrogenic drug that has been used to treat estrogen receptor (ER)-positive breast cancer for decades. Five years of adjuvant treatment with tamoxifen lowers ER-positive breast cancer recurrence and mortality rates.[1] Despite the proven established efficacy of tamoxifen, 25-30% of patients still experience recurrence within 10 years. Variability in response has been attributed to variability in pharmacokinetics (PK), more specifically to variability of endoxifen concentrations, the most important active metabolite of tamoxifen. Dose adjustments based on Therapeutic Drug Monitoring (TDM) of endoxifen as a strategy to improve survival in patients with ER-positive breast cancer are controversial, because the exposure-response relationship has not been well quantified. Additionally, the benefits of TDM have not been shown prospectively. Appropriately designed clinical trials are necessary to demonstrate the potential benefits of TDM. Therefore, clinical trial simulations using a parametric modelling approach based on large patient cohorts were performed. An observational design was simulated aiming to demonstrate an exposure-response relationship between endoxifen concentrations and breast cancer recurrence. Additionally, randomized controlled trials (RCTs) were simulated to support a design (including, power calculations, sampling size and follow-up time) evaluating the benefits of TDM over conventional dosing. These clinical trial simulations can help design appropriate trials and assess the validity of observational trials, in order to put previously conducted retrospective and prospective observational studies into the right perspective.[2,3]

Methods *Data* Recurrence free survival data and endoxifen concentrations were available from 1370 ER-positive breast cancer patients who participated in a previously conducted trial.[2] These data were used to establish a parametric time-to-event model. In addition, TDM data of endoxifen from 658 breast cancer patients treated with tamoxifen in the adjuvant setting were available from the Netherlands Cancer Institute. These data were used to evaluate the effect of a TDM-based dose increment of tamoxifen from 20 mg/day to 40 mg/day on attainment of the steady state target concentration of 5.97 ng/mL. Proportions of patient below and above this target were used for the clinical trial simulations.

Time-to-event model Different time-to-event models (Gompertz, Weibull and exponential distribution hazard functions) were evaluated in NONMEM using the Laplacian estimation method. Tumor grade, tumor stage, menopausal status were evaluated as predictors of recurrence-free survival.

Simulations The patients to be included in the clinical trials were ER-positive breast cancer patients that initiate treatment with tamoxifen 20 mg/day. Tumor grade, stage and menopausal status proportions were sampled from a previously studied cohort.[2] Firstly, simulations were conducted to evaluate the optimal design of an observational trial to evaluate the exposure-response relationship between endoxifen concentrations and breast cancer recurrence. Endoxifen concentrations were determined, though no dose adjustments were applied and only follow up was performed. Recurrence was compared between patients attaining and not attaining the endoxifen target concentration. Secondly, simulations were conducted to evaluate the optimal design of a RCT to determine the benefits of endoxifen TDM on breast cancer

outcome. Two different RCT designs were evaluated. Design 1: patients initiating treatment with tamoxifen 20 mg/day were included and randomized (1:1) to either the control arm, where no TDM was applied and only follow up was performed, or to the intervention arm in which patients with endoxifen concentrations ≤5.97 received a dose increment to tamoxifen 40 mg/day. Design 2: endoxifen concentrations are determined and patients with low endoxifen concentrations are randomized (1:1) or (1:2) either to the control arm (no dose increment) or to the intervention arm, receiving a dose increment to 40 mg/day tamoxifen.

Power calculations Each design was simulated a 1000 times with varying numbers of patients. For each trial the hazard ratio between the intervention and the control arm was determined using a Cox proportional hazards model (mimicking the conventional practice of analysing clinical trial survival data). The Cox proportional hazards model accounted for different covariates. The power was determined by the percentage of trials with a significant difference in recurrence-free survival between the control and the intervention arm, with a $p < 0.05$. A sensitivity analysis was performed to investigate the effect of shorter follow up times. In addition, the uncertainty in the effect of the PK target on the hazard was evaluated by assuming a factor 2 increase or decrease of this effect on the hazard.

Results *Parametric time-to-event model* The baseline hazard was best described by a Weibull distribution model. A higher tumor grade or stage was associated with an increased risk of recurrence. In addition, postmenopausal patients had a decreased risk of recurrence compared to premenopausal patients. A random dropout was used to account for patients that were lost to follow up.

Simulations To demonstrate the exposure-response relationship with a power >0.8, an observational trial design including at least 1500 patients and an intended follow-up of 15 years is needed to find a hazard ratio of 0.71, assuming a 29% reduction in the hazard of recurrence for patients attaining the target >5.97 ng/ml endoxifen concentration compared to patients with lower endoxifen concentrations. In order to prospectively validate application of endoxifen TDM to improve breast cancer outcome (assuming the previously estimated HR of 0.71), using the second study design demonstrated to be most feasible. Design 2 needs 1600 patients per arm to demonstrate the same effect (power of 82.9%). For design 2, a three-fold more patients are needed to identify the 32.5% of patients with low endoxifen concentrations. In comparison to previously conducted trials, the retrospective analysis by Madlensky et al. had around 60% power to find an exposure-response relationship and the recently published prospective CYPTAM study had only around 30% power.[2,3]

Conclusions Currently, no prospective or retrospective trial with sufficient power and follow up has been performed to detect the proposed exposure-response relationship between endoxifen and breast cancer recurrence. Our clinical trial simulations and power calculations indicate that an observational or randomized trial in which only the patients with low endoxifen steady-state plasma concentrations are randomized could both be feasible, although the required sample size would require a multicenter trial and international collaboration. If such a trial would be initiated, follow-up of 15 years is necessary.

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D-02: *Coralie Tardivon* Association between tumor size kinetics and survival in advanced urothelial carcinoma patients treated with atezolizumab: implication for patient's follow-up

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Context:

Immune-oncology is revolutionizing cancer treatment, but the association between treatment response and survival remains poorly understood. The response kinetics, as guided by the longitudinal evolution of a biomarker (e.g. the tumor size), can help detect treatment relapse and identify patients most-at-risk of death or progression. In order to model these two responses, specific approaches, called "joint modelling", are needed that acknowledge the correlation between response to treatment and survival [1]. In these joint models, the hazard rate is modeled by a parametric survival model that directly depends on the biomarker kinetics. Further, the biomarker kinetics, which may be a nonlinear process, is modeled using a nonlinear mixed-effects model [2]. Parameters estimation in nonlinear joint models are complex, as the likelihood does not have an analytical form. It requires specific algorithms such as the Stochastic Approximation Expectation Maximization algorithm [3,4]. Joint modeling of tumor size dynamics and overall survival has so far not been used to improve early detection of patients most-at-risk of death or progression that could benefit from alternative therapies.

Objectives:

To quantitatively evaluate the association between tumor size kinetics, baseline covariates and overall survival in metastatic urothelial carcinoma patients following atezolizumab immunotherapy treatment, using a nonlinear joint model.

To use this model to characterize "in real time" new patient's profile of response, thus assessing its predictive ability for the early detection of patients at risk of death.

Methods:

A phase 2 clinical trial of 309 advanced urothelial carcinoma patients treated with atezolizumab (IMvigor 210) [5] was used to build a joint model for tumor size kinetics and survival. Then the model was validated externally using a phase 3 clinical trial data from 457 patients in the same indication (IMvigor 211) [6]. Model predictions were assessed using time-dependent Area Under the ROC Curve (AUC) and Brier score to evaluate discrimination and calibration, using different follow-up times (called "landmark") and time of prediction (called "horizon") [7].

Results:

The best description of tumor size kinetics was obtained using a biphasic exponential model accounting for differential kinetics in tumor-sensitive and tumor-resistant cells, while overall survival was described using a parametric Weibull model. Using these models, we identified time-to-tumor growth and instantaneous changes in tumor size as the best on-treatment predictors of survival, showing that tumor size kinetics is an independent predictor of survival. As expected, model parameters were highly dependent on patient's disease severity, in particular presence of liver metastasis, hemoglobin and alkaline phosphatase levels, ECOG performance status, or neutrophil-to-lymphocyte ratio.

Using the joint model for prediction on an external validation dataset, we found that the model reproduced the overall survival (OS) observed. Further, using various landmarks and horizons, we found AUC values comprised between 0.73 and 0.84, i.e. significantly higher than the ones obtained with an approach where OS is modeled ignoring tumor dynamic ("No link": between 0.55 and 0.76). The Brier scores, summarizing the predictive performance of the joint model, showed more than 15% improvement with the best joint model compared to the model with no link between tumor kinetics and OS, for horizon times greater than 6 months.

Conclusions:

We showed that including on-treatment tumor dynamic data in a relevant statistical framework improves the prediction of survival probability during immunotherapy treatment. In addition, the proposed model could be used to identify patients most-at-risk of death, in real time, hence giving the opportunity to optimize patients' medical treatment.

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D-03: *Jiajie Yu* A new approach to predict PFS in Ovarian Cancer based on tumor growth dynamics.

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Objectives:

Progression free survival (PFS) is a surrogate efficacy endpoint that is being used for regulatory approval of investigational drugs in ovarian cancer [1]. The PFS has also been shown to be predictive of the overall survival [1], hence being able to predict PFS for new treatments can be of great value. The PFS is usually analyzed by survival analysis methodology and PFS time is based on events such as target lesion related disease progression and non-target related disease progression whichever occurs first. PFS could be linked to tumor growth dynamics by linking the PFS hazard to target lesion tumor size, similarly to what is commonly done for overall survival [2]. With this approach target lesion tumor size data is included twice in the analysis, first as observations informing the model of tumor growth dynamics (TGD) and second influencing the PFS hazard in the time to event analysis. Based on such model it is possible to simulate unrealistic outcomes with a tumor size profile that meets the definition of target lesion disease progression, but without any PFS event occurring.

The aim of this work was to develop an approach for prediction of PFS that avoids duplicate use of target lesion data. A joint modelling approach including two sub-models is proposed: 1. Model for target lesion tumor growth dynamics. 2. Time-to-event model for non-target related progression. These sub-models combined can be used to predict PFS.

Methods:

A joint TGD-survival model was developed using NONMEM 7.4. The model contained three components to predict PFS. First, the TGD was modeled based on the method developed by Claret et al. [2] where the drug effect was introduced on the tumor size shrinkage parameter (ks). Potency difference between compounds were accounted for. The M3 method was applied to handle the censoring of tumor data when tumor size was below the limit of quantification per RECIST guideline [3]. The TGD was used to determine target lesion disease progression which was defined as more than 20% increase in target lesion tumor size from minimum observed value. Second, the hazard for non-target related disease progression was linked to the individually predicted, time varying target lesion tumor size. Third, a drop-out model was introduced to account for patient discontinuation from the study. Observed Kaplan-Meier curves for PFS were compared to simulated predictions where progression was based on either target lesion progression or non-target related disease progression, whichever occurs first in each patient. The model was developed using a pooled dataset including phase I and II data from platinum resistant ovarian cancer patients. Treatments included Anti-MUC16 ADC, Anti-MUC16 TDC, Anti-NaPi2b ADC and Doxorubicin.

Results:

The model could describe the observed dose response well for different compounds, both in terms of target lesion tumor size over time and in terms of PFS. The first derivative of target lesion tumor with

respect to time correlated with the risk for non-target progression and the drug effect on the risk for non-target progression could be predicted based on target lesion tumor size alone.

Conclusion:

A joint model simultaneously estimating TGD based on target lesion tumor size and the risk for non-target related progression was developed. The model could describe the PFS influenced by different drug treatment and may provide a more robust prediction of PFS based on TGD for new treatments in future ovarian cancer clinical trials.

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D-06: *Julie Janssen* A semi-physiological framework to predict changes in pharmacokinetics of cytotoxic drugs in pregnant women

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Objectives:

Physiological changes during pregnancy might have an influence on pharmacokinetics (PK) and hence on the efficacy and toxicity of pharmacological treatment. Recently, it was shown that oncological treatment during pregnancy is safe and recommended.[1] Given the severity of the disease but at the same time high potential impact on both the mother and child, there is a high unmet medical need for adequate and tolerable treatment of this neglected patient population. In order to make adequate dose adjustments, it is important to assess the PK of cytotoxic drugs in pregnant patients. With this work we aimed to develop a methodology enabling the simulation of individual PK profiles of a range of cytotoxic drugs in pregnant patients and subsequently predict adequate and safe dosing regimens.

Methods:

A selection of relevant empirical equations for physiological changes from Abduljalil *et al.* were implemented in our semi-physiological simulation framework.[2] Firstly, the change in unbound drug concentration as a function of estimated gestational age (EGA) was implemented, using the change in albumin or alpha-1-glycoprotein levels. Since the proportion renally cleared drug for all four studied drugs is eliminated by glomerular filtration (GFR), the change in renal clearance was scaled using the change in GFR during pregnancy. To describe the change in hepatic clearance, a well-stirred liver model was used, in which intrinsic clearance was adjusted for gestational changes in enzyme activity. Reported non-pregnant volumes of distribution were scaled with a previously proposed algorithm using the gestational change in total body water, extracellular water and plasma volume.[3]

Non-linear mixed effects population models that described the PK of doxorubicin, epirubicin, docetaxel and paclitaxel in non-pregnant patients were obtained from literature.[4,5,6,7] These models were integrated with the semi-physiological alterations and drug specific characteristics. Individual concentration-time profiles were simulated in R (R package deSolve) and simulations were visually evaluated using PK data from 26, 16, 9 and 19 pregnant patients that were available for doxorubicin, epirubicin, docetaxel and paclitaxel, respectively.[1,8] Individual model fits were obtained for the observed data, by using the MAXEVAL=0 and POSTHOC options in NONMEM (v7.3).[9] The fit of the semi-physiological model was compared for the fit of the model parameters for the non-pregnant versus the pregnant state.

Results:

Typical parameters for an EGA of 28 weeks were predicted. A typical increase of 15.8%, 14.6% and 29.0% was observed for doxorubicin CL, V1 and V2, respectively and 14.2%, 14.5%, 13.7% and 39.0%, for epirubicin. For docetaxel, typical increases were predicted of 18.1%, 18.0%, 20.5% and 38.7% for CL, V1, V2 and V3, respectively. For paclitaxel, an empirical PK model including saturable distribution to the first peripheral compartment and saturable elimination was used. A typical increase of 19.8%, 15.0% and 38.4% for the maximal elimination rate, V1 and V3 was observed. The simulations showed an adequate prediction of the observed pregnant PK for all four drugs at therapeutic doses. Also, the simulations clearly demonstrated that the use of non-pregnant parameter estimates resulted in an overprediction of the observed concentrations for all four drugs. Comparison of the model fit for the individual predictions based on the semi-physiological pregnant parameter estimates versus non-pregnant parameter estimates showed a significantly improved fit for paclitaxel (ΔOFV –18.0, P=0.0004, χ^2-distribution, degrees of freedom (df)=3), epirubicin (ΔOFV –148, P<0.00001, χ^2-distribution, df=4) and doxorubicin (ΔOFV –62.2, P<0.00001, χ^2-distribution, df=3). For docetaxel, a decrease in OFV of 4.66 points (P=0.324, χ^2-distribution, df=4) was observed.

Conclusions:

The semi-physiological framework provided an adequate prediction of the PK for four cytotoxic agents of two distinct drug classes in women over varying stages of gestation. This method may therefore be used for extrapolation purposes to adjust anticancer dosing regimens in pregnant women for drugs for which PK data from pregnant women are unavailable.

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D-07: *James Lu* Integrated efficacy-safety QSP model of acute myeloid leukemia (AML) generates insights into the role of clinical dose schedules on cytopenia

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Introduction: Acute Myeloid Leukemia (AML) is an aggressive hematological malignancy, characterized by an accumulation of leukemic blast cells in the bone marrow and is often accompanied by anemia, thrombocytopenia and neutropenia [1]. Treatment of AML patients aims to eliminate leukemic blasts and hence revert their bone marrow function. In the development of novel therapies for AML, a significant challenge is balancing efficacy with safety: a recent example being the discontinuation of vadastuximab talirine (VT) development due to increased hematologic toxicity and fatal infections [2,3], despite efficacy in blast reduction. The dual effects of therapeutic agents on both the blast reduction as well as hematologic toxicity requires a systems-level description of their interactions.

Objectives: We show how clinical development questions for AML therapies can be addressed by utilizing a quantitative systems pharmacology (QSP) model that describes the life-cycle of leukemic blasts in bone marrow and peripheral blood, as well as disease-induced cytopenia.

Methods: Firstly**,** a model of normal hematopoiesis across the three lineages (neutrophils, platelets and red blood cells) including regulation mechanisms (EPO, TPO and GCSF) was built and calibrated based on published data sets (e.g., [4,5]). Secondly, the proliferation rate of AML blasts in the bone marrow and their transit time into the blood compartment are informed by published tracer kinetic studies (e.g., [6,7])**.** Finally, the model mechanisms by which leukemic blasts result in cytopenia were informed by key experimental publications [8,9] based upon clinical and preclinical data of AML. Therapies are modelled by adding killing effects on both the leukemic blasts and normal progenitor cells. In particular, to predict the hematologic toxicity of a given drug candidate, a novel multilineage hematopoiesis assay is used to generate treatment data across progenitors and mature cells along the three lineages (neutrophils, platelets and red-blood cells). A model of the *in-vitro* assay is used to estimate and translate toxicity parameters *in-vivo* [10]. We evaluated the platform model using VT as a test example, using Emax expressions for drug effects.

Results: The QSP model recapitulates aspects of the AML disease, as well as demonstrates the reversal of cytopenias after the removal of leukemic blasts from the bone marrow. We show that the published neutrophil and platelet recovery times under VT monotherapy [2] are in good consistency with the QSP model, which takes as inputs the estimated efficacy parameters based on data in [2] and hematologic toxicity parameters estimated from *in-vitro* model [10]. We simulate the model for both the single dose as well as fractionated dosing (days 0 and 3) scenarios, and explain the reported clinical outcomes. The model findings suggest that in AML patients the dosing paradigm for an improved neutrophil recovery time may differ from that applicable to solid tumor patients. In the latter, patient baseline blood cell counts are close to normal and dose fractionation is an established approach to avoid blood count nadirs falling below the thresholds corresponding to grades-3/4 hematological AEs. In contrast, blood counts in AML patients prior to receiving treatment are already very low, and the aim of therapies is to remove leukemic blasts sufficiently quickly so that their suppressive effects on normal hematopoiesis can be removed, while not

causing undue hematologic toxicity. Model simulations shed light on the important role of efficacy on the time to count recovery.

Conclusion: AML is a disease where clinical response criteria entail not only leukemic blast elimination but also the recovery of normal blood counts. We demonstrate that the use of a QSP model which integrates both the efficacy and safety aspects generates valuable insights for optimizing the dosing schedule of AML therapies.

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