Model-Informed Drug Development Case Studies

ECP 8506 Clinical Trial Simulation
Dec 13, 2024

Ya-Feng (Jay) Wen, PharmD, PhD
wenxx164@umn.edu | jay.wen3@gilead.com
Clinical Pharmacologist, Gilead Sciences
Adjunct of Assistant Professor, ECP, UMN

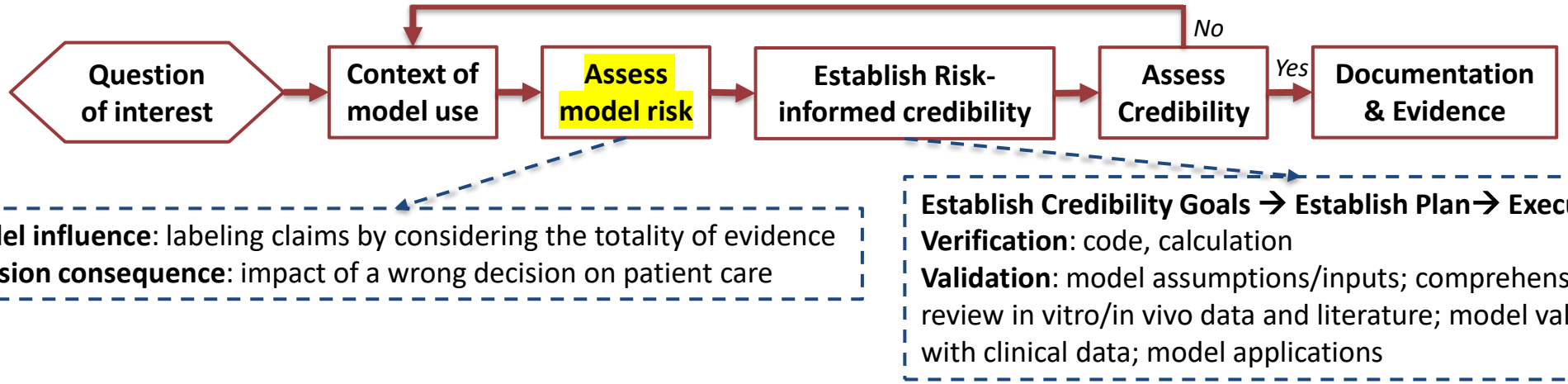
Learning Objectives

- Apply the simulation considerations learned so far and drive simulation plans to address drug development questions
- Present the simulation plans with a clear and succinct manner

Instruction

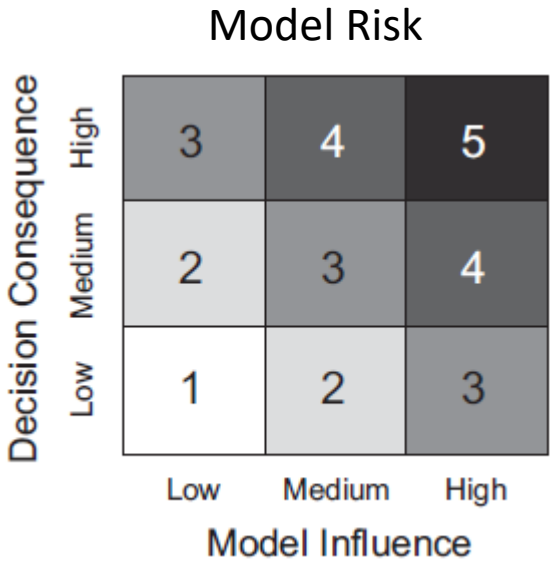
- Students work in a team to propose and present the simulation plan
- The simulation plan should include the following:
  - A credibility assessment (slide 4), including the following component: Question of interest, Context of use, Model risk (Model influence and Decision consequence), Validation plan
  - Simulation scenarios, including but not limited to model(s) to use, number of subjects in a simulation, number of simulations, simulation outcomes

Credibility assessment framework in MIDD



Model influence	Description
Low	Model provides minor evidence; substantial nonclinical and clinical data are available to inform the decision
Medium	Model provides supportive evidence; some clinical trial data are available to inform the decision
High	Model provides substantial evidence; no clinical trial data relevant to the context of use or limited clinical trial data from similar scenarios are available to inform the decision

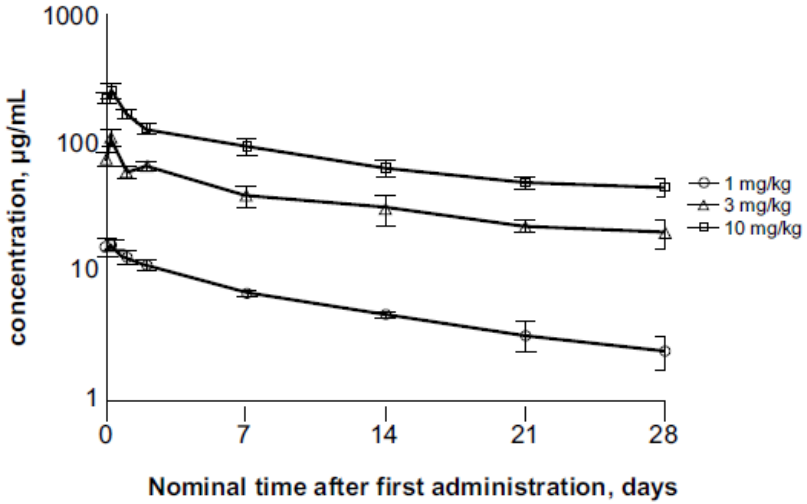
Decision consequence	Description
Low	Incorrect decision would not result in adverse outcomes in patient safety or efficacy
Medium	Incorrect decision could result in minor to moderate adverse outcomes in patient safety or efficacy
High	Incorrect decision could result in severe adverse outcomes in patient safety or efficacy



Kuemmel C, et al. Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(1):21-28.

Case Study 1

- Drug A is a monoclonal antibody in the early clinical development for solid tumors.
- A Phase 1 study was a 3+3 dose-escalation cohort followed by an expansion cohort.
  - Three-patient cohorts sequentially were administered Drug A 1, 3, or 10 mg/kg intravenously over 30 minutes on day 1, day 28, and every 2 weeks thereafter.
  - Seven additional patients were enrolled in an expansion cohort and treated with 10 mg/kg every 2 weeks.
- The concentration-time profile from the phase 1 study is shown below
  - Half-life ranges from 14-22 days
  - Dose seemed to be disproportionally lower at 1 mg/kg than 3 or 10 mg/kg by the plot and AUC assessment
  - Preliminary PopPK models were constructed (next slide)



Case Study 1—Cont'd

Parameter (units)	Linear			Nonlinear		
	Estimate	%RSE	BSV[a] (RSE%)	Estimate	%RSE	BSV[a] (RSE%)
OFV	364.352	—	—	370.950		—
CL (L/d)	0.180	14.2	28.8 (62.5)	0.180	13.6	24.6 (68.1)
V_c (L)	2.537	7.3	—	2.524	8.1	—
V_p (L)	2.154	17.9	—	2.152	18.3	—
Q (L/d)	0.595	31.5	—	0.600	31.9	—
covF1	–0.369	–18.7	14.2 (97.9)	NA		22.4 (63.3)
F_{min}	NA		—	0.200		—
FD_{50}	NA		—	0.582	52.5	—
αCL	0.448	93.6	—	0.455	81.4	—
αV	1.000	18.4	—	0.987	21.7	—
RUV (prop)	0.200	8.4	—	0.202	8.7	—
RUV (add)	0.010		—	0.010		—

Abbreviations: %RSE, relative standard error; αCL, exponent of bodyweight–clearance relationship; αV, exponent of bodyweight–volume relationship; BSV, between-subject variability; CL clearance; covF1; , covariate relationship F for 1 mg/kg F, bioavailability; FD50, dose at half-maximal impact on bioavailability; Fmin, minimal bioavailability; NA, not applicable; Q, intercompartmental clearance; proportional; RUV (add), residual error PK, additive; RV (prop), residual variability PK, proportional; Vc, central volume of distribution; Vp, peripheral volume

[a]BSV was calculated as sqrt(exp(variance)-1)

Case Study 1—Cont'd

- The team wants to enroll additional patients to detect or reject whether Drug A has nonlinearity in PK, while minimizing the probability of drawing the wrong conclusions
- Two study designs were considered by the team:

Design 1	Dose, mg/kg					
Cohort	0.02	0.1	0.3	1	2	10
1 (*n*=3)		X	X		X	
2 (*n*=3)			X	X	X	
3 (*n*=3)	X				X	X
Total (*n*=9)	3	3	6	6	9	6

Design 2	Dose, mg/kg						
Cohort	0.05	0.02	0.06	0.3	1	2	10
1 (*n*=3)	X			X		X	
2 (*n*=3)		X		X		X	
3 (*n*=6)			X		X		X
Total (*n*=12)	3	3	6	6	6	6	6

- The team wants you to propose a simulations strategy to evaluate the likelihood of success between the 2 study designs
  - Note: ideally, re-estimation of PK parameters should be performed based on the simulated data and evaluate the bias and precision of parameter estimates. Since it is out of scope of this course, please only focus on the simulation strategy.

Case Study 2

- Drug B is a monoclonal antibody in the late clinical development for solid tumors with wide therapeutic index
- Seven phase I, two phase I/II, six phase II, nine phase III, and one phase IIIb/IV clinical studies had been conducted
- A PopPK model was built (next slide) based on 32,835 PK samples from 6,468 patients
- The team wants to know whether the dose of Drug B should be adjusted for any intrinsic or extrinsic factors

Case Study 2—Cont'd

Parameter (units)	Estimate	RSE%	BSV[a] (RSE%)
$CL0_{REF}$ (mL/hour)	10.8	1.50	41.2 (5.45)
VC_{REF} (L)	4.27	0.728	40.5 (9.8)
Q_{REF} (mL/hour)	34.9	6.91	-
VP_{REF} (L)	2.70	2.47	-
CL_{BBWT}	0.530	5.40	-
CL_{eGFR}	0.202	9.85	-
CL_{SEX}	−0.181	7.35	-
CL_{PS}	0.181	7.18	-
CL_{RAAA}	0.0374	86.1	-
CL_{RAAS}	−0.0354	47.7	-
VC_{BBWT}	0.534	4.49	-
VC_{SEX}	−0.161	8.76	-
$Emax_{REF}$	−0.240	8.75	30.2 (12.9)
T_{50} (hour)	2,200	5.95	-
HILL	2.77	9.49	-
$Emax_{PS}$	−0.138	14.5	-
RUV (prop)	0.245	1.65	

Final model is represented as following:

$$CL_{i,t} = CL0_i \cdot \exp\left(\frac{Emax_i \cdot t^{CL_{HILL}}}{T50_i^{CL_{HILL}} + t^{CL_{HILL}}}\right) \qquad CL_{i,SS} = CL0_i \cdot \exp(Emax_i)$$

$$CL0_i = CL0_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} \cdot \left(\frac{eGFR_i}{eGFR_{REF}}\right)^{CL_{eGFR}} \cdot e^{CL_{SEX}} \cdot e^{CL_{PS}} \cdot e^{CL_{RAAA}} \cdot e^{CL_{RAAS}} \cdot e^{\eta CL_i}$$

$$Emax_i = Emax_{REF_i} + Emax_{PS} + \eta Emax_i$$

$$VC_i = VC_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}} \cdot e^{VC_{SEX}} \cdot e^{\eta VC_i}$$

$$VP_i = VP_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}} \cdot e^{\eta VC_i}$$

$$Q_i = Q_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} \cdot e^{\eta CL_i}$$

Abbreviation: BBWT, baseline bodyweight; CL, clearance; CL0, clearance at time 0; eGFR, estimated glomerular filtration rate; Emax, the maximal change in clearance; HILL, sigmoidicity of the relationship of clearance with time; PS, performance status; Q, intercompartmental clearance; RAAA, African American race; RAAS, Asian race; REF, reference; T 50, time at which the change in CLt,i is 50% of Emax; VC, central volume of distribution; VP, peripheral volume of distribution

[a]BSV was calculated as sqrt(exp(variance)-1)

Model-Informed Drug Development Case Studies

ECP 8506 Clinical Trial Simulation
Dec 13, 2024

Ya-Feng (Jay) Wen, PharmD, PhD
wenxx164@umn.edu | jay.wen3@gilead.com
Clinical Pharmacologist, Gilead Sciences
Adjunct of Assistant Professor, ECP, UMN