Credibility Evaluation of Paediatric and Orphan Disease Modelling: Paediatric Dosing Regimen of Tetrabenazine

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Ecosystem for Rapid Adoption of modelling and simulation METhods (ERAMET)
Mission: Pioneer a question centric approach and develop AI tools to enhance drug development through the establishment of framework focused on orphan and paediatric disease modelling

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Introduction

- Modelling and simulation provides an alternative method to analyse and offer predictive insights into drug development process and diseases
- Modelling and simulating paediatric and orphan diseases presents many challenges such as limited data, unknown mechanism and optimal extrapolation strategies
- Currently, no established comprehensive credibility framework exists for supporting the development of paediatric and orphan disease modelling
- A comprehensive framework would aid both the research team and the regulatory bodies

Aims

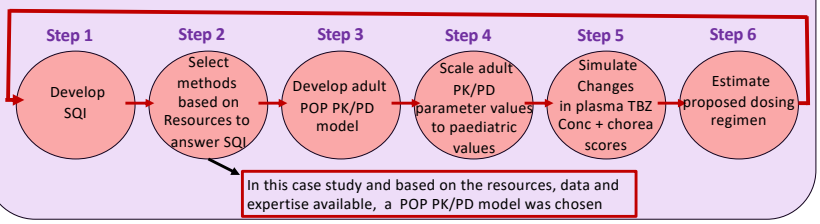
To investigate the model development process

Identify areas which need credibility assessment and the development of AI tools to facilitate this process

Case Study: Juvenile Huntington's Disease

- Patients < 20 years old who are diagnosed with Huntington's Disease
- Rare, neurogenerative disease
- Typical symptoms include mood changes, depression and involuntary limb movements (chorea)
- Standard treatment for management of chorea in adults is tetrabenazine (TBZ)
- TBZ is a monoamine vesicular transporter inhibitor
- Limited information on paediatric dosing

Scientific question of interest (SQI)
what are the optimal TBZ dosing schedules for Juvenile Huntington's Disease ages 2-11 years old ?



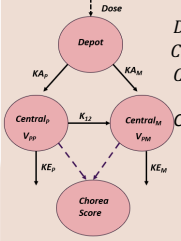
Selected Adult PKPD Model

$$\frac{d(Depot)}{dt} = -(KA_P \times Depot) - (KA_M \times Depot) \quad (1)$$

$$\frac{d(Central_P)}{dt} = (KA_P \times Depot) - (KE_P \times C_{TBZ}) - (K12 \times C_{TBZ}) \quad (2)$$

$$\frac{d(Central_M)}{dt} = (KA_M \times Depot) - (KE_M \times C_{TBZM}) + (K12 \times C_{TBZ}) \quad (3)$$

$$\frac{d(Chorea\ Score)}{dt} = K_{IN} \times \left(1 - \frac{I_{MAX} \times (C_{TBZ} + C_{TBZM})}{IC_{50} + (C_{TBZ} + C_{TBZM})}\right) - K_{OUT} \times Chorea\ Score \quad (4)$$



$$Depot(0) = Dose$$
$$Central_P(0) = 0$$
$$Central_M(0) = 0$$
$$Chorea\ Score(0) = Baseline\ Score$$

$$C_{TBZ} = \frac{Central_P}{V_{PP}} \quad (5)$$

$$C_{TBZM} = \frac{Central_M}{V_{PM}} \quad (6)$$

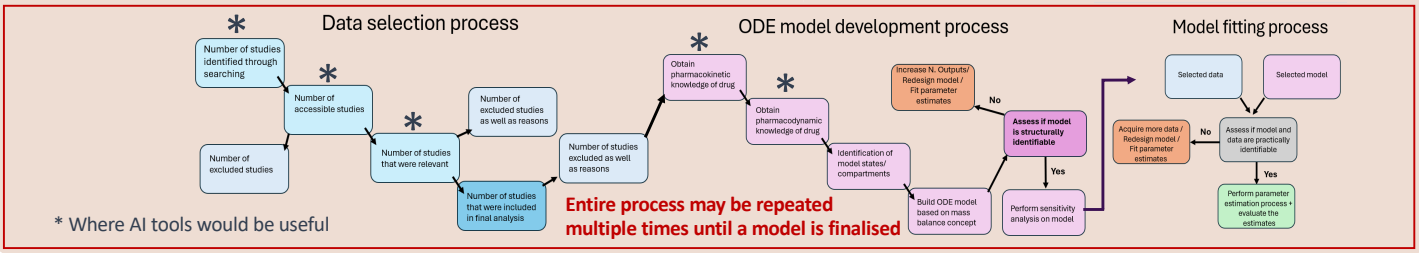
- C_{TBZM} and *Chorea Score* are the observed outputs
- The selected model is **structurally identifiable**
- This model was selected based on low RSE values

Parameters	KA_P (hr^{-1})	KA_M (hr^{-1})	KE_P (hr^{-1})	KE_M (hr^{-1})	K_{12} (hr^{-1})	V_P (mL)	V_M (mL)	K_{IN} (hr^{-1})	K_{OUT} (hr^{-1})	IC_{50} (ng/ml)
Population value	0.75	0.8	0.75	0.06	80.9	992	0.18	0.04	0	0
S.E	-	0.14	-	0.01	19	237	0.02	0.01	0	0
R.S.E	-	17.6	-	13.6	23.5	23.9	11.3	18.4	36.2	16.9
95%CI LB	-	0.57	-	0.049	51.99	631.91	0.14	0.27	0.001	0.003
95%CI UB	-	1.12	-	0.083	125.98	1556.85	0.23	0.54	0.0003	0.006

Table 1: Parameter estimates for selected adult POP PKPD model

Model development and credibility assessment frameworks

- **Investigational product**: TBZ
- **Type of model**: Pop PKPD
- **Question(s) of interest**: what are the optimal TBZ dosing schedules for Juvenile Huntington's Disease ages 2-11 years old ?
- **Context of use**: Estimate TBZ PKPD parameters for both adult and paediatric (ages 2-11 years old)
- **Regulatory impact**: moderate – paediatric PKPD parameter estimates
- **Risk based analysis on decision consequence:** moderate – estimates confirmed in future trial
- **Requirements of credibility activities (examples):** PKPD parameter estimates for adult and paediatrics, verification of scaling process method, simulated plasma levels of TBZ in paediatrics (refer to Table 2)



Requirements of credibility activities

Table 2: Proposed credibility activities assessment for selected data and model

Credibility factors			Example methods Credibility levels key: red = low, yellow = medium, green = high	Credibility levels
Verification	Code verification	Software quality assurance	Certification or proof that software is supported by regulatory bodies	
		Numerical code verification	Test solver with known ODE solution – *R, MATLAB, MAPLE* etc.	
	Calculation verification	Numerical solver error		
		Use error	Submit model code for independent review - https://www.ebi.ac.uk/biomodels/	
Validation	Computational model	Model form	• Supporting evidence for mechanistic/ physiological knowledge • Full ODEs/equations, parameter definitions • Proof of structurally identifiable model – *MATHEMATICA* (EAR analysis)	
		Model inputs: quantification of sensitivities	Sensitivity analysis of model parameters and inputs – Sobol indices ($\bar{\theta}$)	
		Model inputs quantification of uncertainties	Has device/ measurement error been taken into account ? Has variation been accounted for – add noise to input data	
	Input data	Quantity of data, range of characteristics and measurement of data samples	Summary of patient characteristics and data – EDA Sufficient sample size – power's proportional analysis and practical identifiability analysis	
		Uncertainty of data collection	Has variation been accounted for – add noise to input data For primary data collection – protocol for data collections For secondary data – PRISM	
		Method/protocol data collection		
	Assessment	Output comparisons	Do the outputs align with COUs	
		Rigor of output comparisons	For PopPKPD model – population estimates, SE, 95% COIs, parameter distributions For PBPK model – paediatric parameter values, fold errors, residual errors, dosing schedules for range of paediatrics specified in QIs	
		Agreement of output comparison	Are the outputs credible enough for COUs ?	
		Assessed on different data		
Applicability		Relevance of outputs and credibility activities to COUs	Do the activities align with the COUs	

Paediatric scaling

$$KA_{pp} = KA_P \times \left(\frac{Adult\ large\ intestine}{Child\ large\ intestine}\right) \quad (7)$$

$$KA_{Mp} = KA_M \times \left(\frac{Adult\ large\ intestine}{Child\ large\ intestine}\right) \times \left(\frac{child\ liver}{Adult\ liver}\right) \quad (8)$$

$$KE_{Pp} = KE_P \times \left(\frac{child\ kidney}{Adult\ kidney}\right) \quad KE_{Mp} = KE_M \times \left(\frac{child\ kidney}{Adult\ kidney}\right) \quad (9)$$

$$K_{12p} = K_{12} \times \left(\frac{child\ heart\ rate}{Adult\ heart\ rate}\right) \quad (10)$$

$$V_{Pp} = V_P \times \left(\frac{child\ water\ ratio}{Adult\ water\ ratio}\right) \quad V_{Mp} = V_M \times \left(\frac{child\ water\ ratio}{Adult\ water\ ratio}\right) \quad (11)$$

$$K_{INP} = K_{IN} \times 0.9 \quad (12)$$

$$K_{OUTP} = K_{OUT} \times 0.9 \quad (13)$$

Ages 2 and 3 years old

Proposed dosing regimen

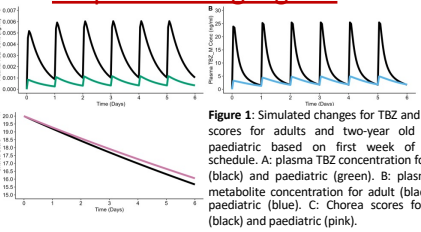


Figure 1: Simulated changes for TBZ and chorea scores for adults and two-year old female paediatric based on first week of dosing schedule. A: plasma TBZ concentration for adult (black) and paediatric (green). B: plasma TBZ metabolite concentration for adult (black) and paediatric (blue). C: Chorea scores for adult (black) and paediatric (pink).

Treatment week	Adult doses (mg) QD	paediatrics (2-11 years old) (mg) QD
1	1 x 12.5	1 x 1.5 - 3
2	1 x 25	1 x 3 - 6
3	1 x 25 & 1x 12.5	2 x 3 - 5
4	2 x 25	2 x 4 - 5

Table 3: Typical adult TBZ dosing schedule and average proposed TBZ schedule for paediatrics (2-11 years old)

Conclusions:

- A proposed dosing regimen for paediatrics was developed based on mixed effects modelling and paediatric scaling
- The credibility analysis of this model (Table 2) suggest that the credibility needs to be improved to support this model as a foundation for optimal dosing design
- Moreover, the model does not consider adverse event modelling which would be crucial to answer the SQI

Future work: Challenges highlighted in this process will be used to develop credibility-based AI tools specific to paediatric and orphan disease modelling