

Modeling and Simulation: challenges for the clinical programmer and for the group leader

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AGENDA

- M&S – what is that? – What do we do?
- Modeling dataset
- Challenges for the group leader
- Challenges for the clinical programmer

M&S – What is that?

- Modeling and Simulation is a key component to speed up drug development and reduce failures

M&S – What do we do

- We don't support all clinical programs.
- We support projects where we think we can impact the drug development:
 - Chose the best dose, set of dose, dose regimen
 - Impact study design
 - Stop the drug development
- We support projects when there is an unexpected problem:
 - Phase 3 failed – What happened
 - Challenges from FDA on study design, dose, dose regimen
 - Safety issue, efficacy issue....

M&S – What we do

- We use “non” traditional pharmaceutical statistical methodology
- Why do we need programmer?
- Modeling need data
- Often large dataset, several studies (sometimes millions observations and >60 variables)
- Pool trials within a project, across projects within the same indication
- Not all modelers have skills to efficiently pool data across many studies

M&S – What we do

- Often complex file
- Need to integrate a lot of information in 1 single file
- Need to deliver harmonized, clean and ready to use modeling dataset
- Need to include complete dose history (including dose change, dose interruption...), Pharmacokinetic, Pharmacodynamic, comedication (what, when, dose...), covariates...

Nonmem file structure – Time event dataset

Need to harmonized and clean

Sort by calendar date, clock time	For all dose events: Patient ID, calendar date, clock time, dose amount	Nonmem variables: Time since first dose	Covariates time dependant: Calcium Magnesium Potassium Sodium Absolute Platelet count Dose amount and dose regimen Flag for estimated dose clock time Flag for comedication	Covariates : Study ID Patient ID Age Gender Race Height Weight BMI BSA Creatine Clearance Dosage formulation Flags for comedications
	For all PK samples: Patient ID, calendar date, clock time, PK concentration	Elapse time Days since first observations		
	For all ECG events: Patient ID, calendar date, clock time, QT interval fridericia	Days since first dose		
	For all lab events: Patient ID, calendar date, clock time, DPLCNT			

Nonmem file structure – Time event dataset

DAR dataset containing dosing event				PK dataset containing PK samples				PD dataset containing PD samples			
CTR1N Center number	SBJ1N Subject number	SMDDOS10 Dosing (date)	TDD1N Total daily dose amount mg	CTR1N Center number	SBJ1N Subject number	SMP_D_T Sampling date and time	CONC Conc in ug/mL	CTR1N Center number	SBJ1N Subject number	SMP_D_T Sampling date and time	CONC Conc in ug/mL
1	5101	01JAN2000:09:00	150	1	5101	01JAN2000:09:10	21	1	5101	01JAN2000:09:10	31
1	5101	02JAN2000:10:00	150	1	5101	01JAN2000:09:20	100	1	5101	01JAN2000:09:20	110
1	5101	03JAN2000:09:00	150	1	5101	01JAN2000:09:30	90	1	5101	01JAN2000:09:30	10
3	5102	01FEB2000:08:00	200	1	5101	03JAN2000:09:10	40	1	5101	03JAN2000:09:10	45
3	5102	02FEB2000:09:00	200	1	5101	03JAN2000:09:20	150	1	5101	03JAN2000:09:20	153
3	5102	03FEB2000:09:00	150	3	5102	01FEB2000:08:10	40	3	5102	01FEB2000:08:10	41
				3	5102	01FEB2000:08:40	130	3	5102	01FEB2000:08:40	128
				3	5102	02FEB2000:08:50	BLOQ	3	5102	02FEB2000:08:50	BLOQ
				3	5102	03FEB2000:09:10	35	3	5102	03FEB2000:09:10	32

ID Derived ID	CENT Center number	SUB Subject number	CMT 1:Dose 2:PK 3:PD	TIME Time since first dose (h)	DV Depending variable	EVID Event identifier	DOSE Dose in mg	AMT Daily dose amount	MDV Missing depending variable	Datetime used for validation purpose in the SAS dataset, but has to be removed in the input NONMEM file (CSV, TXT...)
1	1	5101	1	0	0	1	150	150	1	01JAN2000:09:00
1	1	5101	2	0.1667	21	0	150	0	0	01JAN2000:09:10
1	1	5101	3	0.1667	31	0	150	0	0	01JAN2000:09:10
1	1	5101	2	0.3333	100	0	150	0	0	01JAN2000:09:20
1	1	5101	3	0.3333	110	0	150	0	0	01JAN2000:09:20
1	1	5101	2	0.5	90	0	150	0	0	01JAN2000:09:30
1	1	5101	3	0.5	10	0	150	0	0	01JAN2000:09:30
1	1	5101	1	25	0	1	150	150	1	02JAN2000:10:00
1	1	5101	1	48	0	1	150	150	1	03JAN2000:09:00
1	1	5101	2	48.1667	40	0	150	0	0	03JAN2000:09:10
1	1	5101	3	48.1667	45	0	150	0	0	03JAN2000:09:10
1	1	5101	2	48.3333	150	0	150	0	0	03JAN2000:09:20
1	1	5101	3	48.3333	153	0	150	0	0	03JAN2000:09:20
2	3	5102	1	0	0	1	200	200	1	01FEB2000:08:00
2	3	5102	2	0.1667	40	0	200	0	0	01FEB2000:08:10
2	3	5102	3	0.1667	41	0	200	0	0	01FEB2000:08:10
2	3	5102	2	0.6667	130	0	200	0	0	01FEB2000:08:40
2	3	5102	3	0.6667	128	0	200	0	0	01FEB2000:08:40
2	3	5102	2	0.8333	0	0	200	0	1	02FEB2000:08:50
2	3	5102	3	0.8333	0	0	200	0	1	02FEB2000:08:50
2	3	5102	1	25	0	1	200	200	1	02FEB2000:09:00
2	3	5102	1	49	0	1	150	150	1	03FEB2000:09:00
2	3	5102	2	49.1667	35	0	150	0	0	03FEB2000:09:10
2	3	5102	3	49.1667	32	0	150	0	0	03FEB2000:09:10

Modeling dataset

- The modeling input dataset is like a book, it's the patient history
- Example:
- Patient 1, 60 years old with type 2 diabetes is enrolled in the study ABC123. On February 1st, he took 20 mg of the medication A at 08:00 AM. 5 minutes prior to the dose administration, we measured his PK concentration, the value was 0 ug/mL. 1 hour later, his PK concentration was 30 ug/mL.

Study	PatientID	Age	Time	Dose	PK	Date/time
ABC123	1	60	-0.08333	0	0	01FEB:07:55
ABC123	1	60	0	20	0	01FEB:08:00
ABC123	1	60	0.916667	0	30	01FEB:08:55

Modeling dataset

- The book has to make sense. Now imagine the following story for the same patient
- Patient 1, 60 years old with type 2 diabetes is enrolled in the study ABC123. On February 1st, he took 20 mg of the medication A at 08:00 AM. 5 minutes prior to the dose administration, we measured his PK concentration, the value was 10 ug/mL. 1 hour later, his PK concentration was 30 ug/mL.
- It does not make sense

Study	PatientID	Age	Time	Dose	PK	Date/time
ABC123	1	60	-0.08333	0	10	01FEB:07:55
ABC123	1	60	0	20	0	01FEB:08:00
ABC123	1	60	0.916667	0	30	01FEB:08:55

Modeling dataset

- We have to fix it
- We have to try to understand where the issue is coming from. Problem in the program? data issues? Can we get an updated clinical database? Ultimately, we'll flag this observation
- The story has to make sense, otherwise the modeling results can be impacted
- The quality of the modeling inputs depends on the data quality

What are the challenges for the group leader?

- Planning is difficult – don't have the workload overview for the next months
- Planning resources is difficult – you need to manage all activities with the available resources
- Hiring pharmaceutical programmers with experienced in M&S is difficult, because it's rare
- Coach M&S programmer is a challenge. Why? Because we have to work differently

Challenges for the programmer – „politic“

- Understand the business. What is M&S. How it can impact drug development. Why do we have to work differently compared to a „standard“ biostatistic group
- M&S is a CRO within a pharmaceutical company, i.e. A service provider
- M&S is not a „mandatory“ department in a pharmaceutical company. Therefore we have to always show value to the company: Benefits > cost
- Otherwise.... FTE moved somewhere else

Challenges for the programmer – „politic“

- Some partners pay for modeling : SLA agreement
- 25% of our resources are funded by SLA agreement
- They need to have good quality sciences for what they pay for
- Otherwise the risk is to see some of the SLA not renewed

Challenges for the programmer – „new skills“

- Understand the basics of Pharmacokinetic, pharmacodynamic. What is SS? What is a dose response analysis. What is the half life of a drug?
- Understand the specific softwares for modeling and their restriction, data formats, file structure....
- Know how to convert the „book“ into a modeling input dataset

Challenges for the clinical programmer

- Modeling need data and data specification
- Data specification is based on:
 - Software used
 - What is the clinical question(s) we're trying to address
 - Data issue
 - Modeling results
- Data specification is an interactive process, a living document
- We don't get/write detailed data specifications in advance
- The data specifications are finalized at the same time as the modeling dataset

Challenges for the clinical programmer

- Because M&S is new, not all clinical team fully understand and trust what we do
- If we do a combined analysis with our biostatistics colleagues, and if N is not the same, they'll not like it. M&S will have to update his analysis => changes in data specification at the last minute otherwise the M&S inputs may be lost
- Some of the M&S analysis will be send to Health Authorities – We know them in advance
- Others are not planned, but because the clinical team consider the M&S report can be a crucial document, we have to validate it (double programming) asap

Conclusions

- Most of the M&S Programmers come from a „standard“ biostatistic department
- They often need several months to be used to this new work environment. The difficulties are:
 - Why data specifications are not well defined and finalised a while ago
 - Why do we need to validate this file asap?
 - Why this was not planned earlier
 - ...
- It's still SAS programming – but the work environment is different