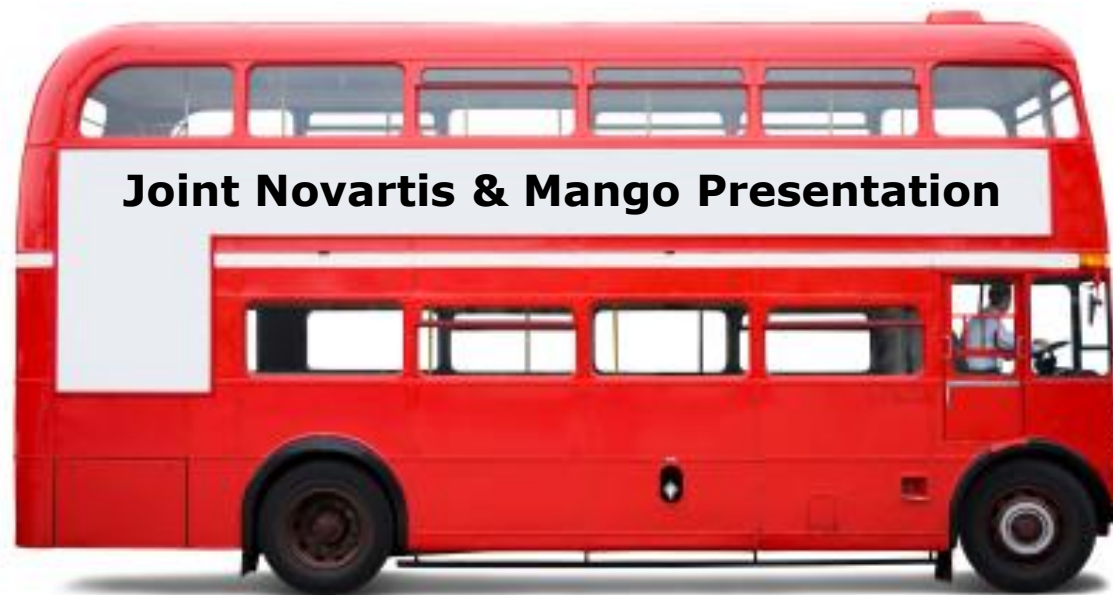
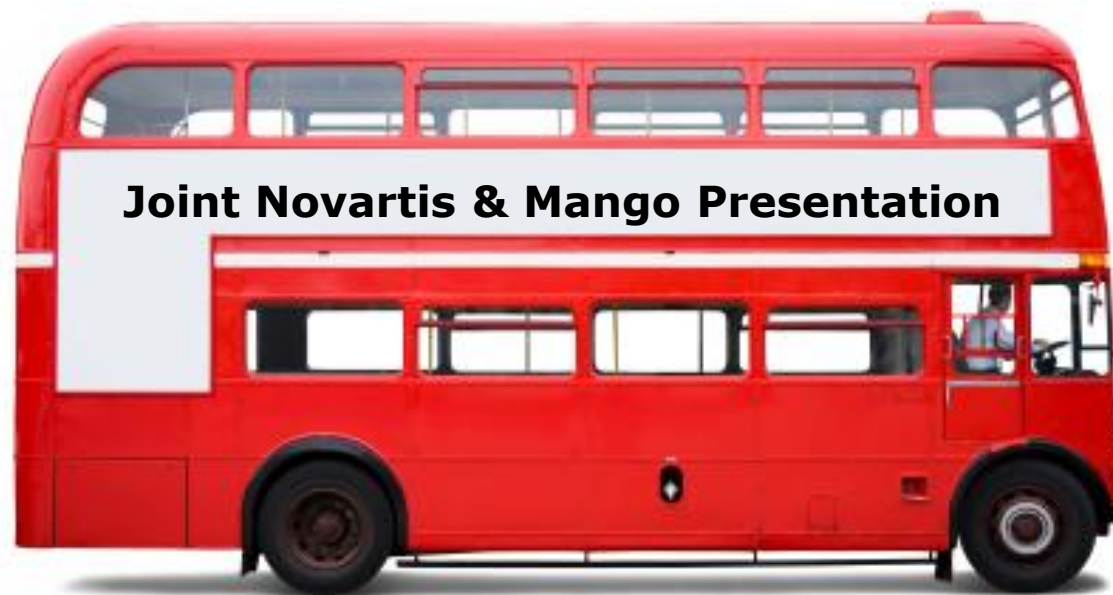




ModSpace: Promoting dissemination and reuse of models and modeling results

Jonathan Chard, Mango Solutions
Henning Schmidt, Novartis CH

The Warm Up Act ...



The Main Event



Web-Based Application for the Reporting of Population PKPD Models

Richard Pugh

Mango Solutions

rich@mango-solutions.com

Justin Wilkins

Novartis

justin.wilkins@novartis.com



Agenda

Background

The Project

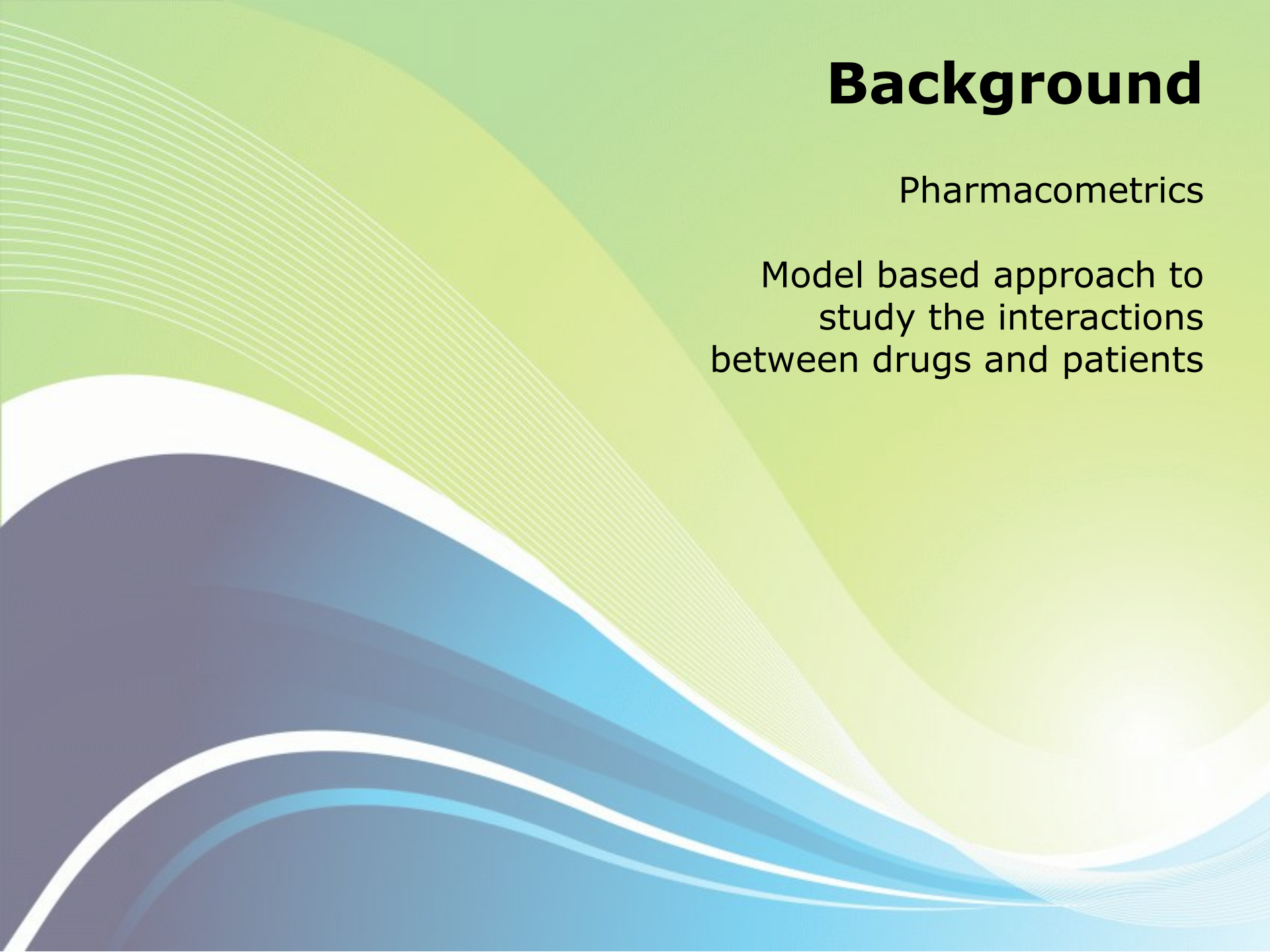
Demonstration

System Architecture

Agile Development

Questions





Background

Pharmacometrics

Model based approach to
study the interactions
between drugs and patients

```
PARAMETER: 0.1000E+00 0.1000E+00 0.1000E+00
0.1000E+00 0.1000E+00 0.1000E+00 0.1000E+00
0.1000E+00 0.1000E+00 0.1000E+00
0.1000E+00 0.1000E+00 0.1000E+00
GRADIENT: 0.1966E+08 0.1966E+08 0.1966E+08
0.1966E+08 0.1966E+08 0.1965E+08 0.1966E+08
0.1966E+08 0.2150E+03 0.1229E+03
-0.6323E+02 -0.5188E+02 0.5640E+03
0ITERATION NO.: 3 OBJECTIVE VALUE: -
0.12497E+01 NO. OF FUNC. EVALS.: 10
CUMULATIVE NO. OF FUNC. EVALS.: 13
PARAMETER: 0.8379E-01 0.9210E+00 0.1140E+00
0.3827E+00 0.2442E+00 0.6915E+00 -0.1404E-01
-0.1765E-01 -0.3216E+00 -0.1377E+00
0.1066E+00 -0.4433E-01 -0.8550E+00
GRADIENT: 0.2991E+02 0.5615E+03 -0.1900E+02
-0.1728E+03 -0.4773E+02 -0.5936E+03 -0.3338E+03
-0.1233E+02 -0.1781E+02 0.2436E+03
-0.2031E+02 -0.4911E+02 0.1571E+03
0ITERATION NO.: 6 OBJECTIVE VALUE: -
0.15803E+04 NO. OF FUNC. EVALS.: 19
CUMULATIVE NO. OF FUNC. EVALS.: 132
PARAMETER: -0.1010E+00 0.7791E+00 0.2492E+00
0.6099E+00 0.7155E+00 0.6917E+00 0.7982E+00
-0.3978E+00 -0.1283E+01 -0.1029E+01
0.2498E+00 0.1374E+00 -0.1648E+01
GRADIENT: 0.2728E+02 -0.5390E+02 -0.1505E+02
0.7018E+01 -0.1792E+02 -0.5981E+03 0.9122E+02
0.1179E+02 -0.1188E+03 -0.9582E+02
0.4064E+02 0.3338E+02 -0.1548E+03
0ITERATION NO.: 9 OBJECTIVE VALUE: -
0.15925E+04 NO. OF FUNC. EVALS.: 20
CUMULATIVE NO. OF FUNC. EVALS.: 191
PARAMETER: -0.6187E+00 0.7701E+00 0.4405E+00
0.5918E+00 0.9914E+00 0.6946E+00 0.8166E+00
-0.9118E+00 -0.1224E+01 -0.1094E+01
0.1527E+00 0.2980E-01 -0.1591E+01
GRADIENT: 0.5553E+01 0.2724E+02 0.1261E+01
```

NONMEM



NONMEM

(NON-linear Mixed Effects Modeling)

Started life in 1972

Developed at the University of
California, San Francisco

Designed to allow the fitting of
complex models to PK/PD data

Heavily used for
pharmacometric model fitting



NONMEM

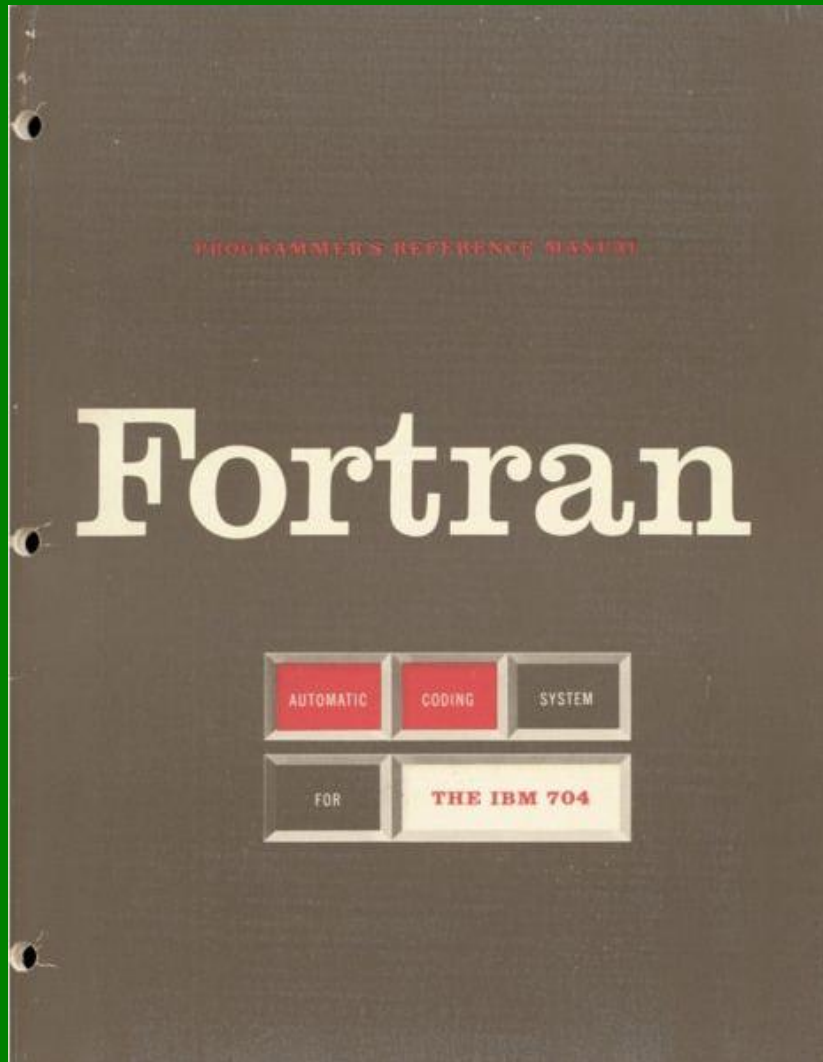
Written in Fortran

Complex model input

Many requirements on
format of input data

Often criticised
(usability & validation)

Difficult to integrate



NONMEM Inputs Control File

Data source
Data format
Output data required
Model
Parameter estimates
User written Fortran code

...

```
$PROB This is the problem statement (like a title)

;This is a comment

$DATA ..\ADS\bas.csv IGNORE=C

$INPUT PROT PT ID TIME AMT RATE DV MDV CYC=DROP SGOT=DROP

$SUBROUTINE ADVAN3 TRANS1

$PK
  "FIRST
  "      COMMON/PRCOMG/ IDUM1, IDUM2, IMAX, IDUM4, IDUM5
  "INTEGER IDUM1, IDUM2, IMAX, IDUM4, IDUM5
  "IMAX=50000000
  TVCL=THETA(1)
  CL=TVCL*EXP(ETA(1))
  TVK12=THETA(2)
  K12=TVK12*EXP(ETA(2))
  TVK21 = THETA(3)
  BETA = 0.5* (K12+K21+K- (SQRT( (K12+K21+K) **2-4*K21*K) )) ;

$ERR
  DEL = 0
  IF (F.EQ.0) DEL=1
  IPRED= F
  W      = F + DEL
  IRES = DV - IPRED
  IWRES= IRES / W
  Y = F+(W*EPS(1)) ; proportional error CCV

$THETA 0 FIXED          ;1 ~ CL (L/h)
$THETA (.01,.18,2)      ;2 ~ K12 (h-1)
$THETA (.001,.05,2)     ;3 ~ K21 (h-1)

$OMEGA 0.325            ;1 ~IIV CL
$OMEGA 0.0 FIX          ;2 ~IIV K12
$OMEGA BLOCK(2) 0.575   ;3 ~IIV K21
                  .124 0.148 ;4 ~IIV V1

$SIGMA .25 ; ~ prop Error

$EST SIGDIGITS=3 MAXEVALS=9999 POSTHOC NOABORT PRINT=5 MET

$TABLE ID DV TIME IPRED PRED WRES IWRES IRES CL V1 V2 Q VS
ETA1 ETA2 ETA3 ETA4 ONEHEADER NOPRINT FILE=TEB1ru01.fit
```

NONMEM Inputs

Input Data

Control file must reference location, name and columns

Rules on columns and format

Control file identifies headers and rows that can be ignored

Header row isn't required

Can drop or rename columns on import

1 Cid	timeh	timed	amt	dv	cmt	evid
2 C	h	d	ug	ng/mL	2	
3 C				g/dL	3	
4 1103	0	0	370	.	1	1
5 1103	0	0	370	.	4	1
6 1103	0	0	1	.	3	1
7 1103	0	0	1	.	6	1
8 1103	13.763	0.573	.	.	3	2
9 1103	27.525	1.147	.	.	3	2
10 1103	41.288	1.72	.	.	3	2
11 1103	55.05	2.294	.	.	3	2
12 1103	68.813	2.867	.	.	3	2
13 1103	82.575	3.441	.	.	3	2
14 1103	96.338	4.014	.	.	3	2
15 1103	110.1	4.588	.	.	3	2
16 1103	123.863	5.161	.	.	3	2
17 1103	137.626	5.734	.	.	3	2
18 1103	151.388	6.308	.	.	3	2
19 1103	165.151	6.881	.	.	3	2
20 1103	178.913	7.455	.	.	3	2
21 1103	192.676	8.028	.	.	3	2
22 1103	206.438	8.602	.	.	3	2

1 0202	0	500	1000	.	1	1
2 0202	0	.	.	0	3	2
3 0202	0.25	.	.	20.27	1	0
4 0202	0.483	.	.	29.87	1	0
5 0202	0.583	.	.	27.41	1	0
6 0202	0.75	.	.	22.46	1	0
7 0202	1	.	.	18.16	1	0
8 0202	1.5	.	.	12.4	1	0
9 0202	2	.	.	1125.63	-3	0
10 0202	2	.	.	9.46	1	0
11 0202	2	.	.	0	3	2
12 0202	3	.	.	5.53	1	0
13 0202	4	.	.	175.96	-3	0
14 0202	4	.	.	3.66	1	0
15 0202	4	.	.	0	3	2
16 0202	6	.	.	216.84	-3	0
17 0202	6	.	.	1.41	1	0
18 0202	6	.	.	0	3	2
19 0202	8	.	.	98.86	-3	0
20 0202	8	.	.	0.54	1	0
21 0202	8	.	.	0	3	2
22 0202	12	.	.	10.6	3	0

```

1
MONITORING OF SEARCH:

OITERATION NO.:      0      OBJECTIVE VALUE:  0.3270E+04      NO. OF
CUMULATIVE NO. OF FUNC. EVALS.:      6
PARAMETER:  0.1000E+00  0.1000E+00  0.1000E+00  0.1000E+00  0.10
GRADIENT:   -0.5155E+04  0.3427E+04  0.1181E+04 -0.2183E+02 -0.23
OITERATION NO.:     16      OBJECTIVE VALUE:  0.3229E+04      NO. OF
CUMULATIVE NO. OF FUNC. EVALS.:    143
PARAMETER:  0.1050E+00  0.9693E-01  0.7792E-01  0.2252E+00  0.17
GRADIENT:   0.8260E+00 -0.5751E+00  0.5583E-01 -0.6629E-02 -0.17
OMINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED:    143
NO. OF SIG. DIGITS IN FINAL EST.:    3.5
1

```

```

THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****

      TH 1      TH 2      TH 3
1.96E+01  8.46E+01  1.66E+00

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****

      ETA1      ETA2      ETA3
ETA1
+      1.64E-01
ETA2
+      0.00E+00  1.65E-01
ETA3
+      0.00E+00  0.00E+00  1.30E+00

```

```

*****
MINIMUM VALUE OF OBJECTIVE FUNCTION
*****
3228.988
*****

```

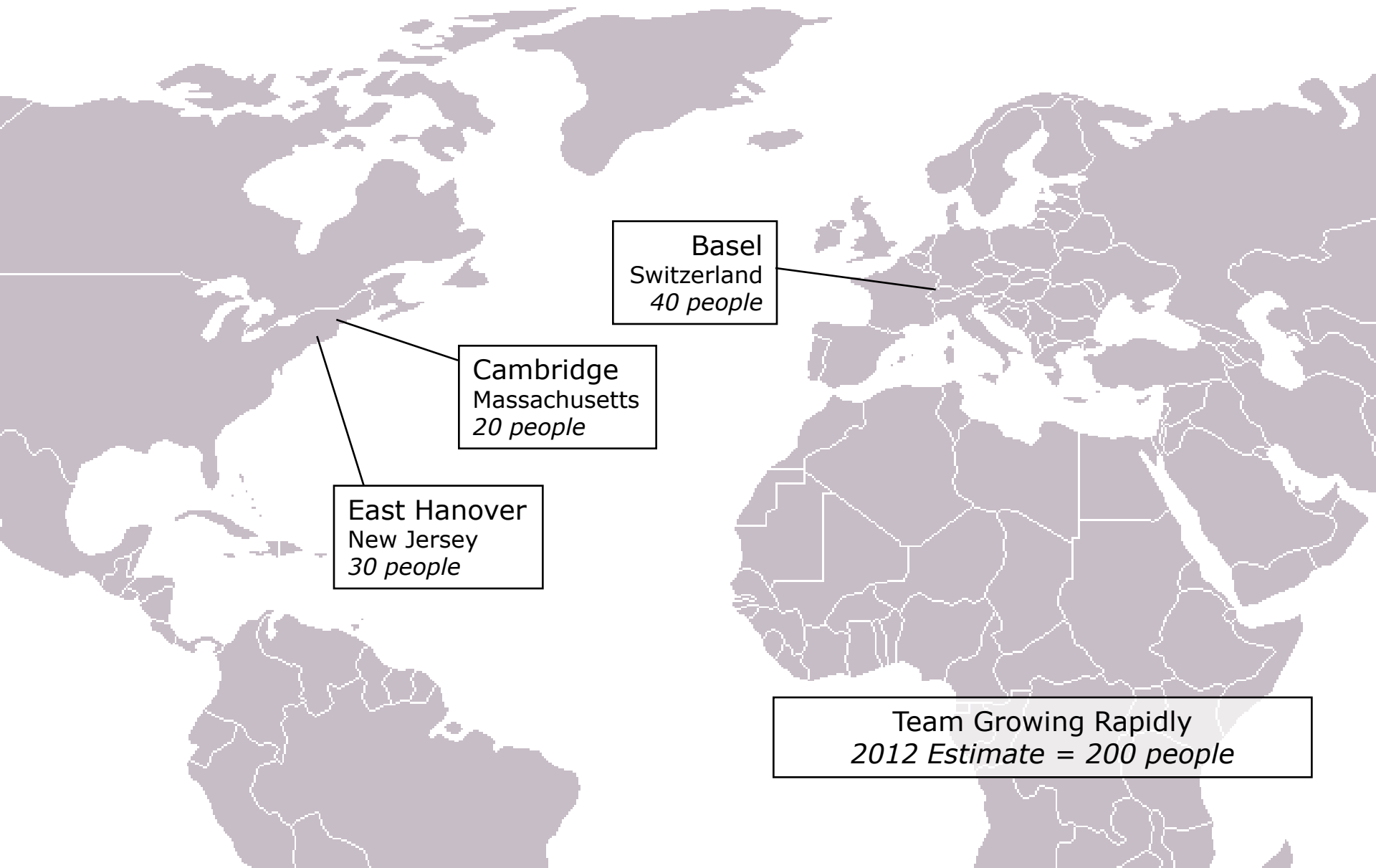
NONMEM Outputs Report File

Final Parameter Estimates
Standard Errors
Covariance Matrices
Correlation Matrices
Iteration Information
Objective Function



COVARIANCE MATRIX OF ESTIMATE								
TH 2 TH 2	TH 3 TH 1	TH 3 TH 2						
5.85E-03	-4.57E-04	-2.15E-03						
TH 4 TH 4	TH 5 TH 1	TH 5 TH 2						
2.38E-01	2.01E-05	-4.70E-04						
TH 6 TH 2	TH 6 TH 3	TH 6 TH 4						
-8.49E-04	2.26E-03	2.61E-03						
TH 7 TH 3	TH 7 TH 4	TH 7 TH 5						
-2.55E-04	-7.89E-04	-6.29E-04						
TH 8 TH 3	TH 8 TH 4	TH 8 TH 5						
-3.95E+00	-1.35E+01	-3.78E-01						

Global Novartis M&S Team



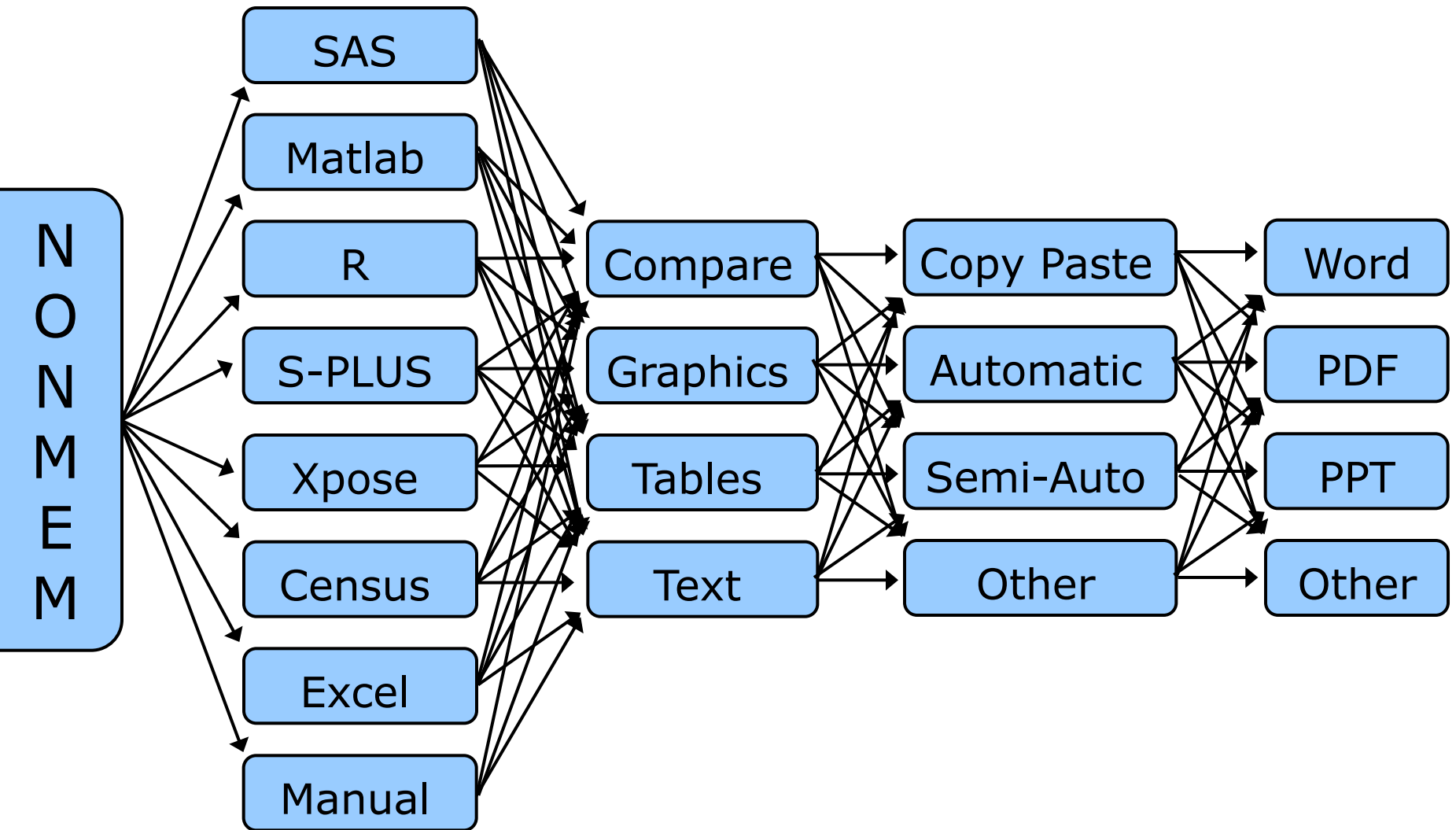
Basel
Switzerland
40 people

Cambridge
Massachusetts
20 people

East Hanover
New Jersey
30 people

Team Growing Rapidly
2012 Estimate = 200 people

Many Methods of Reporting



The Project

Part of wider project

IT project for M&S

RFP process in July 2008

Mango selected as
vendor in October 2008





Standardise Reporting of NONMEM Models
Enable Non-programmers
Provide platform for further development



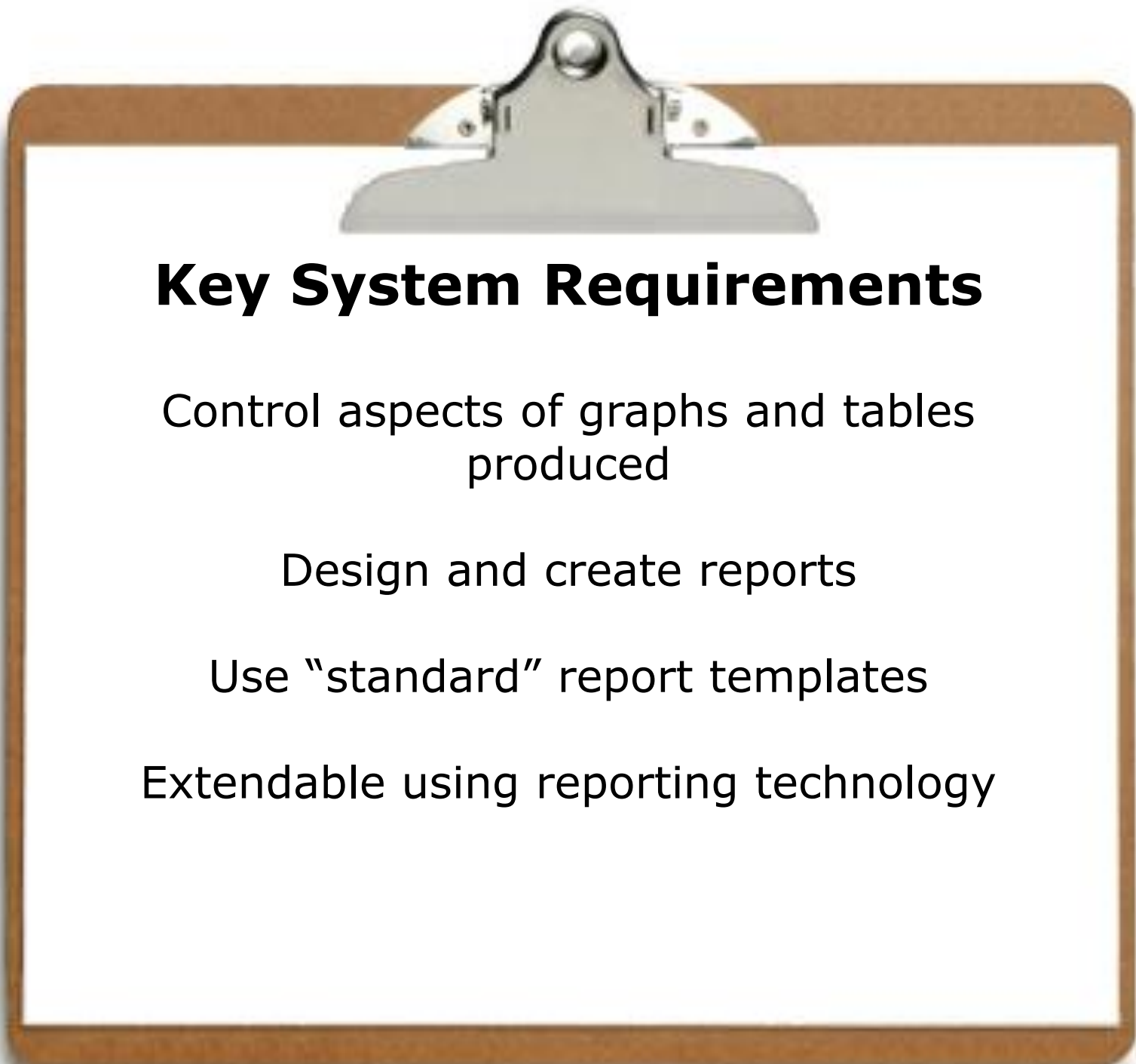
Key System Requirements

Import and store NONMEM run information

Compare runs using tables or graphics

Evaluate individual runs using tables or
graphics

Produce standard tabular and graphical
outputs based on the stored information



Key System Requirements

Control aspects of graphs and tables
produced

Design and create reports

Use “standard” report templates

Extendable using reporting technology



Key System Requirements

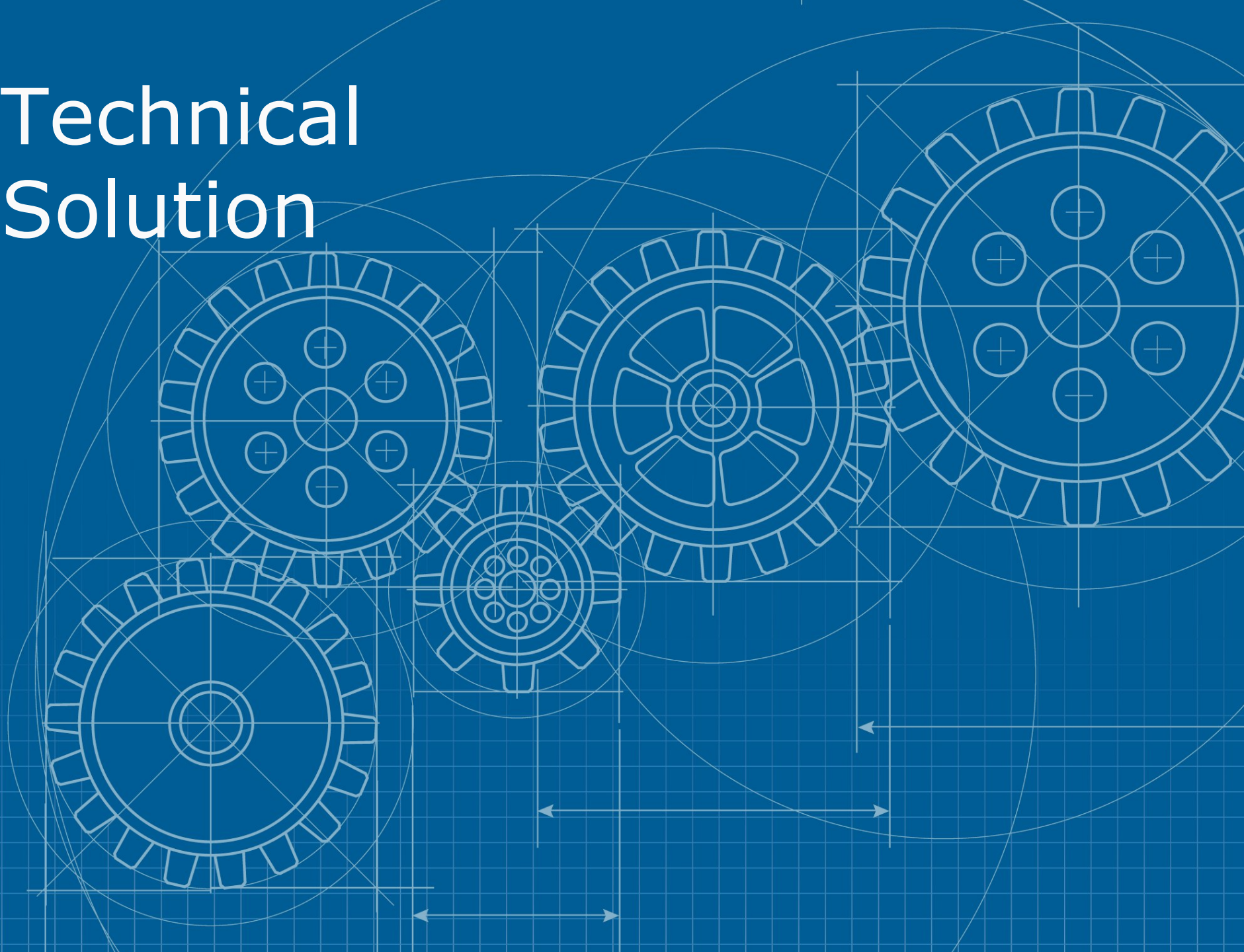
System should support 30+ users

System reflects Novartis security system

All activities be logged as an audit trail

Various performance requirements

Technical Solution



Navigator Application - IE 6.0.2900.2180 SP2 (MSIE)

Address: http://localhost:8080/PopPKPD/ui/views/taskoverview/taskOverview.jsf

Navigator

N:\data\Project\Task\herc

RUN NAME	DESCRIPTION	OBJ. FUNC.	DELTA. OBJ. FUNC.	MINIMIZATION
TEB1RU05	SimHercept: effect of SGPT on CL	16735.215	0.0	MINIMIZATION SUCCESSFUL
TEB1RU02	SimHercept: effect of age on CL	16733.887	-1.33	MINIMIZATION SUCCESSFUL
TEB1RU04	SimHercept: effect of TBIL on CL	16711.209	-22.7	MINIMIZATION SUCCESSFUL
TEB1RU03	SimHercept: effect of WT on CL	16691.814	-19.4	MINIMIZATION SUCCESSFUL
TEB1RU01	SimHercept: Basic run without covariates	16735.225	43.4	MINIMIZATION SUCCESSFUL

Task View

(T) New Tabular View

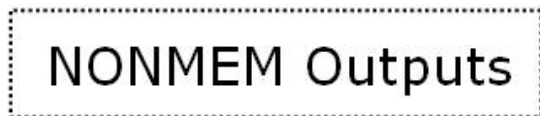
ALL | Pivotal | Deleted | Clear

- TEB1RU01
- TEB1RU02
- TEB1RU03
- TEB1RU04
- TEB1RU05

PopPKPD Reporting Application (Java)

Oracle Database

NONMEM Outputs



Navigator Application - IE 6.0.2900.2180 SP2 (MSIE)

Address: <http://localhost:8080/PopPKPD/ui/views/taskoverview/taskOverview.jsf>

Navigator

N:\data\Project\Task\herc

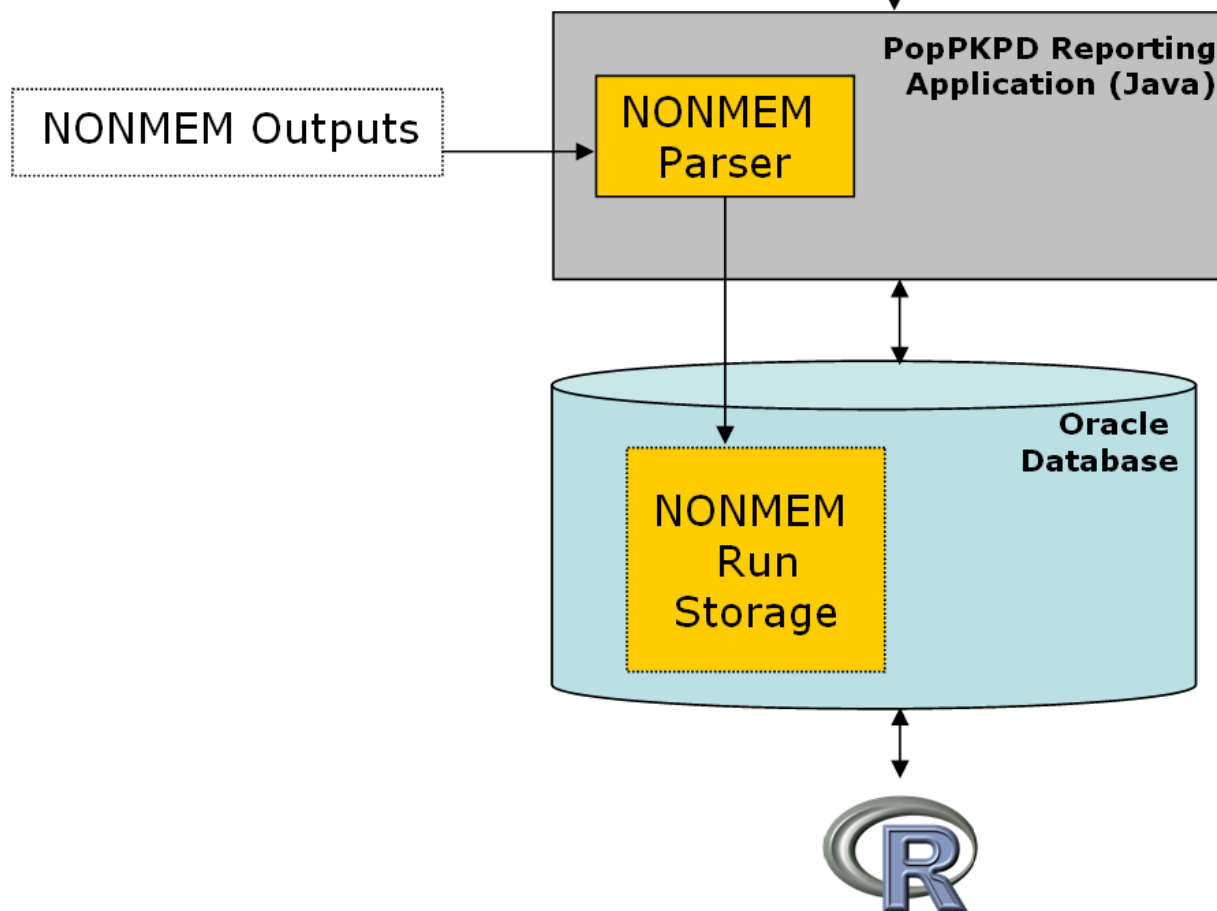
RUN NAME	DESCRIPTION	OBJ. FUNC.	DELTA. OBJ. FUNC.	MINIMIZATION
TEB1RU05	SimHercept: effect of SGPT on CL	16735.215	0.0	MINIMIZATION SUCCESSFUL
TEB1RU02	SimHercept: effect of age on CL	16733.887	-1.33	MINIMIZATION SUCCESSFUL
TEB1RU04	SimHercept: effect of TBIL on CL	16711.209	-22.7	MINIMIZATION SUCCESSFUL
TEB1RU03	SimHercept: effect of WT on CL	16691.814	-19.4	MINIMIZATION SUCCESSFUL
TEB1RU01	SimHercept: Basic run without covariates	16735.225	43.4	MINIMIZATION SUCCESSFUL

Task View

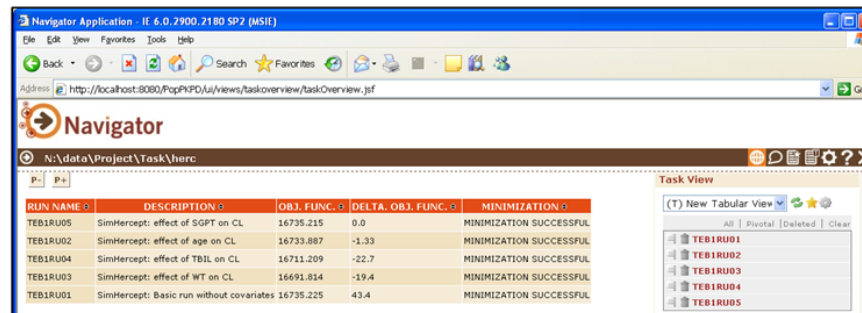
(T) New Tabular View

All | Pivotal | Deleted | Clear

- TEB1RU01
- TEB1RU02
- TEB1RU03
- TEB1RU04
- TEB1RU05



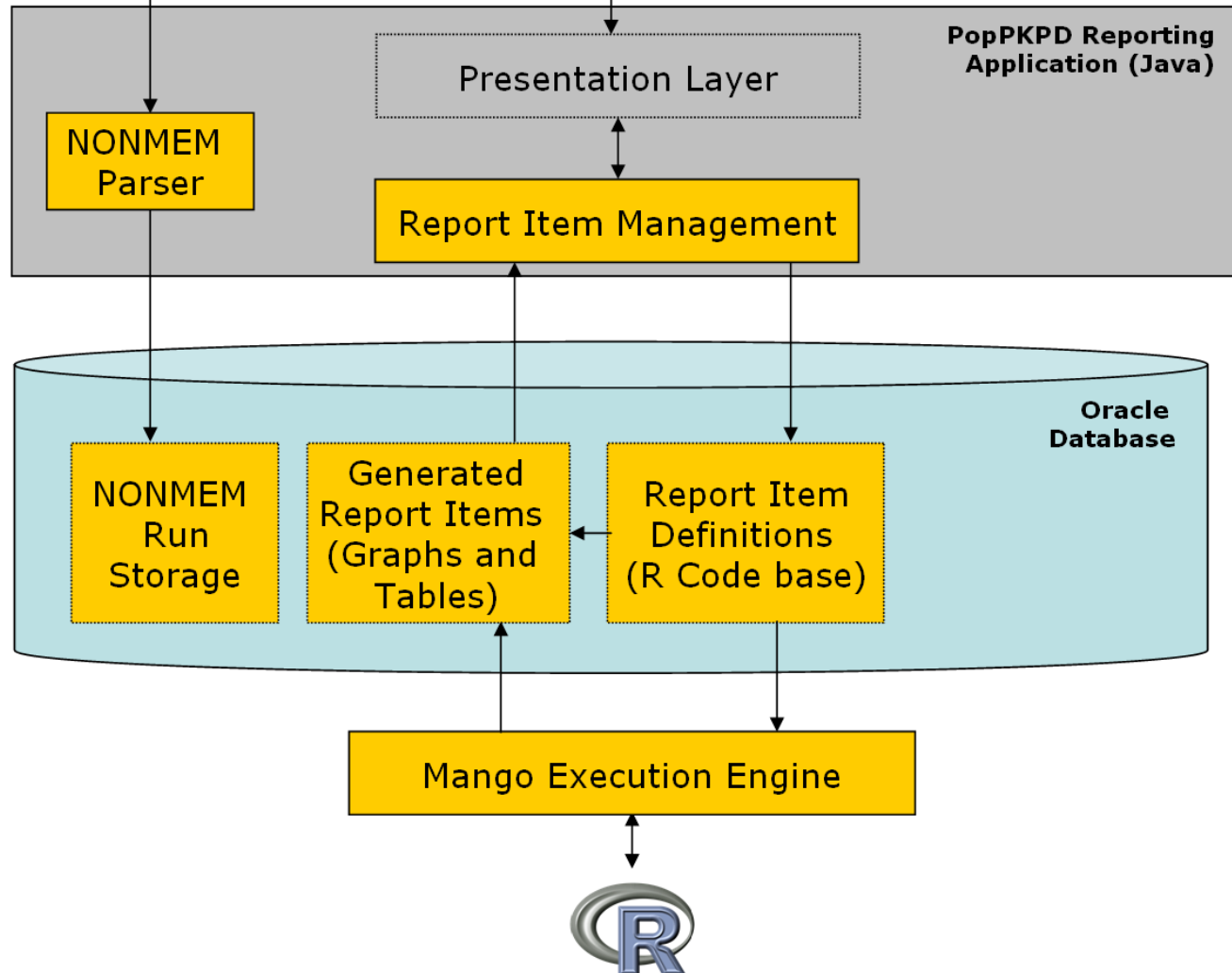
NONMEM Outputs



The screenshot shows a web browser window titled 'Navigator Application - IE 6.0.2900.2180 SP2 (MSIE)'. The address bar shows 'http://localhost:8080/PopPKPD/ui/views/taskoverview/taskOverview.jsf'. The page title is 'Navigator'. The main content area displays a table with the following data:

RUN NAME	DESCRIPTION	OBJ. FUNC.	DELTA. OBJ. FUNC.	MINIMIZATION
TEB1RU05	SimHercept: effect of SGPT on CL	16735.215	0.0	MINIMIZATION SUCCESSFUL
TEB1RU02	SimHercept: effect of age on CL	16733.897	-1.33	MINIMIZATION SUCCESSFUL
TEB1RU04	SimHercept: effect of TBIL on CL	16711.209	-22.7	MINIMIZATION SUCCESSFUL
TEB1RU03	SimHercept: effect of WT on CL	16691.814	-19.4	MINIMIZATION SUCCESSFUL
TEB1RU01	SimHercept: Basic run without covariates	16735.225	43.4	MINIMIZATION SUCCESSFUL

On the right side of the table, there is a 'Task View' panel with a list of tasks: TEB1RU01, TEB1RU02, TEB1RU03, TEB1RU04, and TEB1RU05.



Navigator Application - IE 6.0.2900.2180 SP2 (MSIE)

Address http://localhost:8080/PopPKPD/ui/Views/taskoverview/taskOverview.jsf

Navigator

N:\data\Project\Task\harc

RUN NAME	DESCRIPTION	OBJ. FUNC.	DELTA, OBJ. FUNC.	MINIMIZATION
TEB1RU05	SimIntercept: effect of SGPT on CL	16735.215	0.0	MINIMIZATION SUCCESSFUL
TEB1RU02	SimIntercept: effect of age on CL	16733.887	-1.33	MINIMIZATION SUCCESSFUL
TEB1RU04	SimIntercept: effect of TBIL on CL	16711.209	-22.7	MINIMIZATION SUCCESSFUL
TEB1RU03	SimIntercept: effect of WT on CL	16691.814	-19.4	MINIMIZATION SUCCESSFUL
TEB1RU01	SimIntercept: Basic run without covariates	16735.225	43.4	MINIMIZATION SUCCESSFUL

Task View

(T) New Tabular View

All | Pivotal | Deleted | Clear

- TEB1RU01
- TEB1RU02
- TEB1RU03
- TEB1RU04
- TEB1RU05

NONMEM Outputs

PopPKPD Reporting Application (Java)

NONMEM Parser

Presentation Layer

Report Item Management

Mango Report Generator

Oracle Database

Audit Trail

NONMEM Run Storage

Generated Report Items (Graphs and Tables)

Report Item Definitions (R Code base)

User Settings

Report Template Definitions

Mango Execution Engine





Agile Development

Live Demo!



In Summary ...

Standardise NONMEM Reporting

Delivered web-based application

R is the reporting engine

Close development between
Mango and Novartis

Next development phase
starting soon





People to thank

Novartis: Paul Lewandowski, Peter Forster, Thomas Müller, Justin Wilkins, Celine Dartois Sarr, and an army of testers

Mango: Dylan Browne, Fan Shao, Feng Zhu, Geoff Gibbs, Francisco Gochez, Rich Pugh

PHUSE Committee

Questions?



Richard Pugh (rich@mango-solutions.com)
Justin Wilkins (justin.wilkins@novartis.com)