Drug Disease Model Resources

ddmore

WP6.2

Model based adaptive design

RESULTS OF SURVEY of OCTOBER 2011

France Mentré, University Paris Diderot, France
Iva Gueorguieva, Lilly, UK

Marylore Chenel, Emmanuelle Comets, Joakim Grevel, Andrew Hooker,

Mats Karlsson, Marc Lavielle, Joakim Nyberg

imi efpia

Outline

- What is DDMoRe?
- Survey on population design
  - Context
  - Results
  - Conclusion

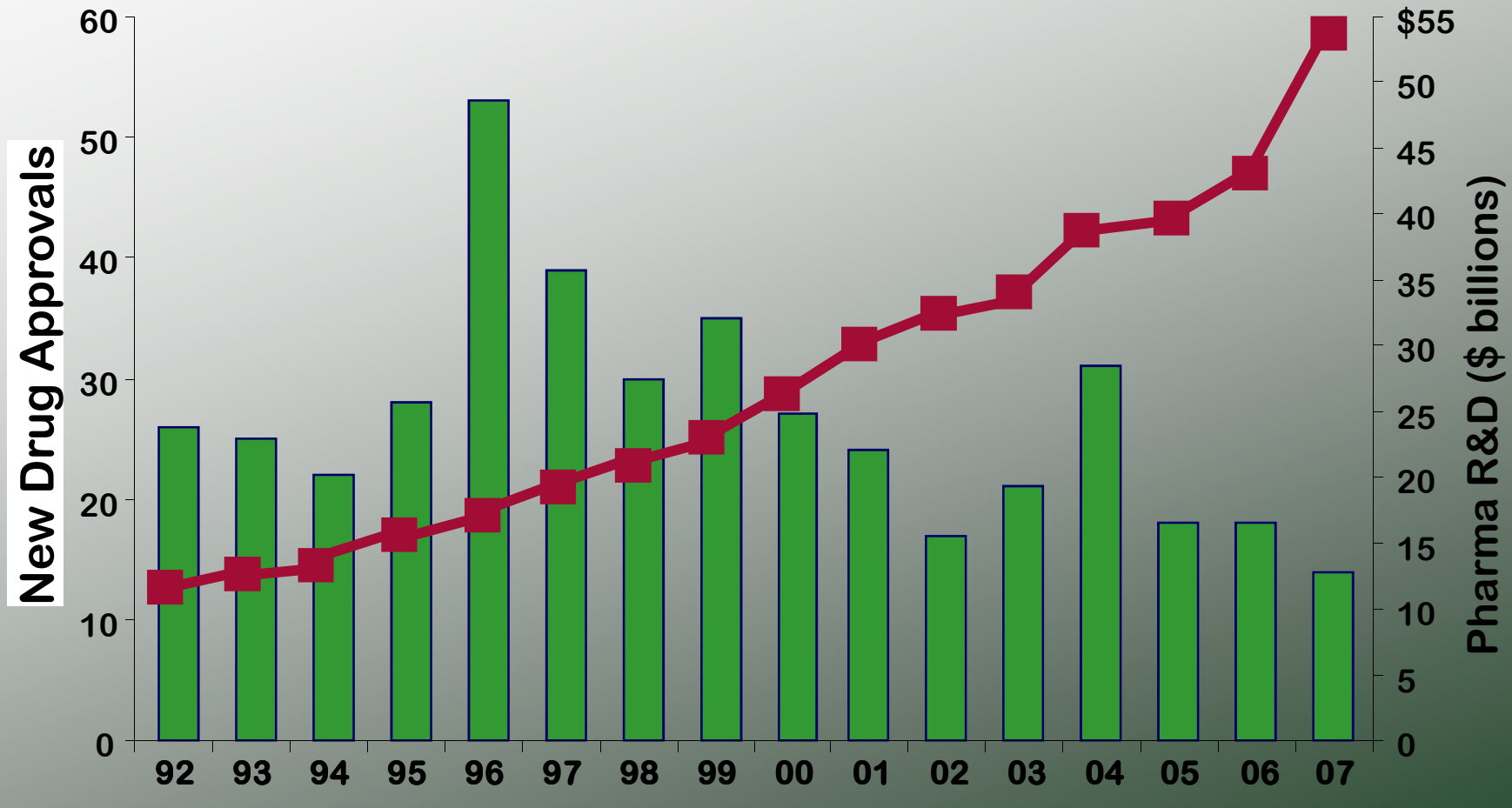
Drug Disease Model Resources

DDMoRe: an evolutionary step in model building and sharing

Lutz Harnisch, Pfizer, UK
Mats Karlsson, Uppsala University, Sweden

On behalf of the DDMoRe consortium

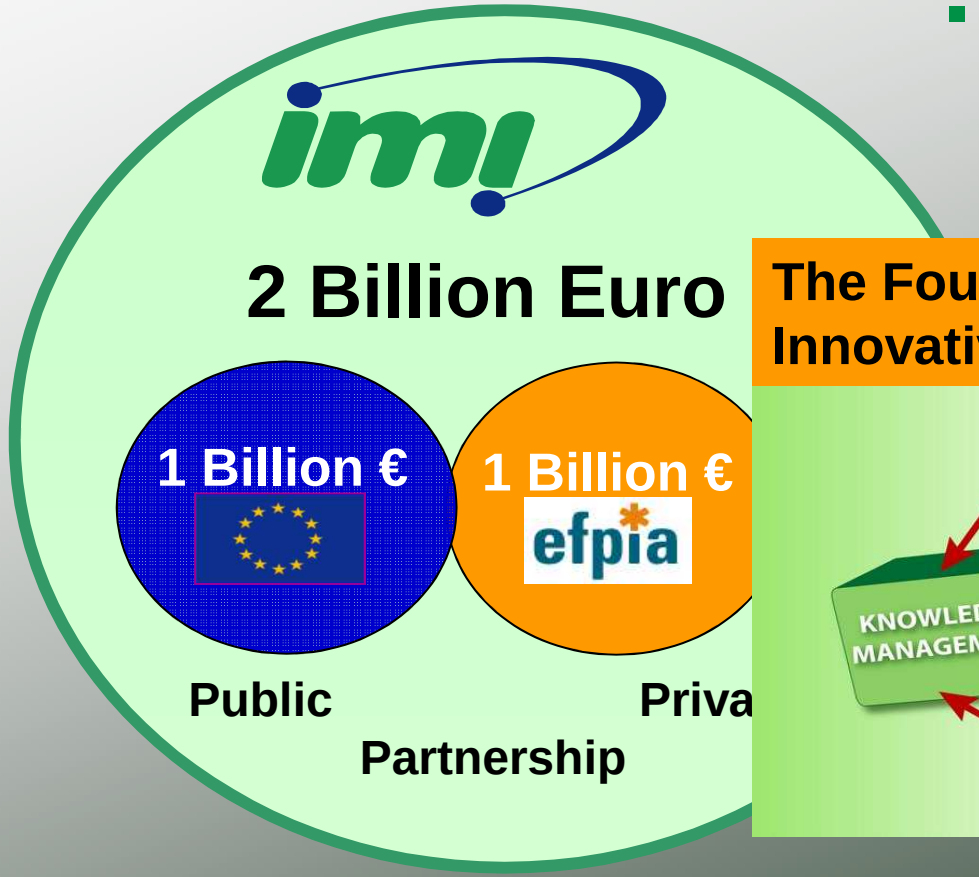
The Productivity Gap in Pharma R&D



Source: Burrill & Company; US Food and Drug Administration.

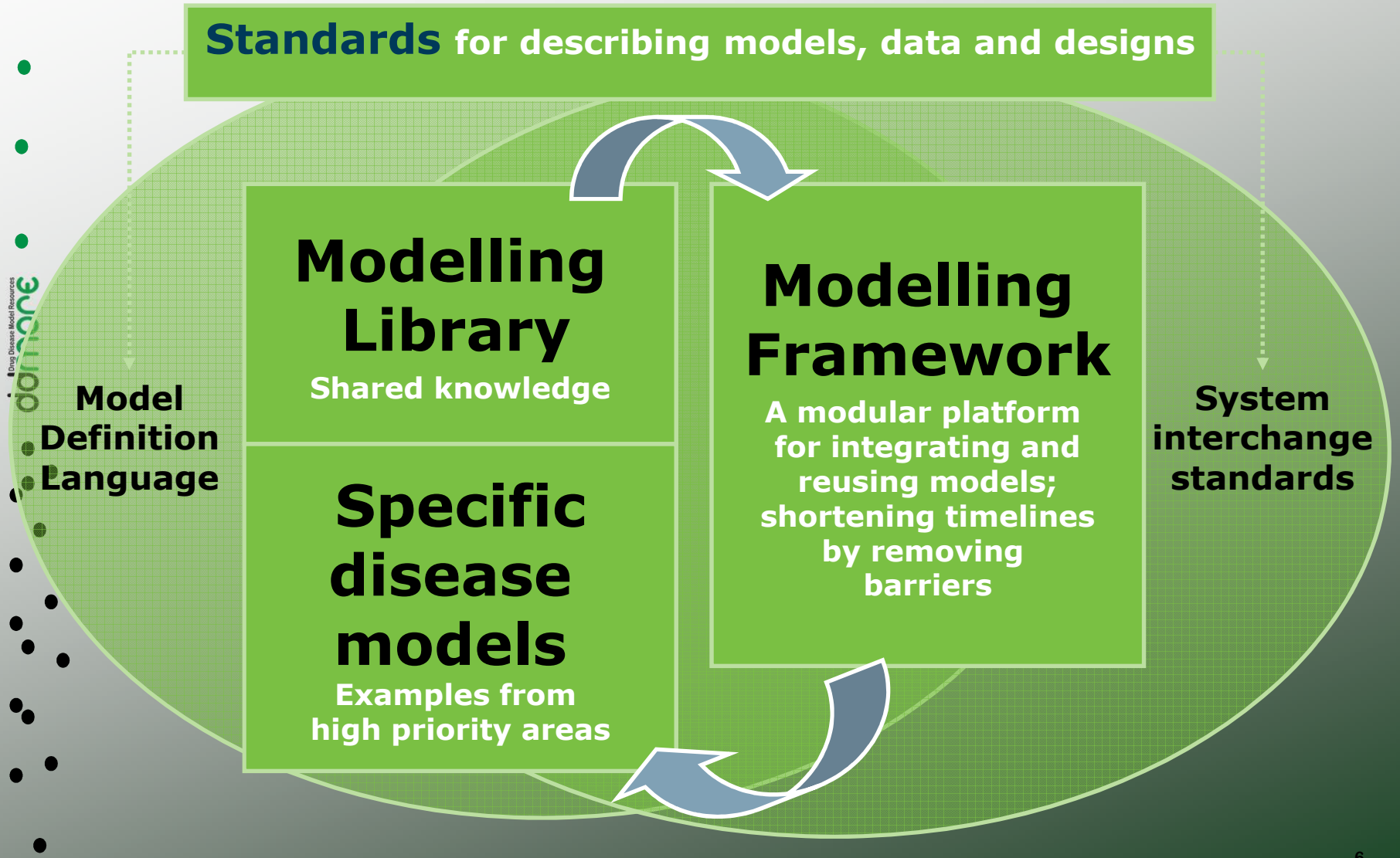
Innovative Medicines Initiative: the Largest PPP in Life Sciences R&D

- Key concepts
  - Open innovation
  - Pre-competitive research



The Four Pillars of the Innovative Medicines Initiative

DDMoRe – The Vision



Participants

are a unique combination of model builders, model users, software developers and teachers

Drug Disease Model Resources

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efpia

NOVARTIS, Pfizer, SERVIER, gsk GlaxoSmithKline, MERCK, Lilly, Roche, novo nordisk, ucb, AstraZeneca

Academia

PARIS DIDEROT, Universidad de Navarra, IsB, EMBL-EBI, INRIA, UPPSALA UNIVERSITET, Universiteit Leiden, Freie Universität Berlin

SMEs

SIMCYP, cyprotex discovery, MANGOSOLUTIONS, LIXOFT, optimata, INTERFACEUROPE

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DDMoRe – Key Benefits

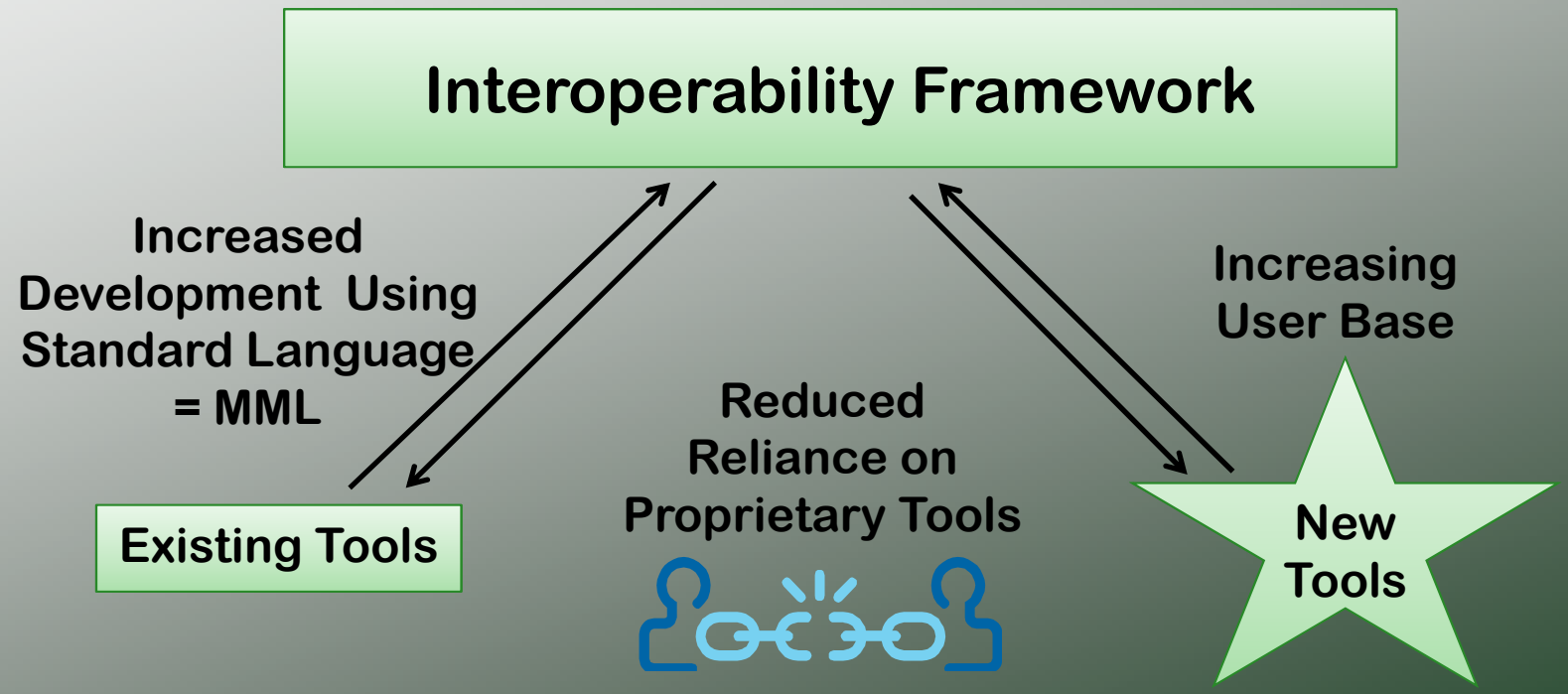
an evolutionary step in model building and sharing

- Improving the **environment** for M&S activities related to MBDD to promote **retention and sharing of knowledge** among industry, academia, regulatory
- Creation of a **common ontology** to address all components of pharmacometric and mechanistic modelling
  - including data, models, code, metadata, analysis results and inferences
- Development of a public **library** for pharmacometric, statistical and systems biology models and a software interoperability **framework** to enable efficient model sharing and tool integration
- unique endeavour, collaboration between **25 partners** from industry and academia in pursuit of common goals

Integration of Existing and New Softwares

The Future

Standards Enable: Backwards Compatibility with Existing Tools, Forward Compatibility with Future Tools



Development & Integration of New Tools - *WP6*

WP6.1 : Clinical Trial Simulator

WP6.2 : Tools for adaptive optimal design

WP6.3 : Tools for model diagnostic & model selection

WP6.4 : Tools for complex models

Drug Disease Model Resources

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WP6.2

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Background

- Objective of WP6.2 of ddmore
  - ➢ develop tools for adaptive design based on NLMEM
- Before planning what to do
  - perform survey on use of optimal design and expectations within EFPIA partners (decided during meeting in Sep 11)
- Survey designed and approved by all members of WP6.2 during Sep 11
  - Part 1: State of the art (i.e. current situation)
  - Part 2: Requests for future developments & adaptive optimal design

Survey completion

- Sent to 10 EFPIA partners in Oct 11
- All answers back in Nov 11
  - Pfizer (Lutz Harnish, Phylindia Chan, Mike Smith)
  - Novartis (Ivan Matthews, Gordon Graham)
  - AstraZeneca (Marcus Bjornsson, Matts Kagedal)
  - GSK (Stefano Zanumer, Shuying Yang)
  - Lilly (Ivelina Gueorguieva)
  - Merck Serono (Pascal Girard)
  - Novo Nordisk (Niels Rode Kristensen)
  - Roche (Annabelle Lemenuel)
  - Servier (Marylore Chenel)
  - UCB Pharma (Miren Zamacona)

Survey results: General

Approaches to optimally design trials/studies in your company

- **Practice/ heuristic approach**
  - 9 yes, mainly Phase 1 and 2
- **Simulation**
  - 9 yes, Phase 1 to 3, main approach for some companies
- **Optimal design software in NLMEM**
  - 9 yes but 1 with limited use

Survey results: Current situation

How/when do you use of optimal design software in NLMEM

NB: answered by 9 companies

- What for?
  - Most: PK, PD, PK/PD
  - Some: dose selection, dose response, enzyme kinetics
- Special populations?
  - Pediatrics (3), patients, hepatic impairment, elderly
- What phases?
  - Most: phases 1 and 2
  - Some also phase 3

Survey results: Current situation (ctd)

Which software?

- PFIM & PFIMopt: 6
- POPDES: 3
- POPED: 3
- WinPOPT & POPT: 3

- NB:
  - answered by 9 companies
  - five companies use more than one software

Survey results: Current situation (ctd)

For what?

	YES (out of 9)
Design evaluation?	7
Design optimisation?	8
Power evaluation?	6
Dose/input optimisation?	6
Sampling windows?	7
Several groups of elementary designs	7
Bayesian/robust	5
With complex error models?	3
With Inter-Occasion Variability?	3
With covariates?	5
Multiresponse?	4

- NB: if several answers in a company, at least one yes = yes

Survey results: Current situation (ctd)

Present limitations (verbatim)

- Need to implement the model in an other tool than estimation (2)
- Need to train every modeller; lack of training
- Need methods dealing with a wider range of models (more complex error models, flexible covariate models, flexible BSV matrices, event type data models)
- Inclusion of continuous covariates
- Flexibility in residual error structure, covariate support, batch processing

Survey results: Current situation (ctd)

Present limitations (verbatim)

- Poor graphical presentation of results (especially in PFIM)
- Availability of optimal Bayesian Design
- Does not prevent from high shrinkage
- Optimisation algorithms are time consuming, especially when the model is written with ODE
- Need possibility to fix some sampling times and to optimise some
- Commonly geared for PK sampling, rather than more general

Survey results: Adaptive design

- **How useful? (from 0 to 5, 10 answers)**
  - **Median 4, range 1 to 5 (5 quoted by 4 companies)**
- **Specifications**

	YES (out of 9)
Start from prior information	9
Design optimisation after each new cohort	8
Stopping rules	6

- **Comments (verbatim)**
  - Adaptive design is a very wide field
  - Not very relevant in the therapeutic areas where we are active, because we deal with endpoints that develop slowly over time, whereas recruitment is fast
  - Very useful in some cases and not useful at all in others

Survey results: Future improvements

How important? (from 0 to 5, 10 answers)

	Median	Range
Handling data below quantification limit	4	2-5
Discrete data	4	1-5
Repeated time to event (rtte)	3	1-5
Joint continuous/discrete	4	1-5
Joint continuous/rtte	3	1-3
Continuous covariates	5	3-5
Prediction of shrinkage	3	1-5
SE for individual parameters	3	1-5
Other optimality criteria (DT, Ds, …)	3	1-5
Robustness across models	4	2-5

Survey results: Future improvements (ctd)

Any other priorities (verbatim)

- Software that is convenient to use
- Coordinate optimal design with clinical trial simulator!
- Better graphical presentation of results for optimal design
- Want to examine efficiency of various design options for Phase 2A dose-finding or dose-response studies, but optimal designs are rarely acceptable due to the need for low doses
- Bayesian optimal design may be useful in future
- OptDes bridging from one population to another may also be a key area for the future.

Conclusion: current situation

- All companies (except one) use optimal design in NLMEM
  - Mainly for phase 1 and 2 and PKPD
- All software are used and some companies use several
  - NB: all software developed by academia
- Mostly used for: design evaluation, design optimisation, power evaluation, dose/input optimisation, sampling windows, several groups of elementary designs
- Presently several limitations (slide 8), especially need to change software from estimation to design

Conclusion: future developments

- Adaptive design of high priority for most companies
  - Start from prior information
  - Design optimisation after each new cohort
  - Stopping rules
  - NB: not useful when slow endpoints
- Other high priorities in design
  - Continuous covariates
  - Handling data below quantification limit
  - Robustness across models
  - Discrete data
  - Joint continuous/discrete

➢ Next ddmore meeting of WP6.2: discuss of action to be taken

LINSTAT, Poland, 16-20 July

"Optimum Design for Mixed Effects Regression Models" session organized by Basia Bogacka

- The International Conference on Trends and Perspectives in Linear Statistical Inference, LinStat'2012, and the 21st International Workshop on Matrices and Statistics, IWMS 2012. Held at Będlewo, the Mathematical Research and Conference Center of the Polish Academy of Sciences.
- The conference fee covers the accommodation, full board conference materials, the conference banquet :
  - Regular - 450 EUR / 500 EUR (before / after April 30, 2012);
  - PhD students presenting talk or poster - 350 EUR / 400 EUR
- some of the topics: estimation, prediction and testing in linear models, generalizations to nonlinear models, design and analysis of experiments, including optimality and comparison of linear experiments, and applications of matrix methods in statistics.
- **Abstracts deadline:** May 31, 2012

Backup: Survey questions

General

WP6.2 Survey on adaptive model-based optimal design
Final Version 5/10/ 2011

Questions	*Comments*
EFPIA name	*name of company*
Author's name	*who was in charge to fill the survey*
Date	*before Oct 31*
Approaches to optimally design trials/studies in you company	
practice/heuristic approaches	*yes/no, if yes indicate phase of drug development*
simulation	*yes/no, if yes indicate phase of drug development*
optimal design software in NLMEM	*yes/no, if yes please fill below*

Part 1

How/when do you use of optimal design software in NLMEM	
what for?	*e.g. PK, PD,PKPD,…*
special populations?	*yes/no, if yes, which?*
what phases?	*2A, 3 ..*
which software(s)?	*give name(s)*
design evaluation?	*yes/no*
design optimisation?	*yes/no*
power evaluation?	*yes/no*
dose/input optimisation?	*yes/no*
sampling windows?	*yes/no*
several groups of elementary designs	*yes/no*
Bayesian/robust	*yes/no*
With complex error models?	*yes/no*
With Inter-Occasion Variability?	*yes/no*
With covariates?	*yes/no*
Uniresponse/Multiresponse?	*1- Uni only, 2-both*
What are the present limitations in the use of optimal design approaches	*Please comment*

Backup: Survey questions (ctd)
Part 2

Adaptive optimal design in NLMEM	
how usefull?	*Priority from 0 (no) to 5 (a lot)*
start from prior information	*yes/no*
design optimisation after each new cohort	*yes/no*
stopping rules	*yes/no, if yes which*
any other comments	
How important would be the following improvements (if time allows)?	
handling data below quantitation limit	*Priority from 0 (no) to 5 (a lot)*
discrete data	*Priority from 0 (no) to 5 (a lot)*
repeated time to event (rtte)	*Priority from 0 (no) to 5 (a lot)*
joint continuous/discrete	*Priority from 0 (no) to 5 (a lot)*
joint continuous/rtte	*Priority from 0 (no) to 5 (a lot)*
continuous covariates	*Priority from 0 (no) to 5 (a lot)*
prediction of shrinkage	*Priority from 0 (no) to 5 (a lot)*
SE for individual parameters	*Priority from 0 (no) to 5 (a lot)*
other optimality critera (DT, Ds …)	*Priority from 0 (no) to 5 (a lot)*
robustness across models	*Priority from 0 (no) to 5 (a lot)*
Any other priorities	*Please comment*