Survey on the current use of optimal design approaches and the developments needed in adaptive optimal design for model based analysis performed amongst DDMoRe's EFPIA members

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Drug Disease Model Resources

DDMoRe: an evolutionary step in model building and sharing

Lutz Harnisch, Pfizer, UK

Mats Karlsson, Uppsala University, Sweden

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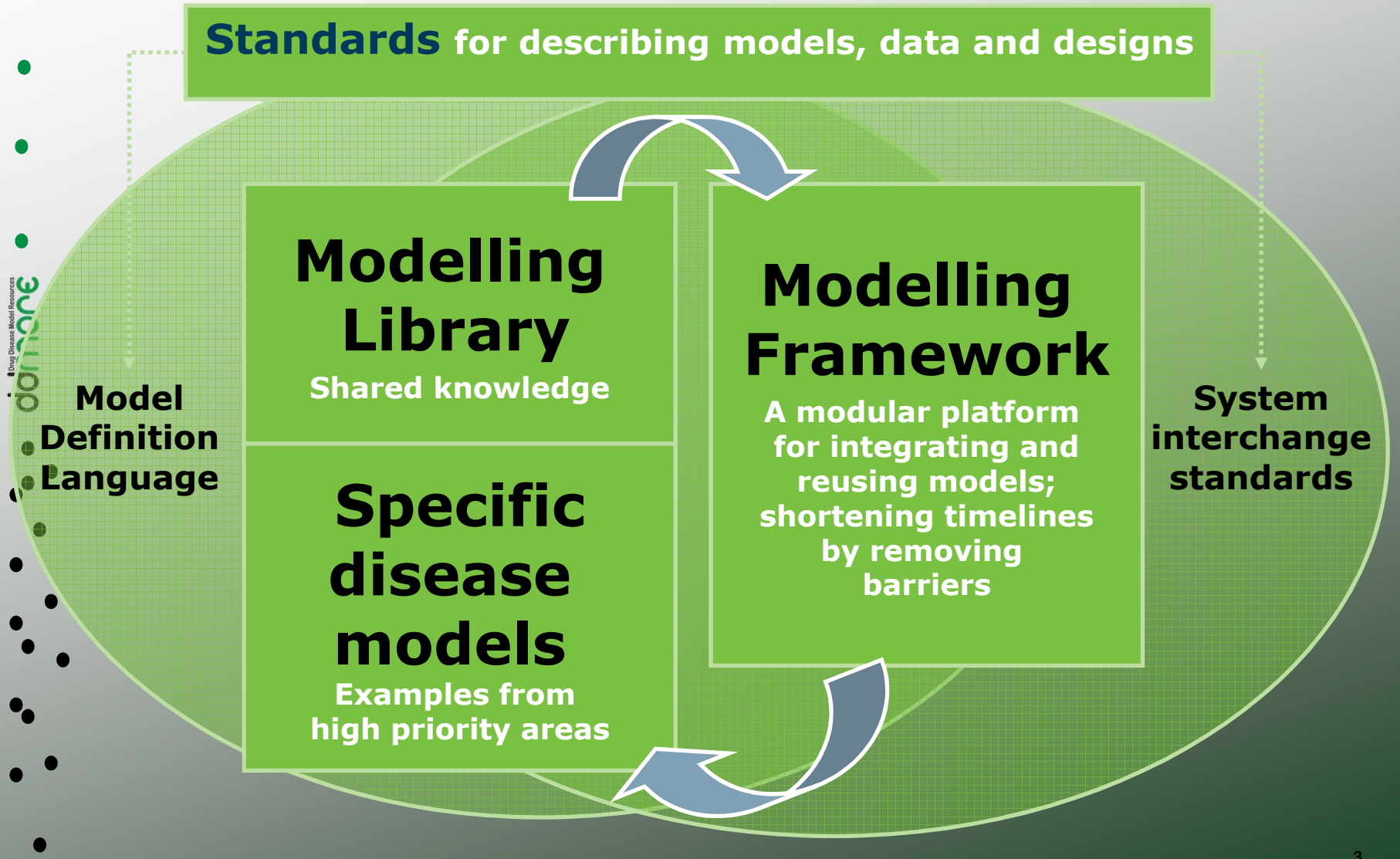
DDMoRe – The Vision



Participants

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

Drug Disease Model Resources

ddmore

efpia

Academia

SMEs

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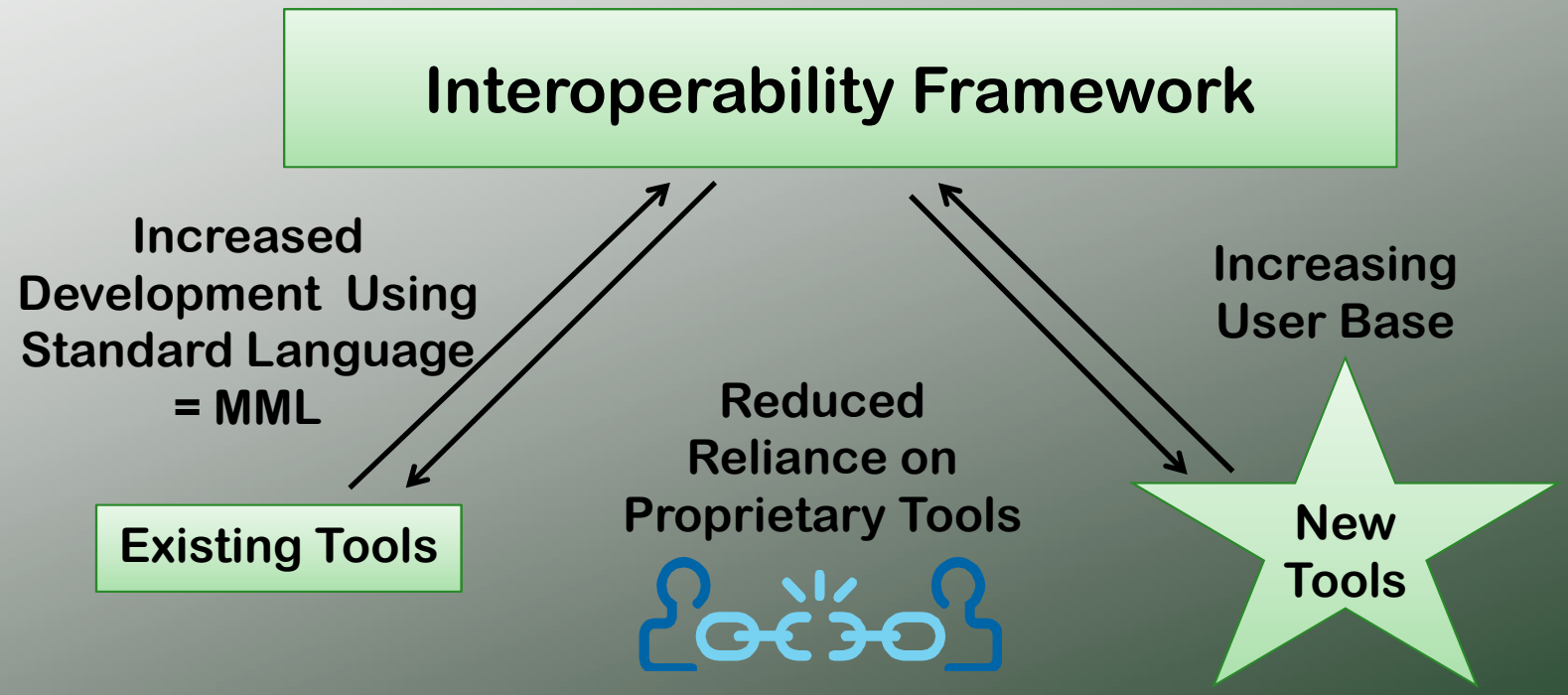
Integration of Existing and New Softwares

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

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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
- Survey designed and approved by all members of WP6.2 during Sep 11
  - Part 1: State of the art (i.e. curent 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

Q1: Approaches to optimally design trials/studies in your company

- **Practice/ heuristic approach**
  - 9 yes (/10) , mainly Phase 1 and 2
- **Simulation**
  - 9 yes (/10) , Phase 1 to 3, main approach for some companies
- ➢ **Optimal design software in NLMEM**
  - 9 yes (/10) but 1 with limited use

Survey results: Current situation

Q2: 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: 6 (University Paris Diderot & INSERM)**
- **POPDES: 3 (University of Manchester)**
- **POPED: 3 (University of Uppsala)**
- **WinPOPT & POPT: 3 (University of Otago)**

- **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)

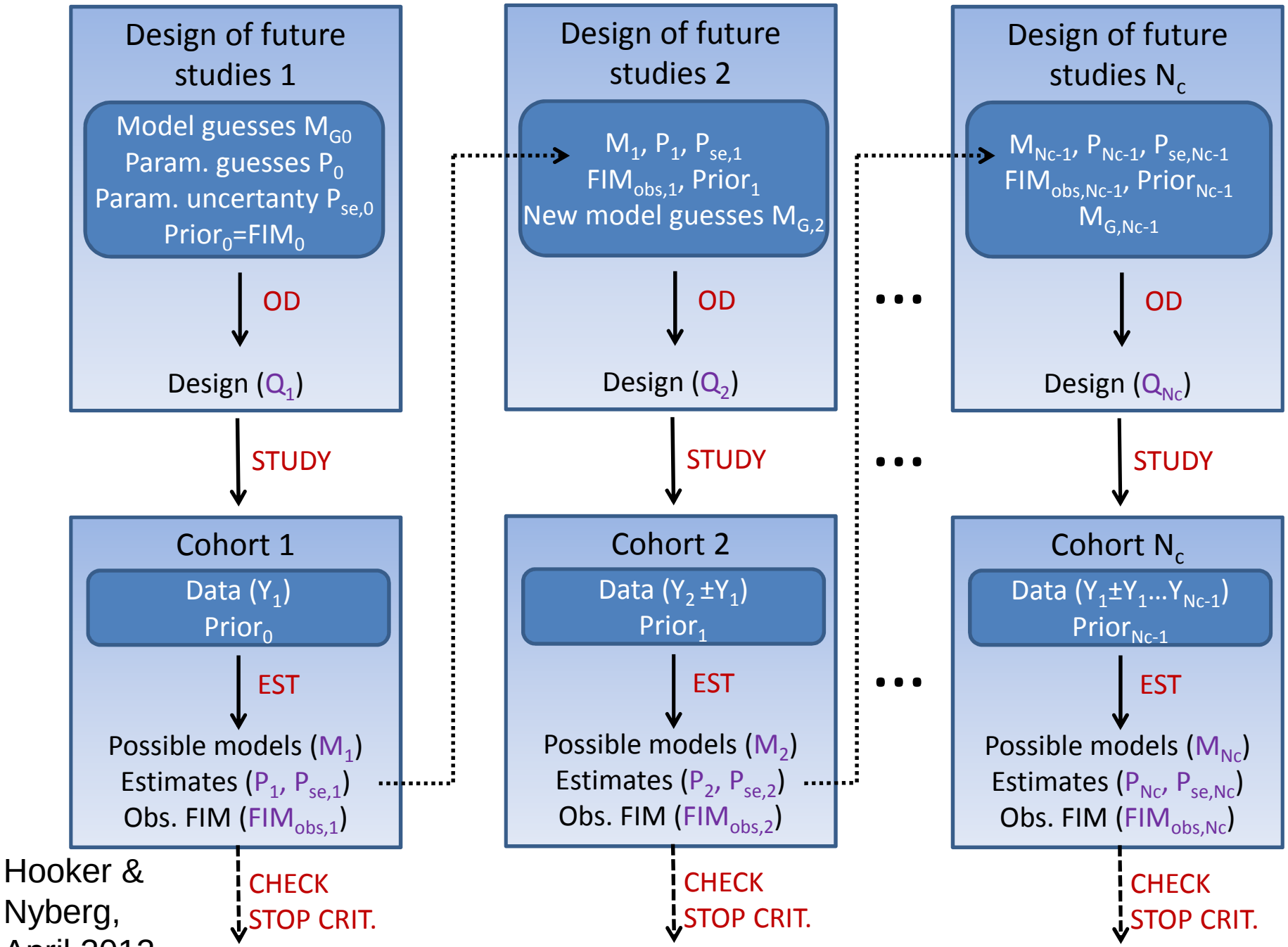
- Software that is convenient to use
- Coordinate optimal design with clinical trial simulator!
- Better graphical presentation of results for optimal design
- Want to examine efficiency of various design options for Phase 2A dose-finding or dose-response studies, but optimal designs are rarely acceptable 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, especially need to change software from estimation to design

Conclusion: future developments

- Adaptive optimal design (AOD) in NLMEM 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



Hooker & Nyberg, April 2012