MODELERS PERSPECTIVES

Extrapolation workshop; Session 1:
Experience with the current extrapolation approach/perspective, 30/9-2015

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Outline

- What is modeling?
- How modeling and simulation can address gaps in knowledge when planning a paediatric development?
- How modeling and simulation can fill gaps in knowledge?
- What do you expect from the clinicians and the statisticians?
- What are the challenges of modeling and simulation when evaluating extrapolation?

The philosophy of modeling

Why should clinicians and regulators encourage modeling?

A method to test how advanced our understandig of a particular system is

- useful to describe a set of data and can integrate different sources of data
- facilitates testing our understanding, identify uncertainty and help explore impact of uncertainty
- helps making assumptions explicit
- leads way to predictions to inform transitions; bridging from the known to the unknown

The sign of a mature science -> not only describe, but able to predict

Not quite there for all domains, but we are moving…

Should be used to describe and to inform decisions

PK – generally accepted modeling is a good method for integrating information

PD and efficacy– increasingly recognising modeling is a good method for integrating information

the full potential not reached on the translation into clinical efficacy and safety

What can MID3* bring to extrapolation?

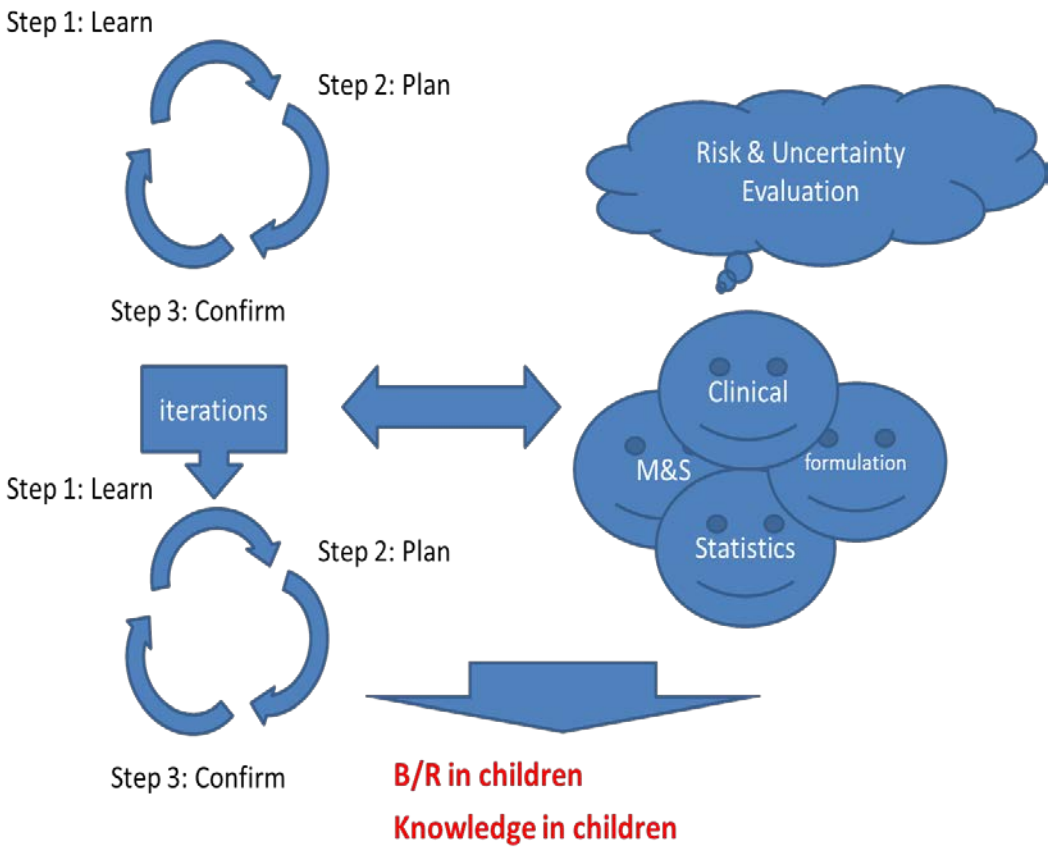
<u>Quantitative framework</u>

for integrating information

- **data and knowledge**

Useful for

- systematically evaluating the existing knowledge and
- preparing the integrated discussion of similarity and possibilites for extrapolation and reduced data requirements



*Model informed drug discovery and development, Presentation by Scott Marshall for EFPIA, PAGE Meeting 2014

Process

Learn

- Collect relevant **data and knowledge**
- **Systematic synthesis** of data; evaluate possibility to integrate the data in a model
- Explore **impact of study methodology** on outcome
- Report **confidence in data or predictions**
- Define **methodology for decision making**

Plan

- **Decision making**; decide the content of the extrapolation concept and the development plan. **Which questions** need to be answered and what are the possible study designs that can provide clinically useful answers considering also the reality of opportunities and limitations of performing studies.

- **Update** the extrapolation concept and development plan as new data emerges from the source population or other supportive sources

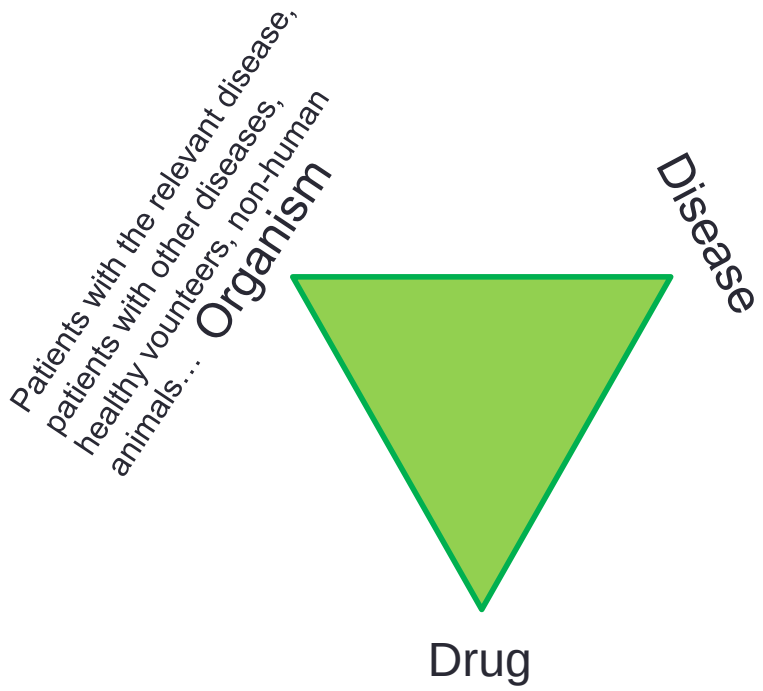
Confirm

- **Confirm** appropriateness of extrapolation concept with data from the target population

- **Update** the extrapolation concept and development plan if conflicting evidence emerges

System data

At the heart of paediatric modelling approaches there should be a systems pharmacology understanding

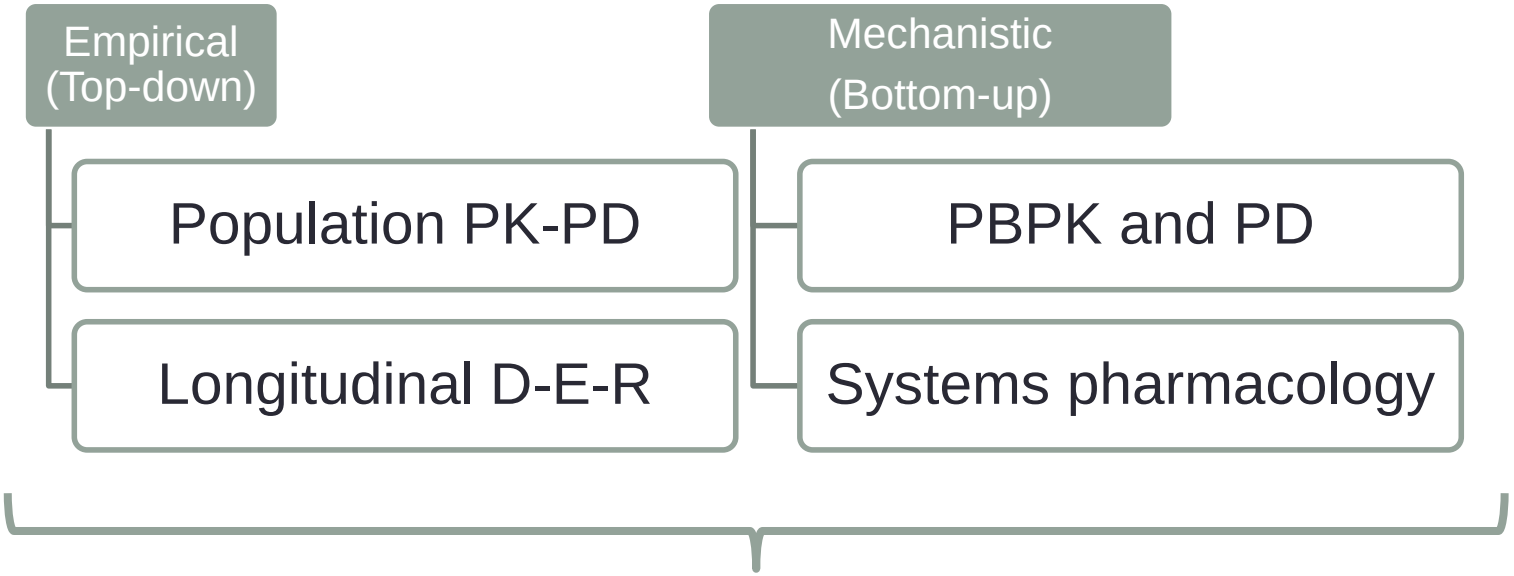


In a pharmacological drug development setting, a system can be defined as the interplay between an organism, which could be human or other animal species, a disease and a drug.

Systems knowledge, which is lost if drugs are developed in silos, can be factored into the analysis of the dose exposure response (D-E-R) relationship, and disease relationship across populations can inform and potentially increase confidence in decision-making.

- Systems data can inform the structure of the models, the expected variability, uncertainty and covariate effects and may eventually reduce requirements for additional clinical data to build confidence in MID3.
- The value of modelling systems data extends beyond product specific extrapolation questions and can facilitate paediatric drug development as a whole.

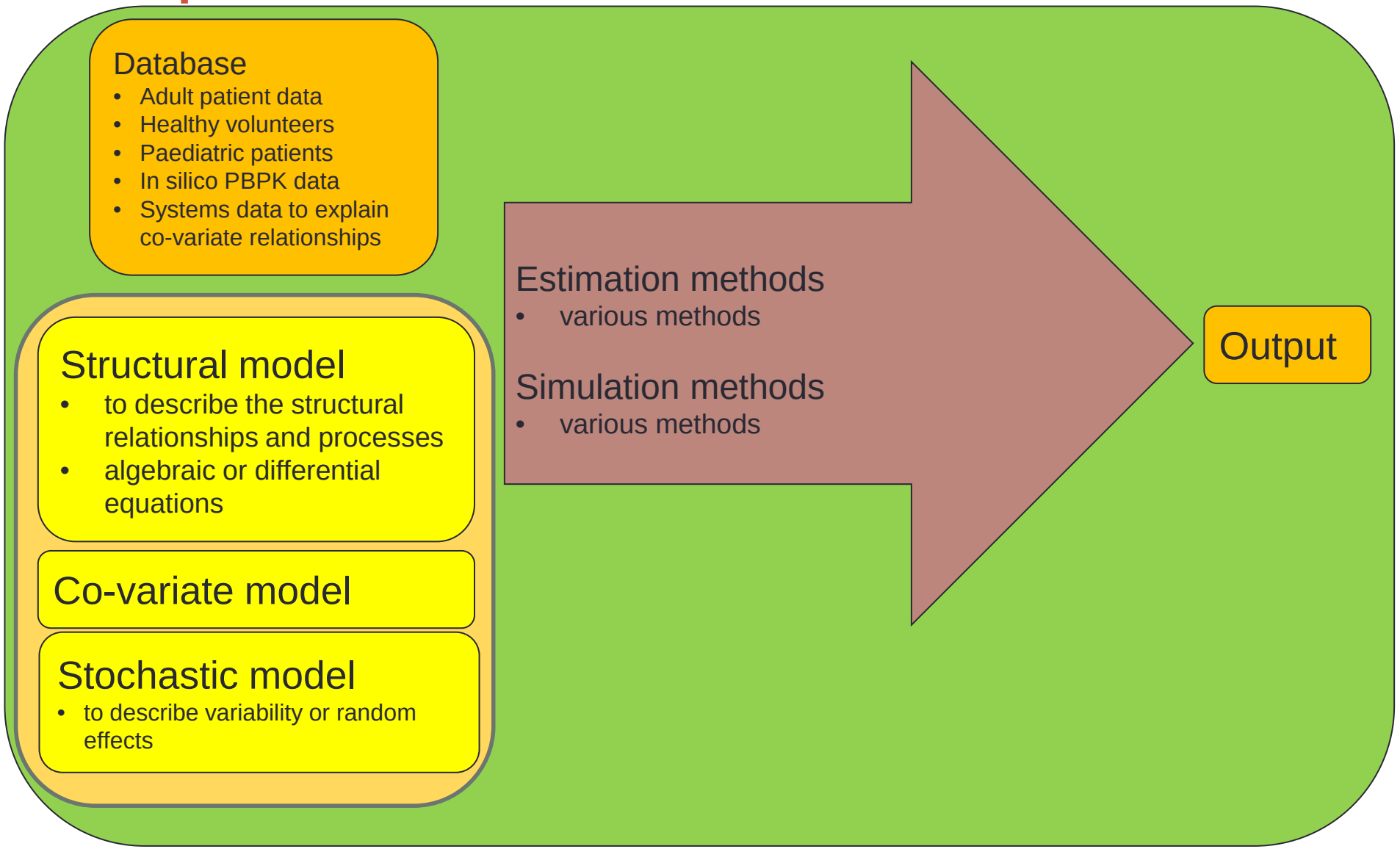
Tool box for pharmacological M&S



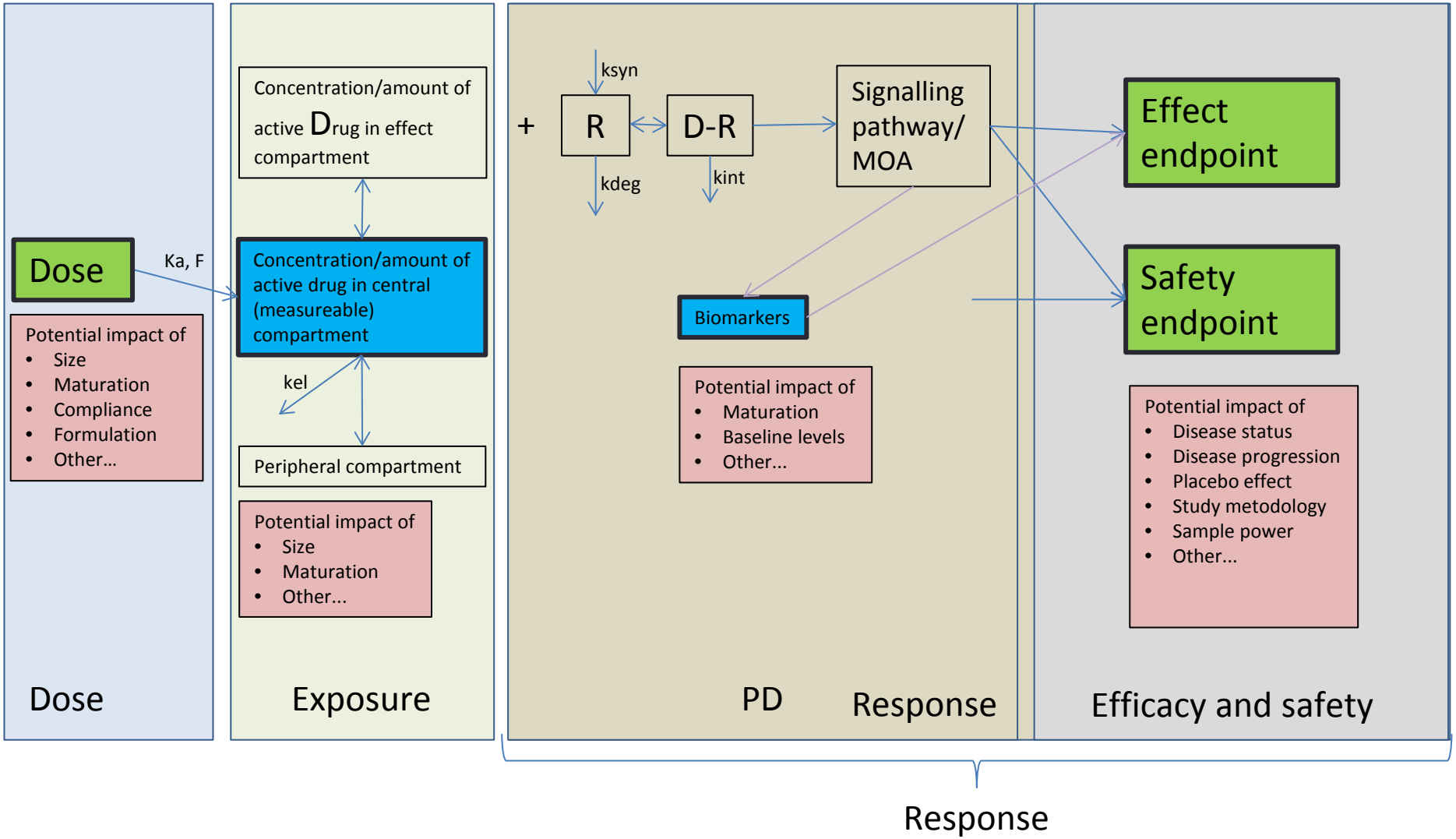
Combine methods to use all existing knowledge

Clinical trial simulations to optimize trial design

Population models



Dose exposure response



Disease characteristics

Models can help characterize the basal disease characteristics

- by linking the diagnosis or even «omics» data on the pathogenesis to the disease manifestation and progression

- the type of models vary, but can in principle be similar to the population PD-E-S models
  - without the drug intervention
  - or can incorprate several other drugs, standards of care or placebo used in the condition

Examples

- Alzheimer (qualification opinion)
- Diabetes (several models and publications available)

- Models can be useful to explore
  - impact of study design; sensitivity of endpoints etc
  - potentially also impact of differences in PD, translation into clinical response

Identify gaps

- Gaps in knowledge
  - the processes, the structural relationships
  - co-variate relationships
  - variability
  - assumptions
- by testing the ability to describe/predict the source data sets
- iterative loops of testing, learning and model refinement
- Additional focus in developments
  - to reduce uncertainty
  - collect supportive data

Fill gaps

- Describe
  - also in cases of sparse data generation
- Derive dosing recommendations
  - First in paediatrics dose recommendation
- Optimize study methodology
  - sensitivity of endpoints
  - impact of differences in disease status or progression
  - determine appropriate times for measuring endpoints
  - choice of trial design, sample sizes
- Predict for inference/extrapolation
- Confirm
  - dosing rationale for subsequent studies or MA
  - PK-PD-E-S relationships for subsequent studies or MA

Expectations - from clinicians and statisticians

Clinicians, pharmacologists

- Quality of data
- Assumptions and uncertainty
- Consequences of violating assumptions
- Limits of similarity (therapeutic index or other criteria for setting limits)

How to do?

- Structured lists of type of data/knowledge, assumptions and uncertainty per therapeutic area?
- Sets of standardized questions to be posed?
- Providing such information when procedures are referred to MSWG?
- Guidance for MID3 for the procedures not referred?

Expectations - from clinicians and statisticians

Statisticians

- Weight of input data?
- Quantify data/knowledge (plausible ranges, betaPERT…)?
- Uncertaintly quantification (how to best perform UQ, global sensitivity analysis)?
- Input on stochastic parts of quantitiative models?

How to do?

- ?

Challenges

- Communication between domains of expertice
  - How to get needed information on uncertainty in input data, assumptions etc?
  - How to report impact of uncertainty and confidence in models in an informative way to clinicians/regulators?

- Need for improved supportive data
  - need for high quality systems data
  - PD endpoint bridging in adult clinical studies
  - bridging from non-clinical to clinical studies (allometry and beyond)
  - need for consistency in approaches to learn across developments
  - longitudinal PK-PD-E-S modelling and increasingly QSP have a key role to play on this understanding, in the design of trials and in the decision making process.

Challenges

- Need for improvements in reporting and methodology for evaluation of predicitive models

- the available data should be suffcient to allow confidence in conclusions (seldom systematically addressed)
- the proposed models need to show good validity against source data (lack of information on the models)
- agree needs for scenario analysis on uncertainty (clinical, pharmacology, statistics, trial methodology..)

- need to (repeatedly) introduce an uncertainty risk assessment step or other tools to support an integrated informed decision making
- define key interim stages to report and agree impact on plan
  - Extrapolation possible?
  - Extrapolation plan acceptable?
  - Key interim deliveries acceptable?