EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Extrapolation framework

Status quo and issues to be resolved

EMA extrapolation workshop 2015-09

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Objectives

- Outline of extrapolation framework (concept paper)
- Rationale for extrapolation
- Status quo of extrapolation (in PIPs)
- Agreed principles
- Issues to be resolved

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19 March 2013
EMA/129698/2012
Human Medicines Development and Evaluation

Concept paper on extrapolation of efficacy and safety in medicine development

Final

Agreed by Scientific Advice Working Party	25 April 2012
Agreed by Biostatistic Working Party	15 May 2012
Agreed by PK Working Party	30 May 2012
Agreed by COMP	10 May 2012
Adoption by PDCO	16 May 2012
Adoption by CHMP	24 May 2012
Start of public consultation	29 June 2012
End of consultation (deadline for comments)	30 September 2012

Extrapolation definition

Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), *or in related conditions or with related medicinal products*, to make inferences for another subgroup of the population (target population), *or condition or product*, thus minimizing the need to generate additional information (types of studies, number of patients required) to reach conclusions for the target population.

EMA 2013, Concept paper on extrapolation of efficacy and safety in medicine development

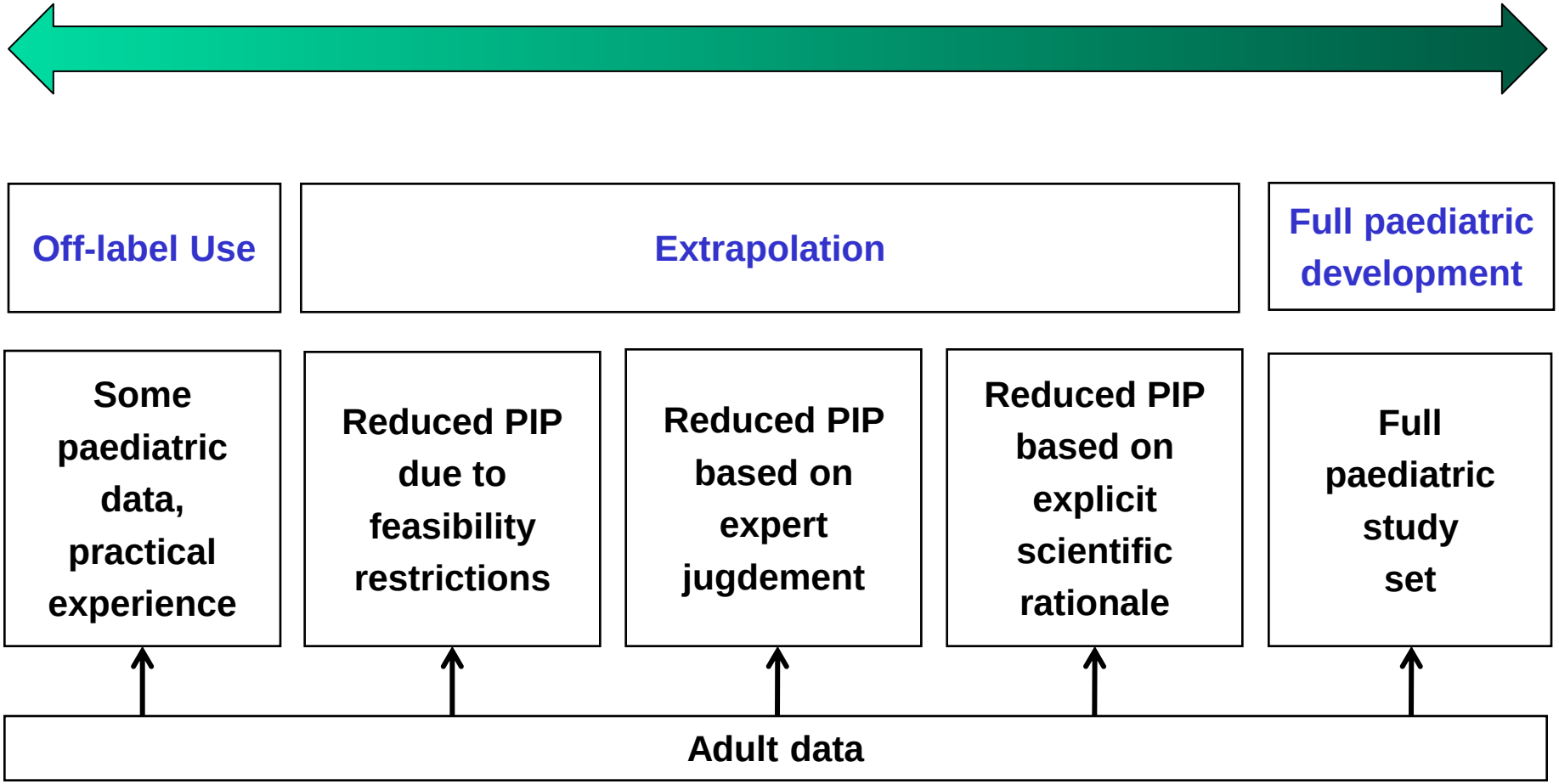
Rationale for extrapolation

1. **Avoid ‚unnecessary' studies – if extrapolation from other sources is scientifically justified**
   - Ethics / efficiency / ressource allocation

2. **Feasibility restrictions**
   - Apply extrapolation principles for rational interpretation of the limited evidence in the context of data available from other sources

Status quo:

Evidence base for medicine use in children



Extrapolation Framework

1. Rationale for extrapolation
   - scientific, clinical practice, ethical issues
   - feasibility

2. Develop quantitative assumptions on the similarity of the disease, PK/PD and clinical response

3. Define tools (e.g. M&S) and studies needed to complete the knowledge gap and to validate the assumptions

4. In light of emerging data test previous assumptions and if needed modify assumptions

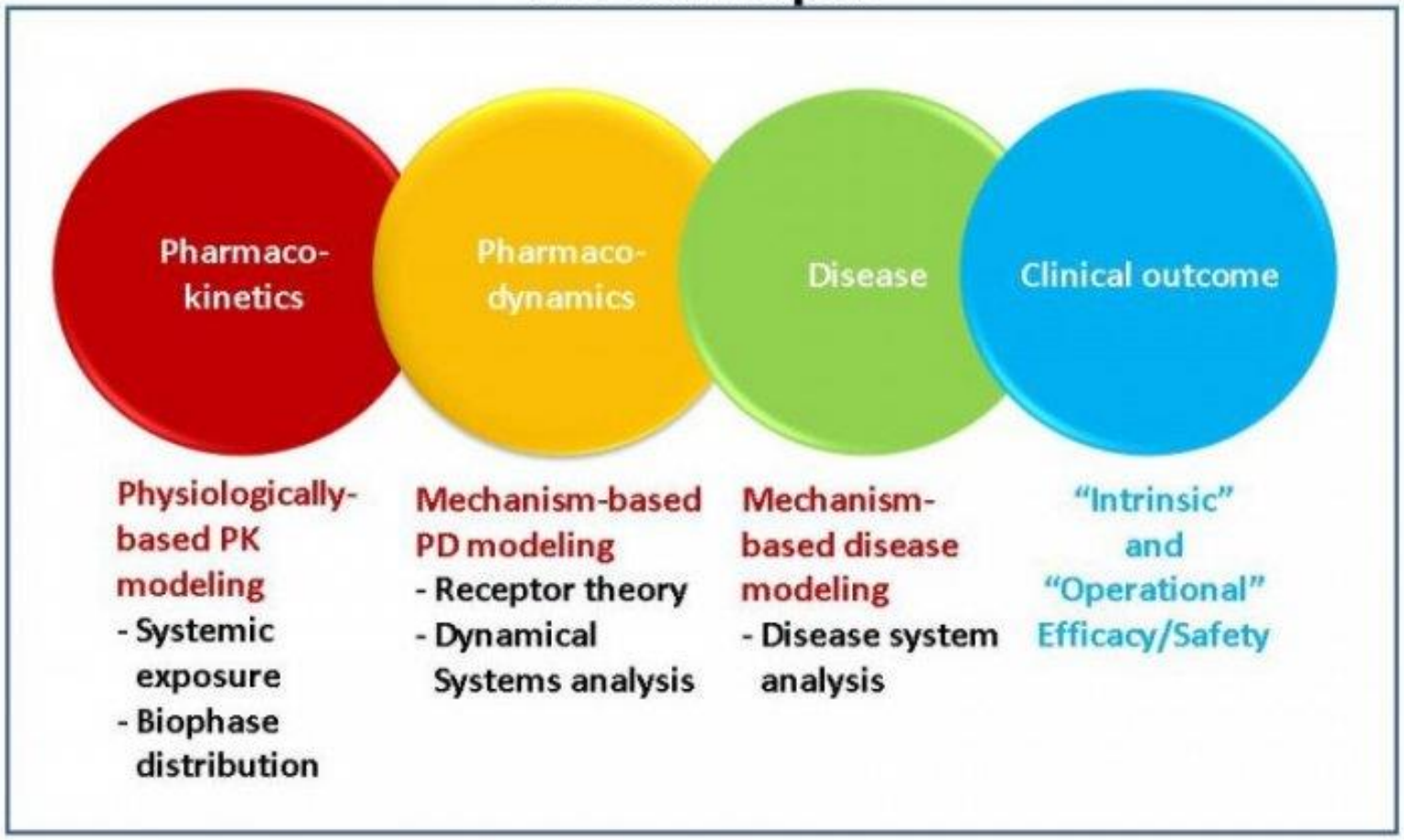
5. Interpretation of the limited data in the target population in the context of information extrapolated from the source population

6. Evaluate impact of violation of the assumptions. Define strategies to mitigate risks and further evaluate assumptions

Adapted from E. Manolis

		Pharmacology	Disease	Clinical response
SOURCE POULATION **Adults**				
TARGET POPULATION **Children, different paediatric age groups**	**Extrapolation concept**			
	Mechanisms	Age-related differences in - ADME - mode of action - PD effects (E-R) - toxicity	Age-related differences in - aetiology - pathophysiology - manifestation - progression - Indicators	Age-related - differences, - applicability, - validation of efficacy & safety endpoints
	Quantitative evidence	PB-PK/PD models Pop-PK/PD models Covariates: - age, maturation, etc - disease, comorbidity ➢ existing data ➢ progressive input of emerging data	Quantitative synthesis of natural history data Disease progression models Covariates: - age - disease types, severity - comorbidity	Quantitative synthesis or meta-analysis of treatment data Disease response models Covariates: - age - disease types, severity - comorbidity
	Prediction	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety per age group	Describe/predict differences in natural course of disease progression by age group	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by age group
	Extra-polation plan	PK studies or PK/PD studies needed for confirmation of doses in target population	Epidemiological data - natural history data - SOC treatment in target population	- Design of clinical studies - Sample size(s) required in target population to conclude on benefit-risk balance

Mechanism-based PKPD modeling the concepts



Danhof M. et al., (2007) Ann. Rev. Pharmacol. Toxicol. 47: 357-400.

Extrapolation concept
Issues to be resolved

How to …

- judge the quality and quantity of existing data?
- weigh the strength of prior information?
- quantify similarity of PK/PD, disease progression, clinical response to tx?
- quantify the uncertainty of extrapolation assumptions?
- integrate expert judgement in the extrapolation concept?

SOURCE POULATION
Adults

TARGET POPULATION
Children, different paediatric age groups

		Pharmacology	Disease	Clinical response
Extrapolation concept	**Mechanisms**	Age-related differences in - ADME - mode of action - PD effects (E-R) - toxicity	Age-related differences in - aetiology - pathophysiology - manifestation - progression - Indicators	Age-related - differences, - applicability, - validation of efficacy & safety endpoints
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Extrapolation plan

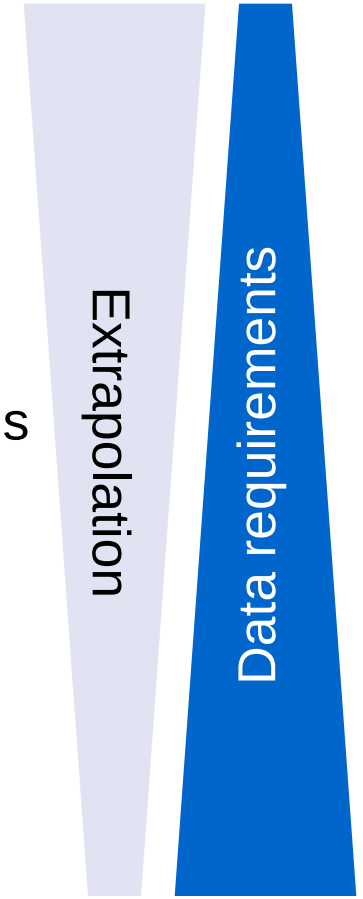
Generate a set of rules and methodological tools for the **reduction of data requirements** (*types of studies, design modifications, number of patients*) **in accordance with**

- Predicted degree of similarities
- Strength of existing evidence (≠ uncertainty)

- Should confirm the extrapolation concept
- Should complement the information extrapolated from source population(s)

Inventory of extrapolation approaches used in PIPs

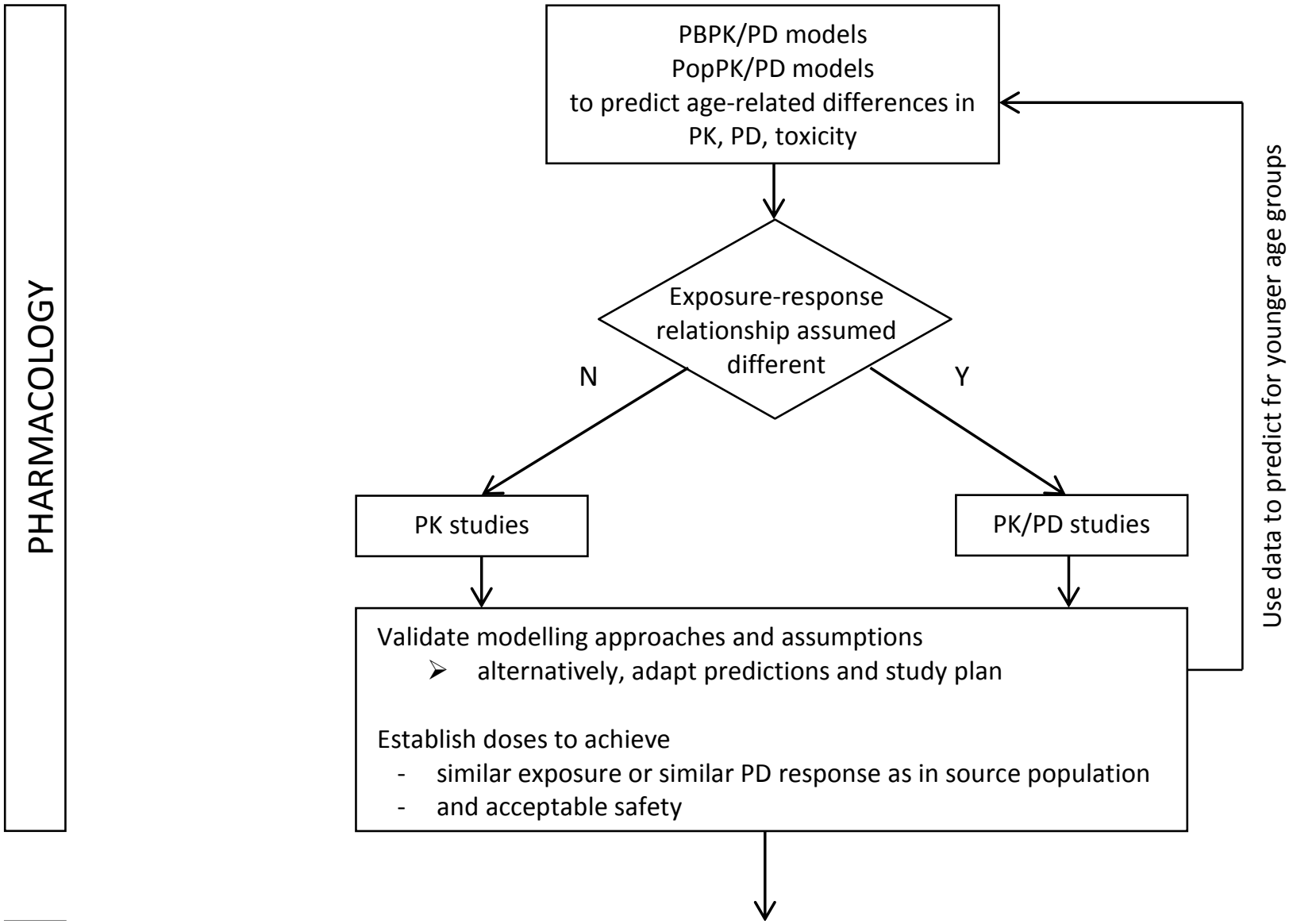
- PK/PD studies only (including M&S)
- Dose-ranging or dose-titration studies
- Non-controlled ‚descriptive' efficacy / safety study
- Controlled study but ‚arbitrary' sample size
- Larger significance level, lower %age confidence intervals
- Studies powered on surrogate endpoint
- Intrapolation (bridging)
- Modelling prior information from existing data sets (Bayesian, meta-analytic predictive)
- etc



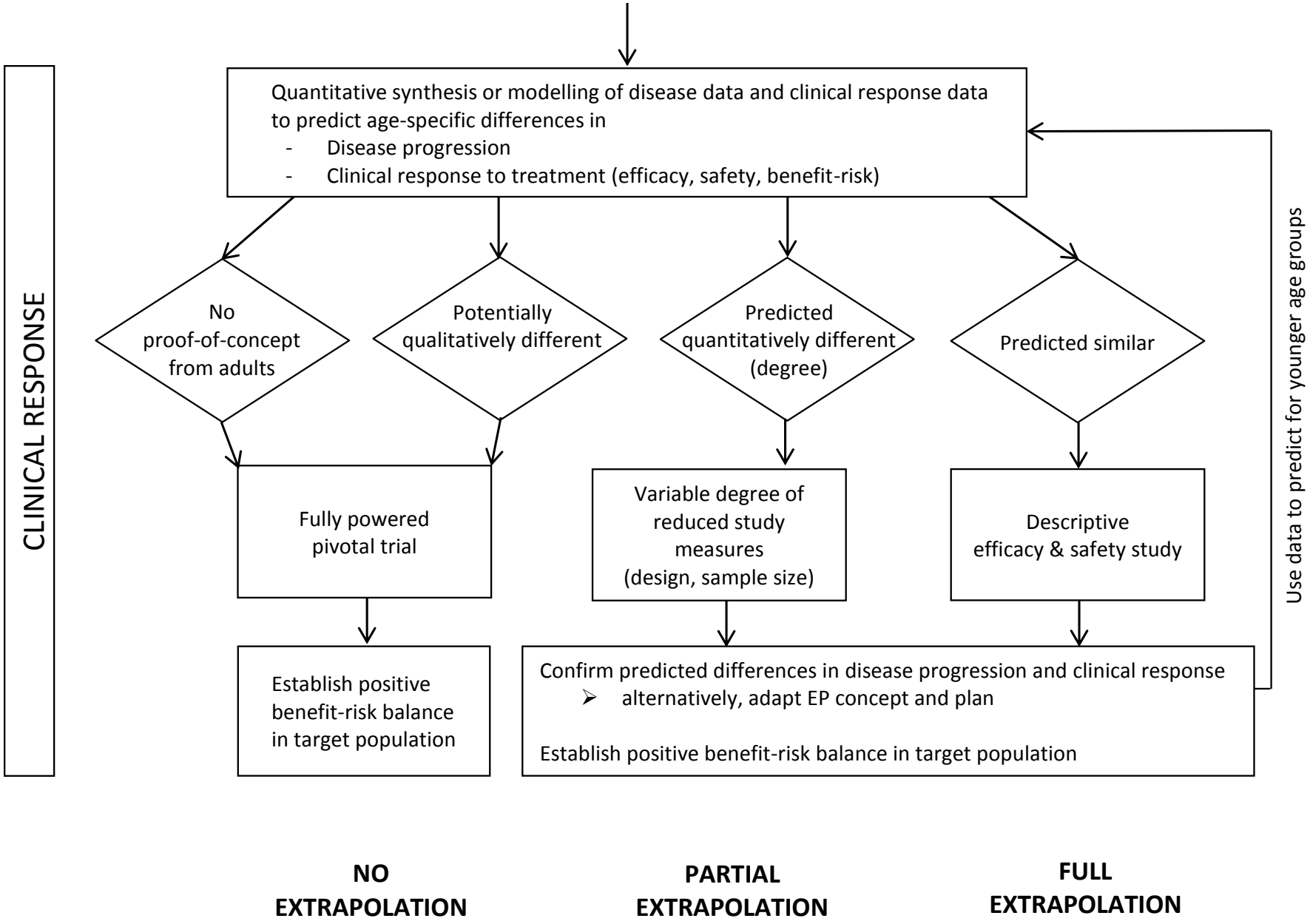
Extrapolation plan
Issues to be resolved

Algorithm(s) linking degree of similarity with reduction in data requirement

EMA extrapolation decision tree (proposal)



EMA extrapolation decision tree (continued)



		Pharmacology	Disease	Clinical response
SOURCE POULATION **Adults**	**EP concept** **Prediction**	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety per age group	Describe/predict differences in natural course of disease progression by age group	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by age group
	Extrapolation plan	PK studies or PK/PD studies needed for confirmation of doses in target population	Epidemiological data - natural history data - SOC treatment in target population	- Design of clinical studies - Sample size(s) required in target population to conclude on benefit-risk balance
TARGET POPULATION **Children, different paediatric age groups**	**Validation**	Validate - modelling approaches - modelling assumptions Establish appropriate doses in the target population ➢ alternatively, adapt EP concept and plan	Confirm predicted differences in disease progression	Confirm predicted differences in clinical response Establish positive benefit-risk in target population
	Further validation	PK/PD data from - phase III trials - post MA studies	Epidemiological data Other drug developments	Post MA studies Prospective meta-analyses Pharmacoepidemiological data Other drug developments

Validation

Use of emerging data to

- Validate the modelling approaches used for extrapolation
- Confirm the PK and PD model assumptions and predictions
- Establish appropriate doses, drug exposures, or PD response

- Confirm the predicted degree of differences in disease progression and clinical response (efficacy, safety)
- Establish positive benefit-risk in target population

➢ Alternatively, revisit assumptions and refine EP concept and plan

➢ Iterative loops when moving into successive population subsets (age)

Mitigating risk and uncertainty

With increasing degree of extrapolation

→ decreasing amount of data for validation

⇒ increasing risk of false conclusions

➢ Collateral criteria and measures:

- Biological plausibility (in-vitro, preclinical and clinical data)
- Iterative loops of model building and data generation
- Concordant responses on different endpoints
- Prospectively planned meta-analysis including future trials
- Confirmation by post-authorisation data
- Validation of extrapolation approaches over several developments in related conditions, or related medicines

Validation
Issues to be resolved

How to

- validate assumptions in the extrapolation concept?
- formally interprete data in target and source population in conjunction?
- deal with uncertainty and risk?
- analyse and report post-authorisation data to support extrapolation?

Need to agree on consistent use of terminology

Extrapolation – intra/interpolation – bridging

Similarity – differences

Assumption – hypothesis – prediction

Validation – confirmation – evaluation

Strength of evidence – certainty

Extrapolation concept – plan – validation

etc.

Summary: Issues to be resolved …

- How to weigh the strength of prior information?
- quantify similarity of PK/PD, disease progression, clinical response?
- quantify the uncertainty of extrapolation assumptions?
- integrate expert judgement in the extrapolation concept?
- link degree of similarity with reduction in data requirement
- validate assumptions in the extrapolation concept?
- formally interprete data in target and source population in conjunction?
- deal with uncertainty and risk?
- analyse and report post-authorisation data to support extrapolation?
- Terminology