Medicines & Healthcare products Regulatory Agency

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Extrapolation; regulatory need, examples and emerging guidance.

Rob Hemmings, MHRA

Acknowledgements to Andrew Thomson & Cécile Ollivier

Abstract

Extrapolation is defined as ‘extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), 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 reducing the amount of, or general need for, additional information (types of studies, design modifications, number of patients required) needed to reach conclusions for the target population, or condition or medicinal product’. The talk will illustrate the potential need for, and benefits of, this concept in regulatory work with a primary focus on extrapolation from adults to children. An overview of the EMA Reflection Paper on this topic will be presented and discussed, highlighting areas for further discussion and research.

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Definition

Extrapolation is defined as ‘extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), 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 reducing the amount of, or general need for, additional information (types of studies, design modifications, number of patients required) needed to reach conclusions for the target population, or condition or medicinal product’.

I will talk about extrapolation from adults to paediatric age subsets

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Contents

- Need for extrapolation
- Benefits of extrapolation
- EMA Reflection Paper
- What changes?

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Need for extrapolation: Can we extrapolate?

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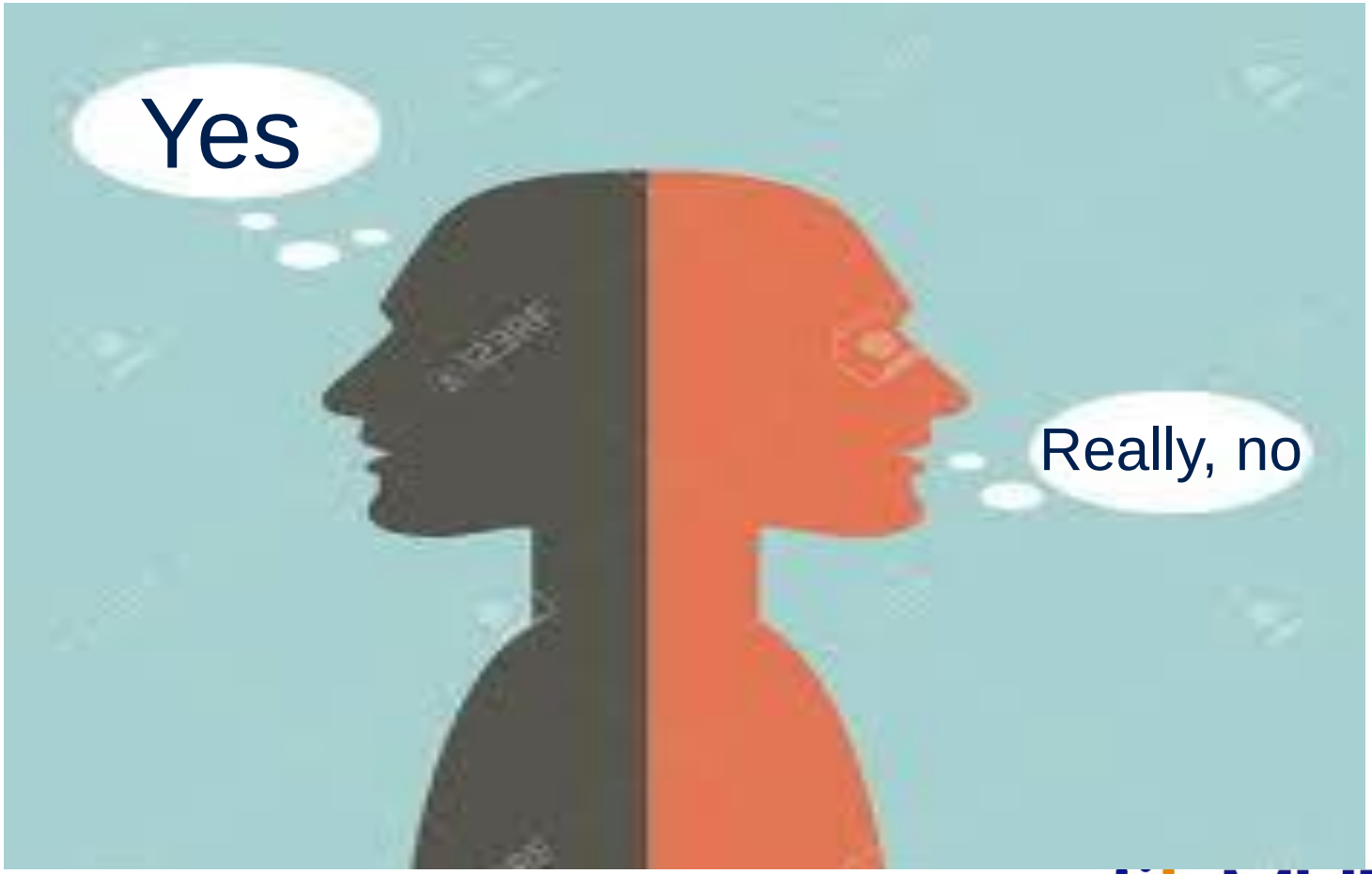
Need for extrapolation: Can we extrapolate?



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Need for extrapolation: Can we extrapolate?

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Need for extrapolation: How to extrapolate?

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Need for extrapolation

- Earlier efforts addressed something about ‘How’
- The EMA framework attempts to bring quantitative approaches to the basis for, as well as the methods for, extrapolation
- *a priori* rationale, based on development in adults, that a safe and efficacious dose exists in children enabling different approaches to clinical trial design and success criteria.

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Benefits of extrapolation

- More targeted paediatric research
- Robust evidence for decision making without fully powered RCTs
- Not directly to address small populations / lack of feasibility, but it should anyway help…

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EMA Reflection Paper

First published	13/10/2017
Last updated	13/10/2017
Consultation start date	**13/10/2017**
Consultation end date	**14/01/2018**
Email address for submissions	extrapolation@ema.europa.eu

4 Reflection paper on the use of extrapolation in the
5 development of medicines for paediatrics
6 Draft

Draft agreed by Biostatistics Working Party	September 2017
Draft agreed by Modelling and simulation group	September 2017
Draft agreed by PKWP	September 2017
Draft agreed by Scientific Advice Working Party	September 2017
Draft Adopted by PRAC	29 September 2017
Draft Adopted by PDCO	12 October 2017
Draft Adopted by CHMP	12 October 2017
Start of public consultation	13 October 2017
End of consultation (deadline for comments)	14 January 2018

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Comments should be provided using this template. The completed comments form should be sent to extrapolation@ema.europa.eu

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Keywords	Paediatrics, extrapolation, medicine development, biostatistics, modelling and simulation

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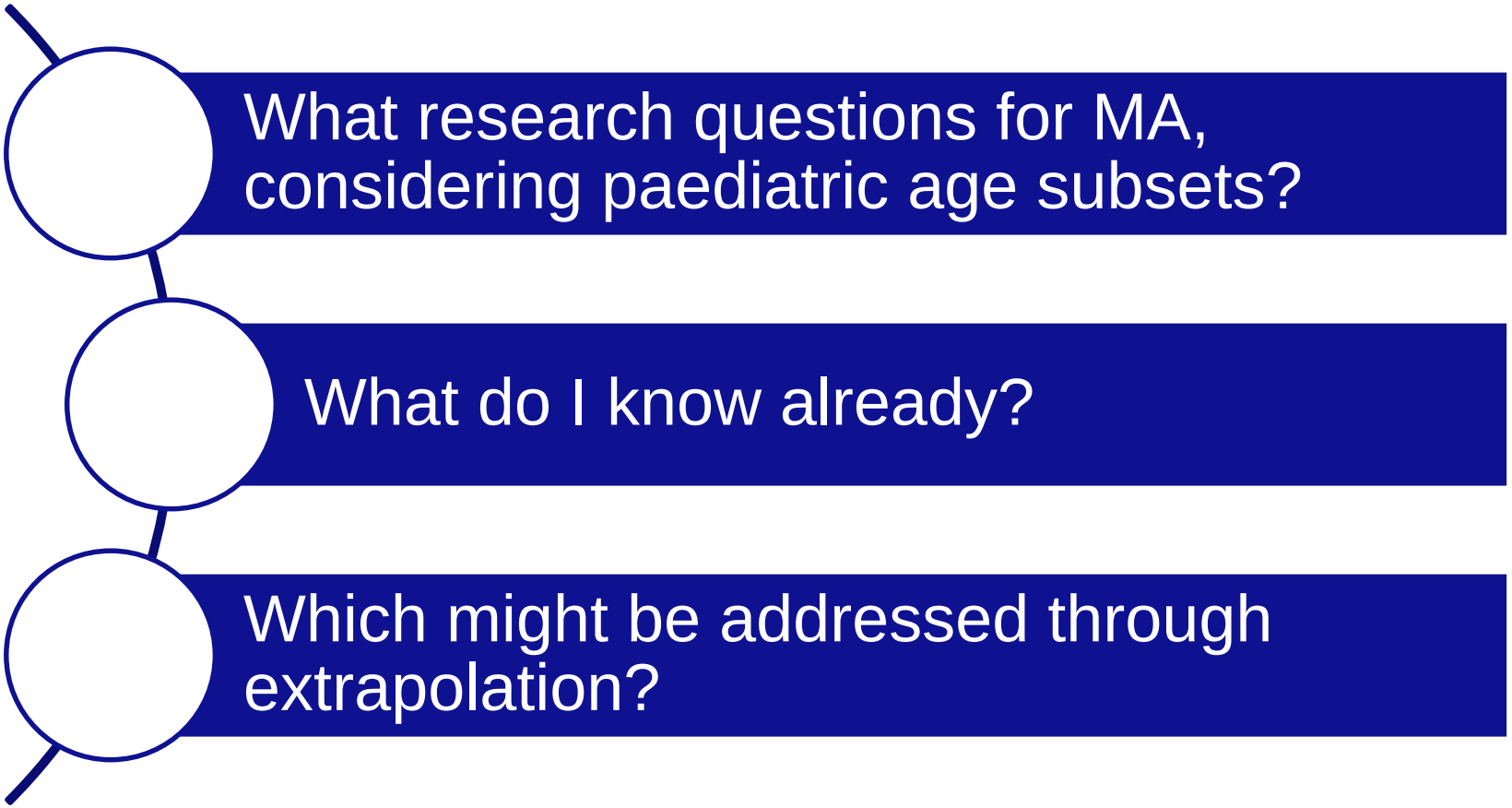
EMA Reflection Paper



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EMA Reflection Paper

Concept

- Existing information should be quantified.
- Assess whether clinical efficacy can be predicted

Plan

- Specific objectives(s) for the tests and trials to address identified assumptions and uncertainties

Mitigation

- It may be important to gather additional data post-authorisation to address residual uncertainties.

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Extrapolation concept

- Consider at least 3 areas: disease, drug pharmacology and populations

These 3 statements are not the same:

- Is the disease similar in children and adults?
- How similar is the disease in children and adults?
- **What data do we have to assess how similar the disease is?**

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SOURCE POULATION Adults

TARGET POPULATION Children, paediatric age groups

Extrapolation concept

	Pharmacology Drug disposition & effect	Disease manifestation & progression	Clinical response to treatment
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, size, maturation, etc - disease, comorbidity,	Quantitative synthesis of natural disease data Disease progression models Covariates: - age, maturation - disease types, severity - comorbidity	Quantitative synthesis or meta-analysis of treatment data Disease response models Covariates: - age - disease types, severity - comorbidity
	➢ existing data ➢ progressive input of emerging data		
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
	➢ refine predictions using emerging data		

EXTRAPOLATION CONCEPT

Extrapolation concept

If differences in disease, drug pharmacology and/or clinical response can be quantified with sufficient precision, an extrapolation plan might be constructed based on the relationship between dose, exposure and pharmacodynamic response or efficacy. Equally the understanding of disease and pharmacology might be such that a mechanistic model can be developed.

No restrictions on ‘How’; defined by identified uncertainties and assumptions

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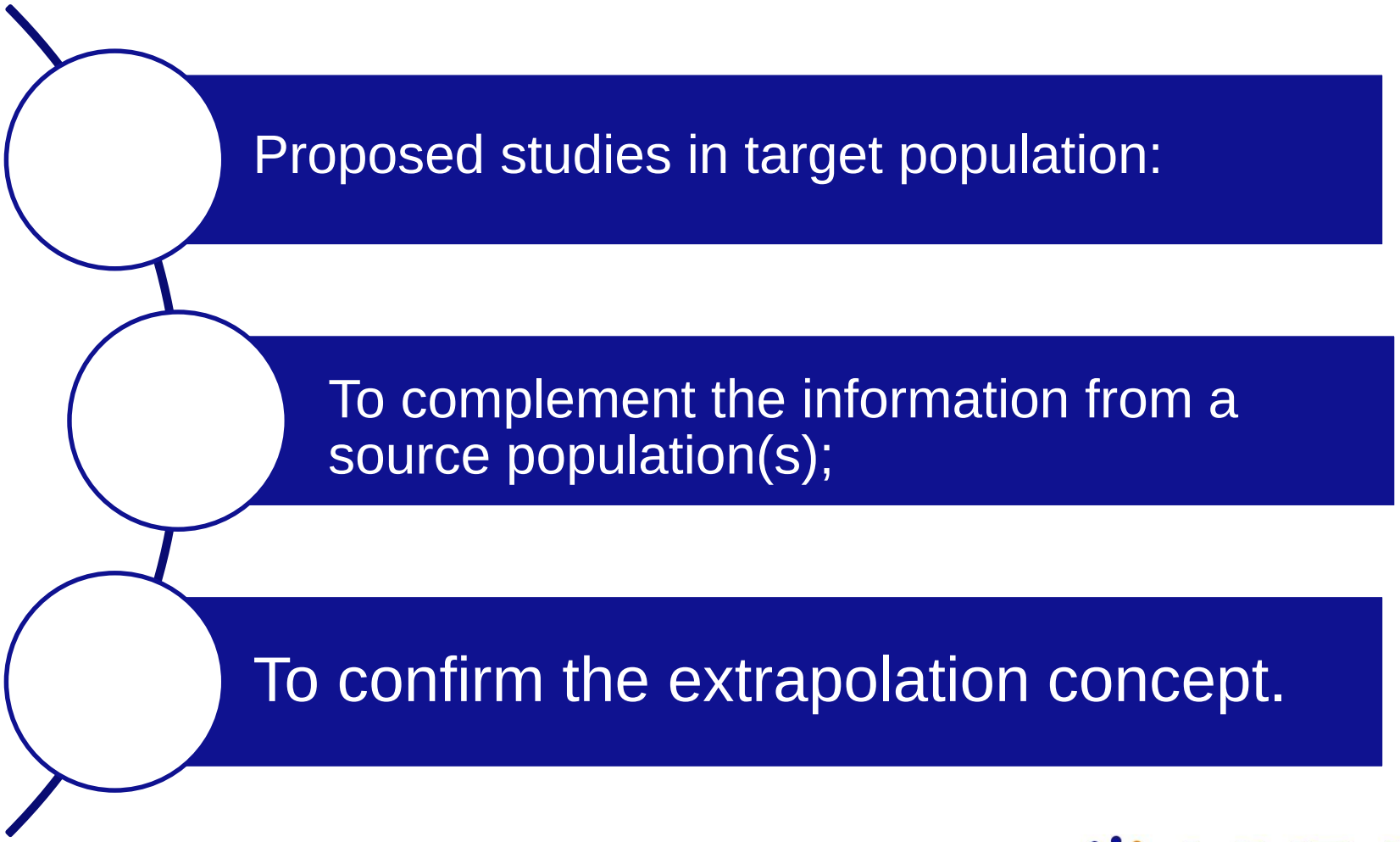
Extrapolation plan



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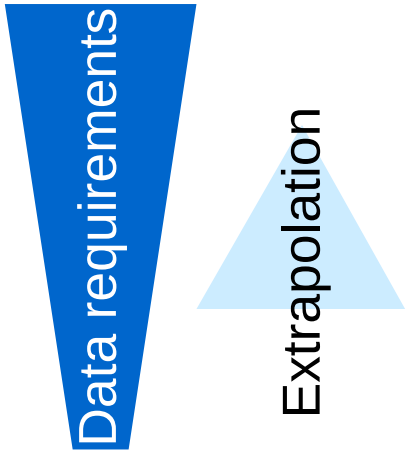
Extrapolation plan

Reduction of data requirements in accordance with:

- degree of similarities;
- strength of evidence (degree of uncertainties).



No extrapolation - Full paediatric study programme

Extrapolation:

- Controlled E&S study with reduced sample size
- Non-controlled ‚descriptive' E&S study
- PK
- PK/PD study
- etc.

Extrapolation plan

- “Tests and trials should primarily aim to generate evidence that strengthens and ultimately, based on success criteria, validates the extrapolation concept. This validation confirms whether regulatory decisions can rely on the initial, or revised, predictions for the expected effects of treatment in the target population or if more data needs to be generated.”

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An easy example: anti-infectives Research question: efficacy

Concept

- Concentration-response established in-vitro and in adults
- Agree this applies regardless of patient age
- If exposure is matched, regardless of age subset, efficacy can be predicted.

Plan

- Understand drivers of exposure in different age subsets
- Confirm posology that matches, according to certain success criteria, exposure.

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Mitigation of uncertainty and risk

- Data generated in the target population may not be sufficient to address all uncertainties related to efficacy and safety

- In some situations it may be important to gather additional data post-authorisation to address residual uncertainties.

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Integrating clinical efficacy data

- Less ‘natural’ for extrapolation: which specific uncertainty is addressed?
- Bayesian or Frequentist
- How to weight information from the source population:
  - Quantitative approaches to understand disease, drug pharmacology and population similarities and differences?
  - Expert guesswork
  - ~~Sample size to get P<5% minus feasible recruitment target = weight given to source population data~~
- No carte blanche to use adult data in all paediatric development programmes.

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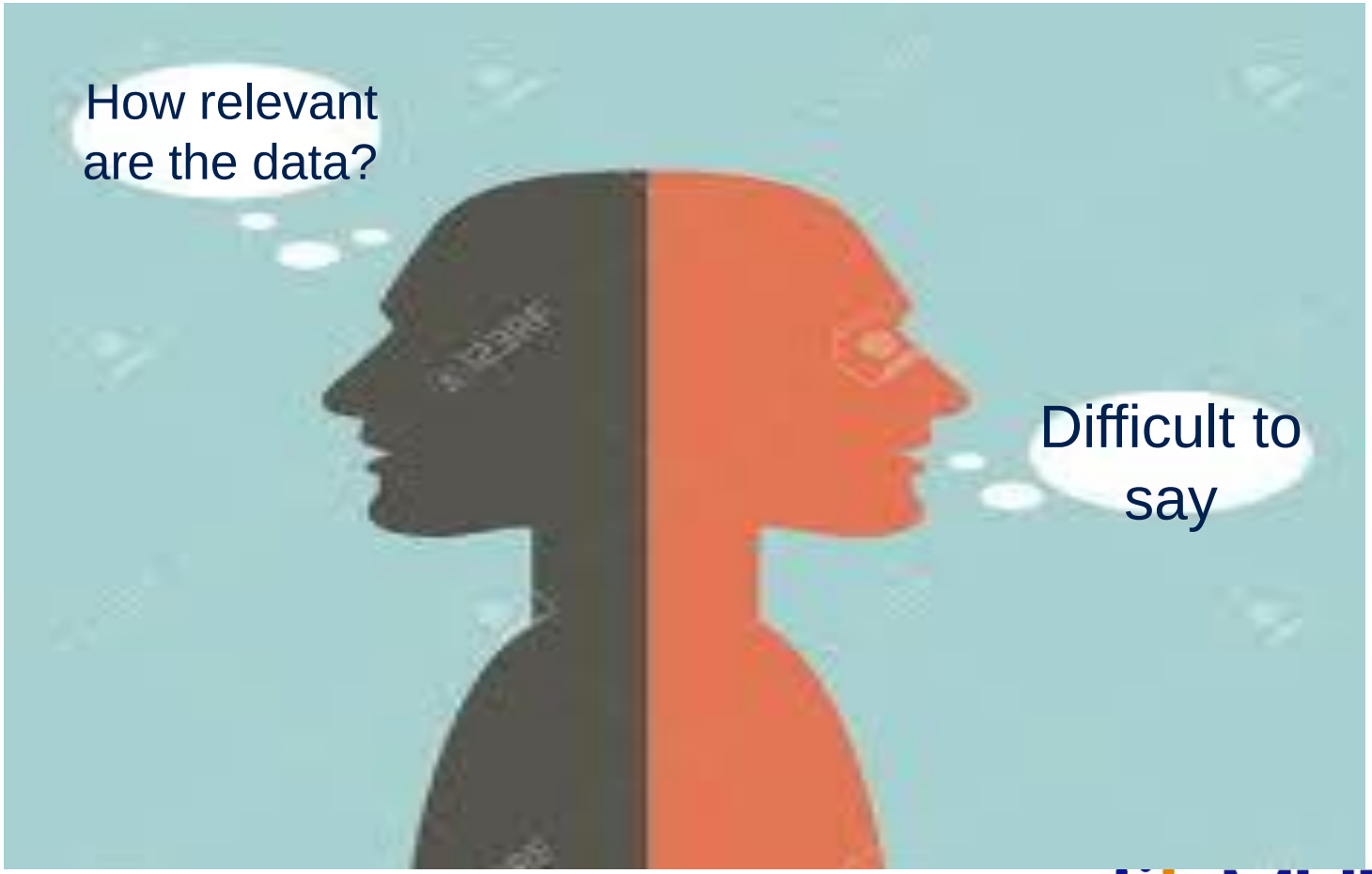
How to weight information from the source population



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How to weight information from the source population

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Integrating clinical efficacy data

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What changes?

- Increase clarity for regulators and developers
  - Discuss objectives as much as designs
- More work up front; quantitative sciences to be engaged earlier, and together?
- Enhanced programme in adults to support demonstration of efficacy and to facilitate extrapolation

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What changes?

- Pivotal evidence: new methods, same principles?
- ICH E11(R1) and the Paediatric Extrapolation Expert Working Group
- ‘Success criteria’
  - RCT; $p<0.05$ by convention
  - BE; (80-125) by convention
  - What if we have no convention?

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