# Dose selection and benefit-risk assessment in chronic paediatric diseases

**Oscar Della Pasqua**

# Dose Selection and Benefit-Risk Assessment in Chronic Paediatric Diseases

*Conclusions & recommendations*

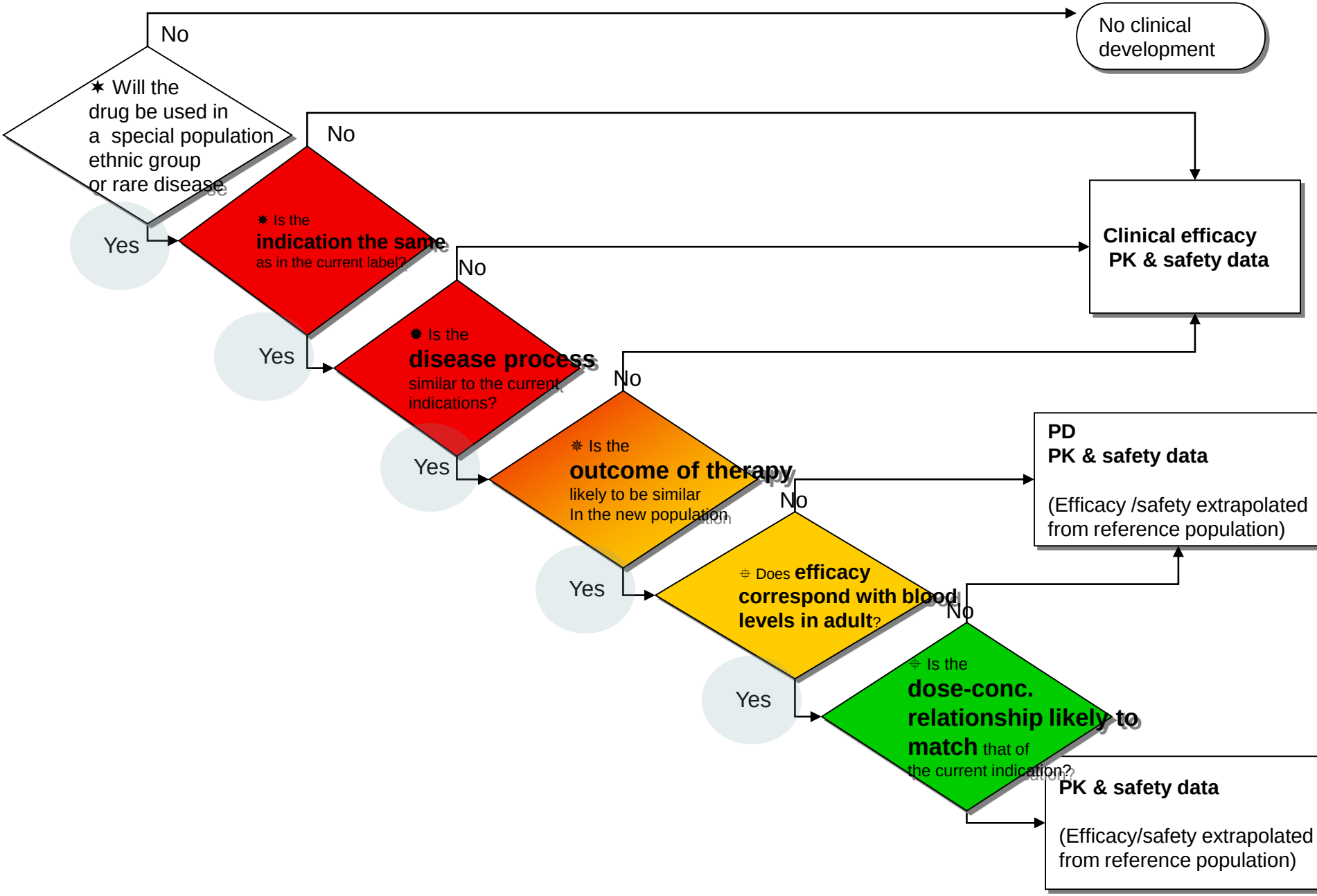
Points to consider in a paediatric development plan: what is the right dose?

Model-based PK and PKPD bridging

Extrapolation studies and risk assessment

Extrapolation studies: Benefit-risk balance

# ICH E11 – Decision tree for paediatric studies



**If a paediatric medicine is to be approved, which are the long term net benefits?**

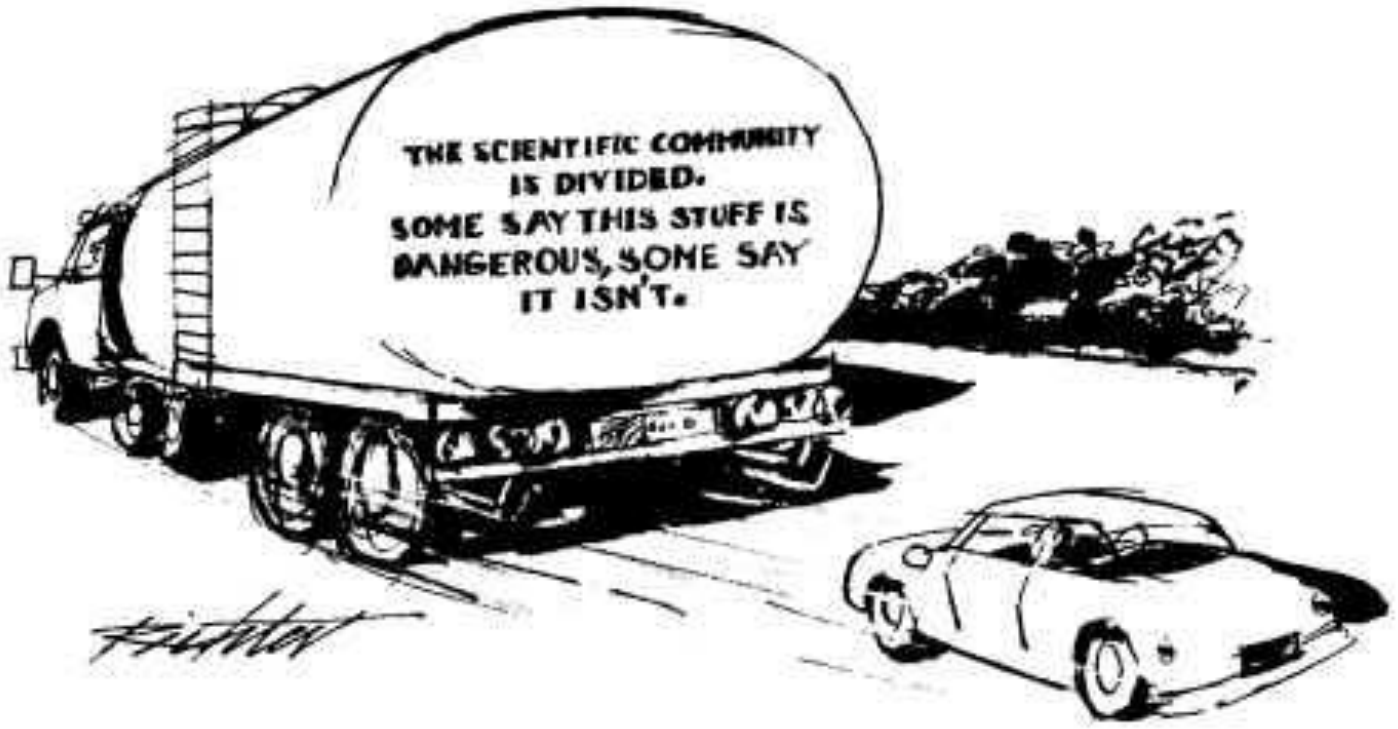



FIGURE 2.2 SOURCE: Drawing by Richter; ©1988 The New Yorker Magazine, Inc.

# Adverse Drug Reactions – 15 drugs ~ 41% of case reports


January 16, 2014 — Special Report on Children , 2008-2012

| Rank | Drug name | name* | Cases | Medical use* | Psych** | Most freq ADE | 2d most freq ADE |
|---|---|---|---|---|---|---|---|
| 1 | Infliximab | REMICADE | 1772 | Crohn's Disease | N | Crohn's disease | Ulcerative colitis |
| 2 | Montelukast | SINGULAIR | 944 | Asthma | Y | Suicidal ideation | Aggression |
| 3 | Somatropin | NUTROPIN | 606 | GH deficiency | N | Headache | Convulsion |
| 4 | Baclofen | LIORESAL | 579 | Muscle spasticity | N | Hypertonia | Drug ineffective |
| 5 | Isotretinoin | CLARAVIS | 447 | Acne | Y | Suicidal ideation | Depression |
| 6 | Methylphenidate | CONCERTA | 418 | ADHD | Y | Sudden death | Aggression |
| 7 | Lamotrigine | LAMICTAL | 335 | Epilepsy | Y | Convulsion | Stevens-Johnson synd |
| 8 | Lisdexamfetamine | VYVANSE | 314 | ADHD | Y | Suicidal ideation | Aggression |
| 9 | Aripiprazole | ABILIFY | 297 | Bipolar disorder | Y | Weight increased | Dystonia |
| 10 | Ibuprofen | MOTRIN | 242 | Pyrexia | N | Hypersensitivity | Renal failure acute |
| 11 | Etanercept | ENBREL | 231 | Juvenile arthritis | N | Injection site pain | Vomiting |
| 12 | Atomoxetine | STRATTERA | 227 | ADHD | Y | Suicidal ideation | Chest pain |
| 13 | Quetiapine | SEROQUEL | 210 | Bipolar disorder | Y | Weight increased | Tardive dyskinesia |
| 14 | Levetiracetam | KEPPRA | 206 | Epilepsy | Y | Convulsions | Drug ineffective |
| 15 | Risperidone | RISPERDAL | 195 | Bipolar disorder | Y | Aggression | Weight increased |

* Most frequently cited in case reports. **Psychiatric side effects > 25% of reports.

GH = Growth hormone. ADHD = Attention deficit hyperactivity disorder. Additional note in Methods Summary

# EMA: BENEFITS AND RISKS

| | |
|---|---|
| Favourable Effects | Uncertainty of Favourable Effects |
| Unfavourable Effects | Uncertainty of Unfavourable Effects |

**Definitions**

Favourable effects are any beneficial effects for the target population (often referred to as "benefits" or "clinical benefits") that are associated with the product.

Unfavourable effects are any detrimental effects (often referred to as risks, harms, hazards both known and unknown) that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients' health, public health, or the environment.

Uncertainties about both types of effects arise from variation, important sources of bias, methodological flaws or deficiencies (including GCP, compliance, etc.), unsettled issues, and limitations of the data set, e.g., due to sample size, study design, or duration of follow-up.

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COMMENTARY

# Pediatric Dose Selection

DR Abernethy[1] and GJ Burckart[1]

Selection of a drug dose in pediatrics is generally based on no or incomplete pharmacokinetic data. Traditionally, allometric, or scaling, techniques have been used; however, they have inherent limitations and may not make optimal use of the drug-specific clinical pharmacokinetic information that is available. Modeling is a tool that ho
approach tc

See COMMENTARY page 270

Dose selectio
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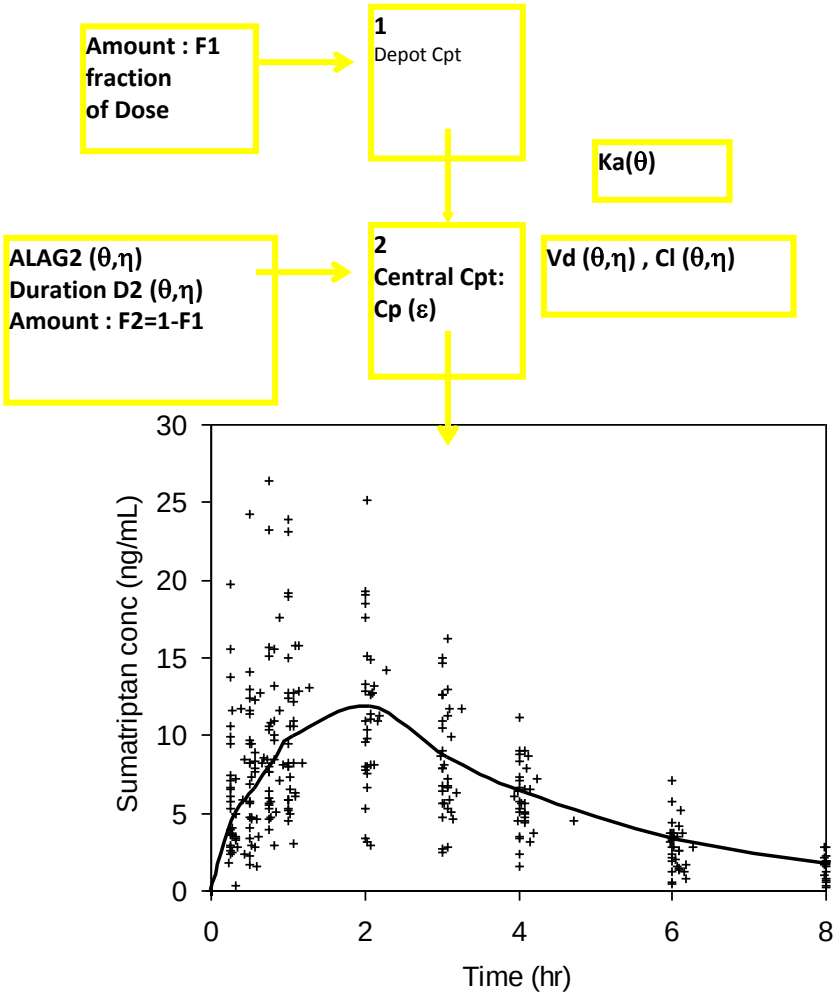
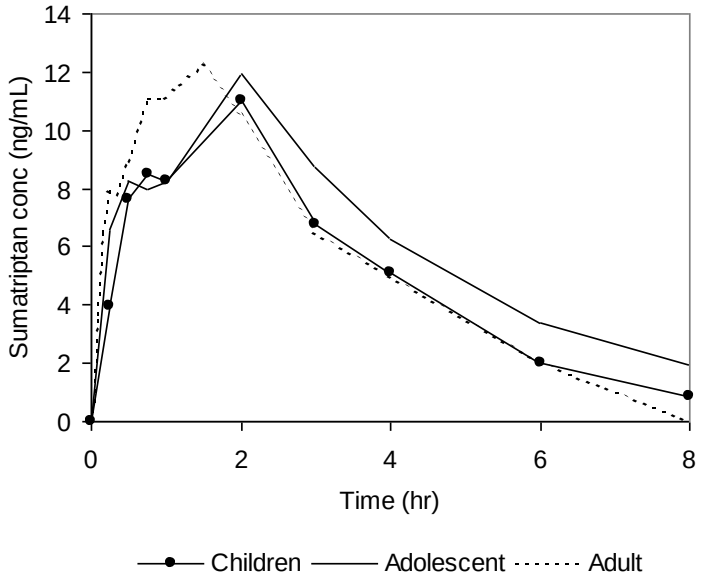
# A Model-Based Approach to Dose Selection in Early Pediatric Development

M Cella[1], F Gorter de Vries[1], D Burger[2], M Danhof[1] and O Della Pasqua[1,3]

Clinical Pharmacology & Therapeutics , 2010

# PK BRIDGING STUDY – ADULT DATA INTEGRATION

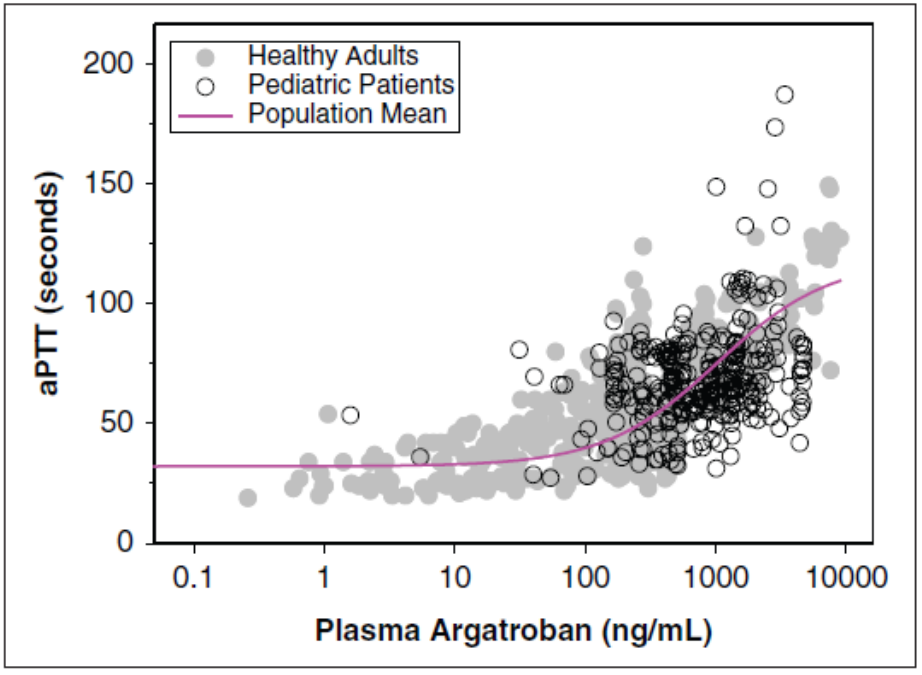


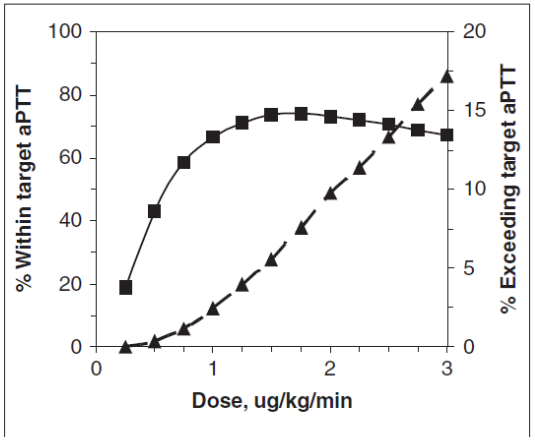



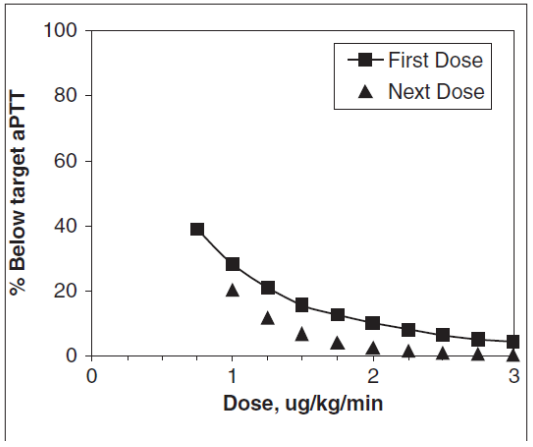

Population pharmacokinetic model
(common to all populations)

# Pharmacokinetic and Pharmacodynamic Basis for Effective Argatroban Dosing in Pediatri

*Rajanikanth Madabushi, PhD, Donna S. Cox, PhD, Mohammad Hossain, PhI*
*Duane A. Boyle, PharmD, Bela R. Patel, PhD, Guy Young, MD, Young-Moon Choi,*




*Journal of Clinical Pharmacology, 2011;51:19-28*

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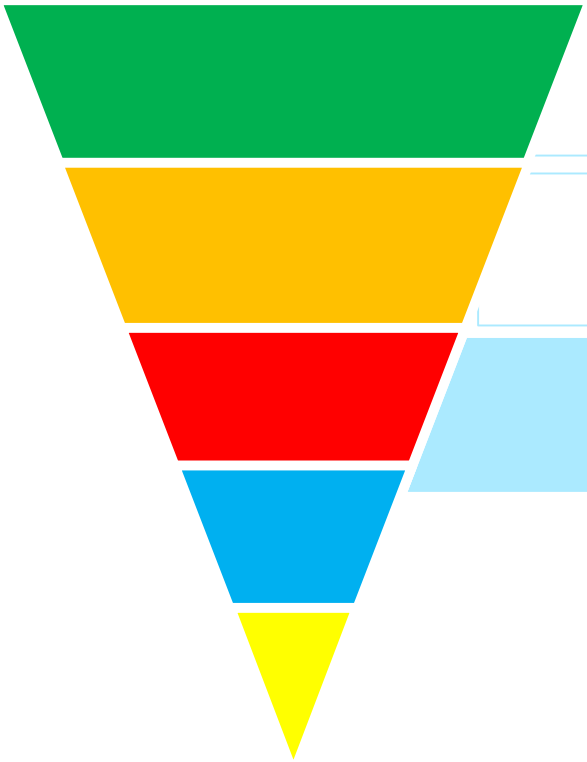

*Conclusions & recommendations*

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Extrapolation studies: Benefit-risk balance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 June 2012
EMA/129698/2012
Human Medicines Development and Evaluation

Concept paper on extrapolation of efficacy and safety in medicine development

Draft

As defined in the draft EMA concept paper, extrapolation may be generally defined as “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 reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product”

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e28; doi:10.1038/psp.2013.6

www.nature.com/psp

PERSPECTIVE

# Modeling and Simulation as a Tool to Bridge Efficacy and Safety Data in Special Populations

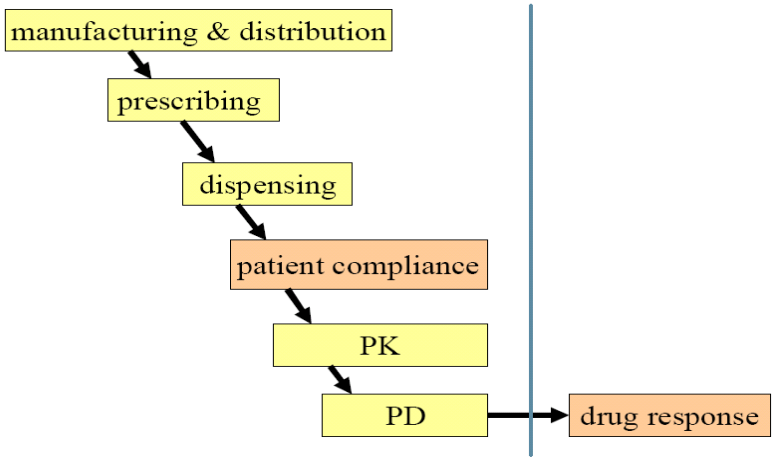
L Harnisch[1], T Shepard[2,3], G Pons[3,4] and O Della Pasqua[5]

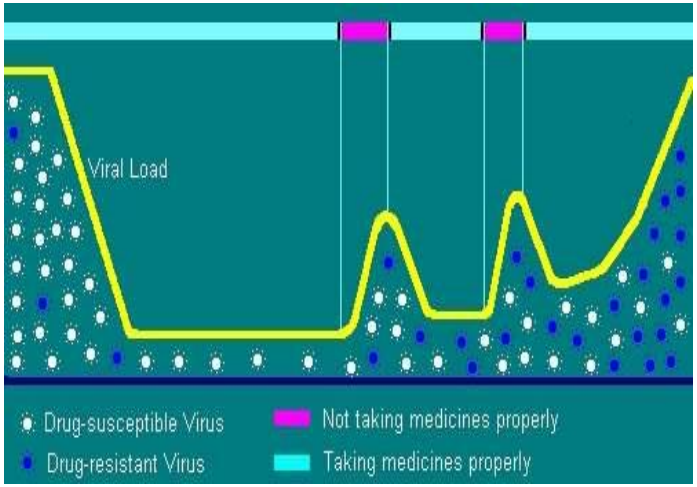
The registration and approval of novel medicines have traditionally been based on evidence arising from large prospective trials. Such an approach is often not possible or unsuitable to evaluate the benefit-risk balance in special populations (e.g., children, ethnic groups, rare diseases). Inferences by modeling and simulation can play a major role in evidence synthesis. A framework is proposed that promotes its acceptability and the basis for decision making during development, registration, and therapeutic use of drugs.
*CPT: Pharmacometrics & Systems Pharmacology* (2013) **2**, e28; doi:10.1038/psp.2013.6; advance online publication 27 February 2013

# Adherence to therapy

- Inadequate adherence to the prescribed dosing regimen is one of the major causes of viral failure.

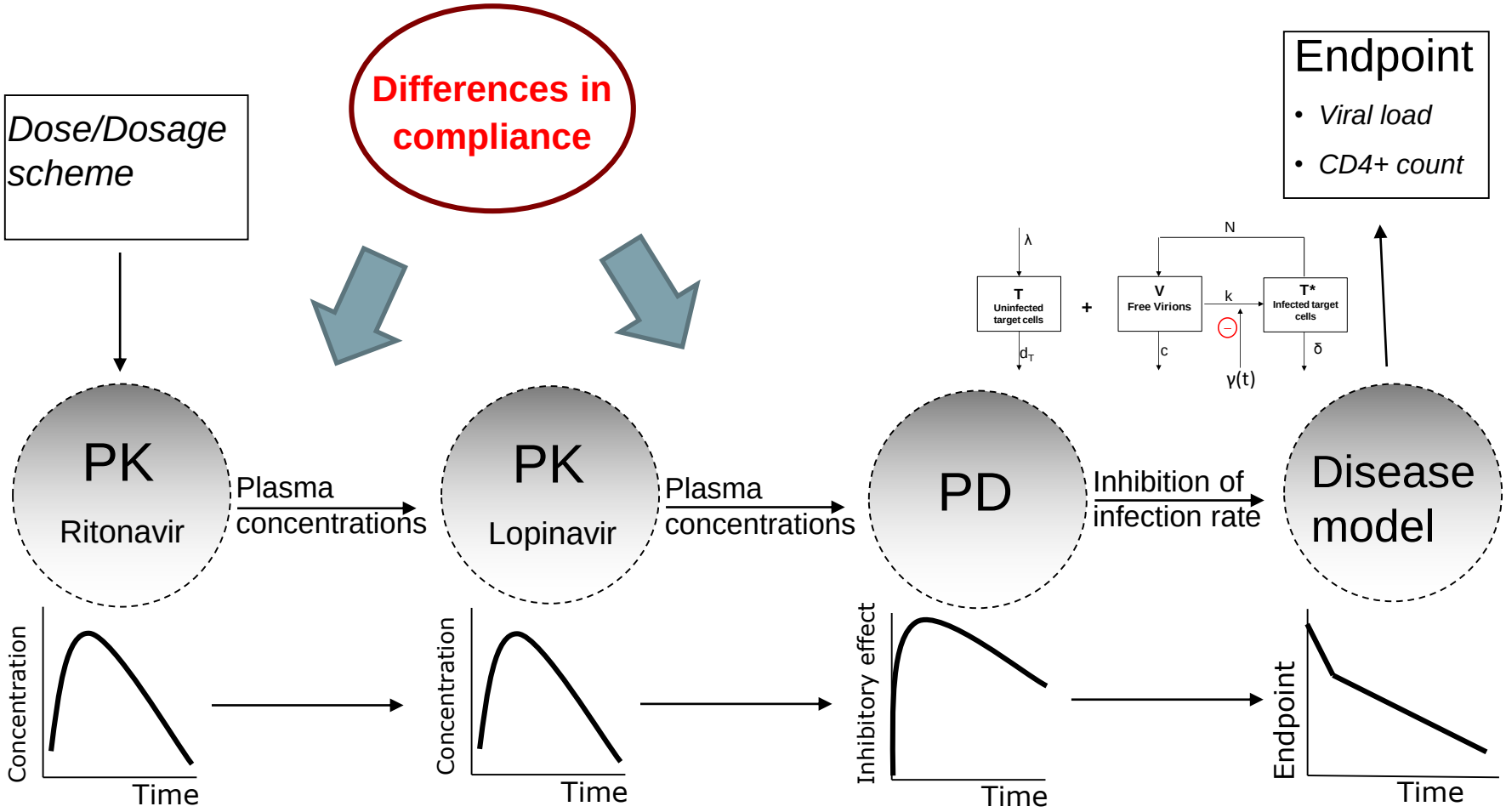
- The impact of poor adherence to antiretroviral therapy has never been evaluated in a systematic manner in children



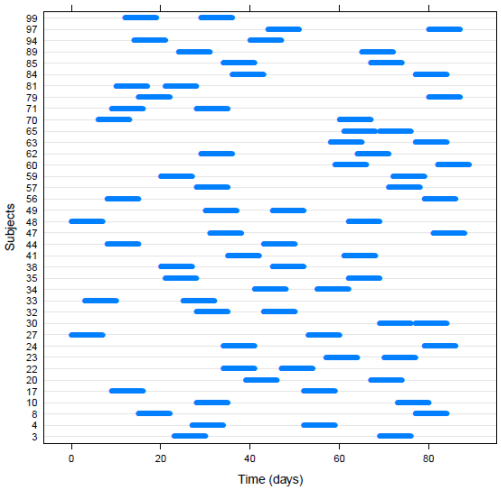

- Do different regimens alter the clinical implications of poor adherence to antiretroviral drugs?

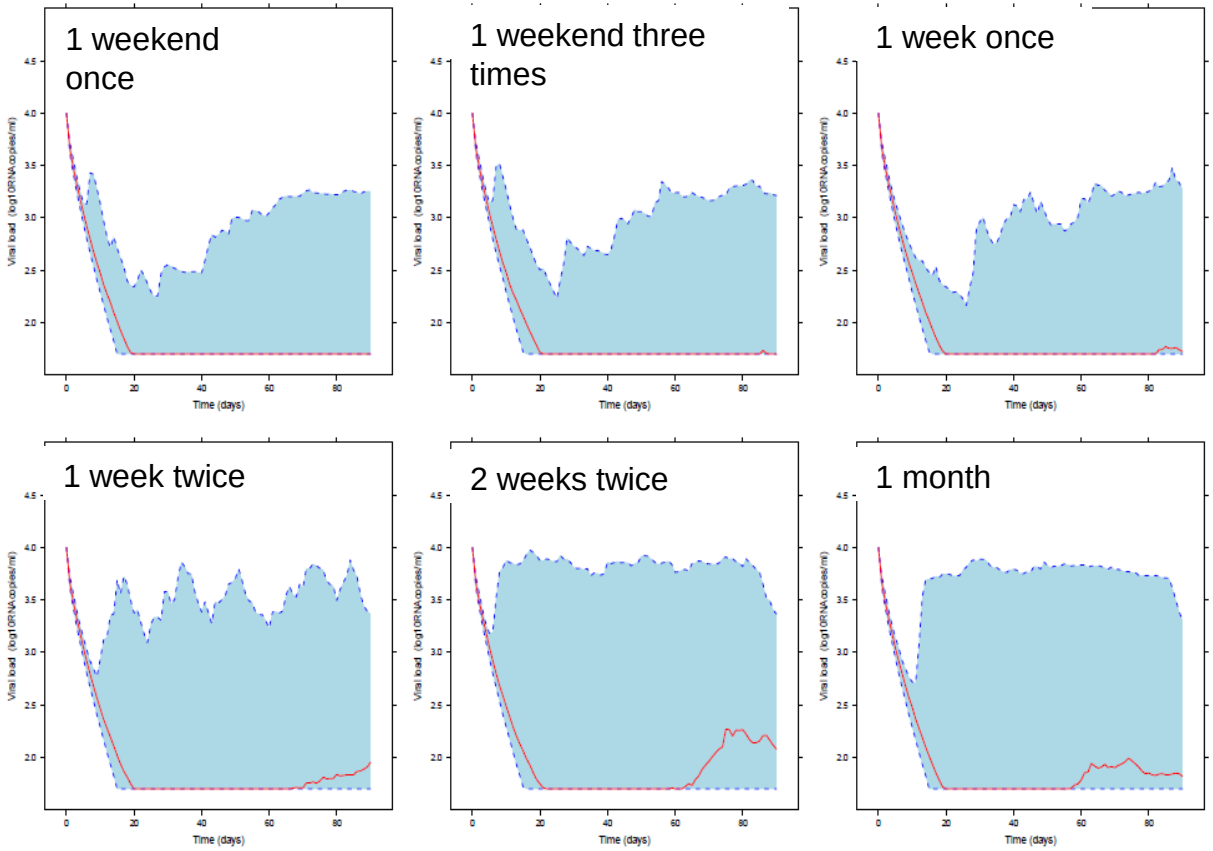
***Does an increase in dosing interval from twice to once daily increases the risk of clinical failure ?***



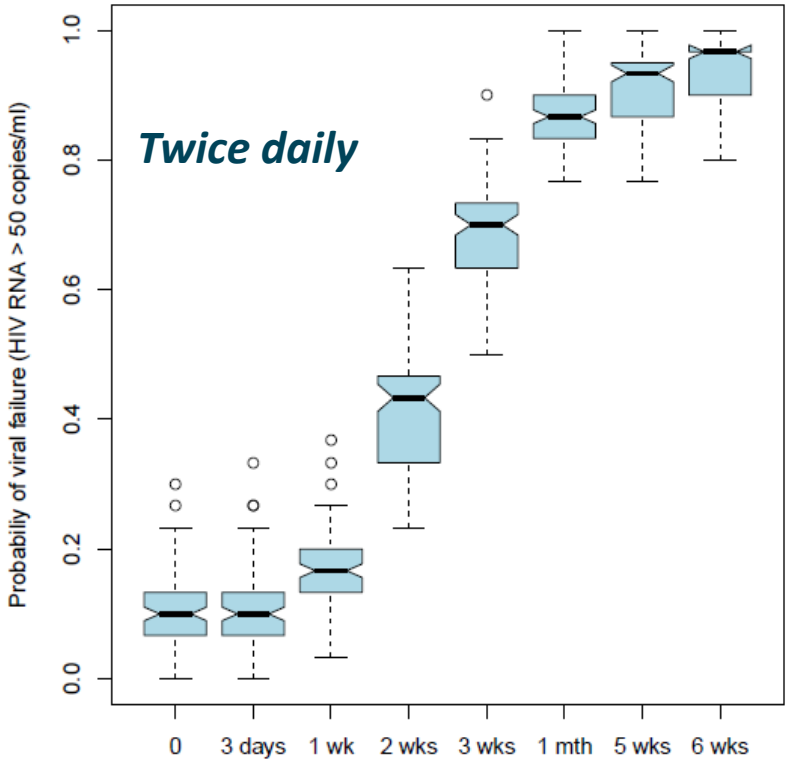
# CLINICAL IMPLICATIONS OF POOR ADHERENCE

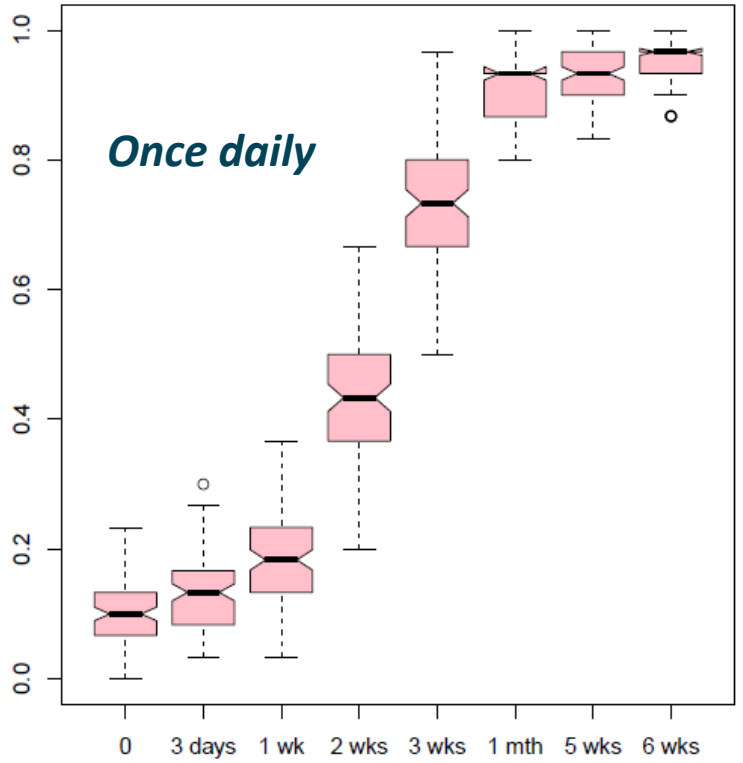
Assumption: 40% of patients showing variable adherence



# CLINICAL IMPLICATIONS OF POOR ADHERENCE




**Treatment interruptions**

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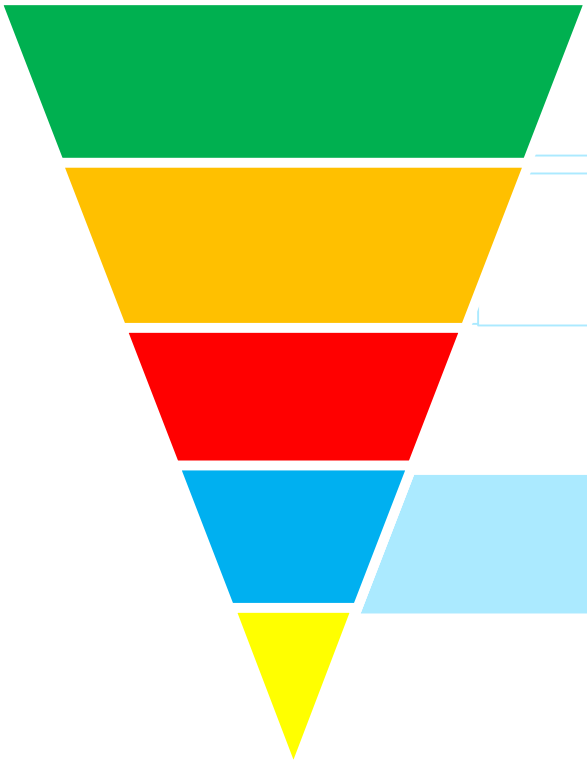

Points to consider in a Paediatric Development Plan

Model-based PK and PKPD bridging

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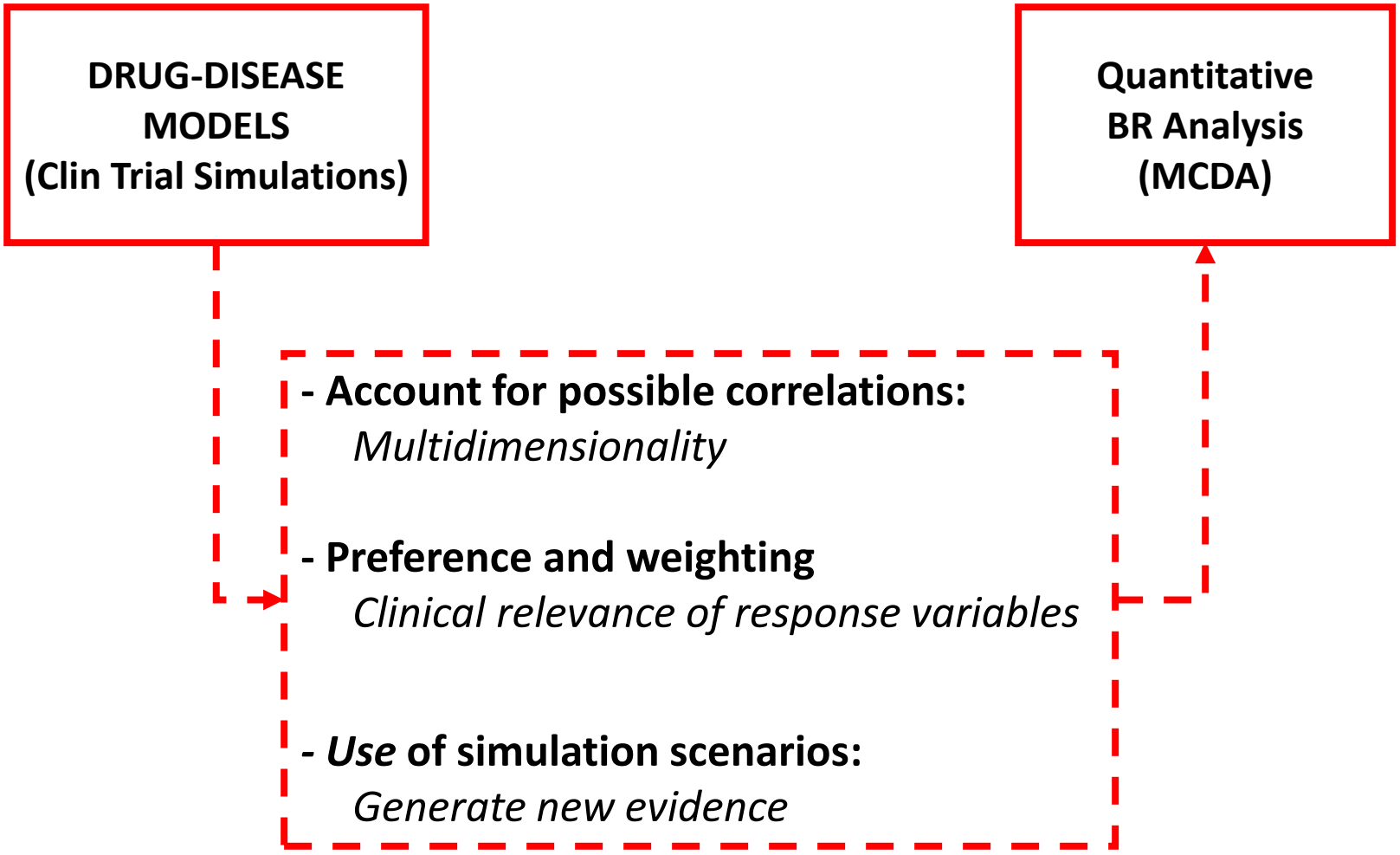
Extrapolation studies: Benefit-risk balance

*Conclusions & recommendations*

# A FRAMEWORK FOR BR ASSESSMENT IN CHILDREN



# CLINICAL TRIAL SIMULATIONS - TREATMENT RESPONSE

Disease + Drug + Population + Endpoint Measurement

Placebo Effect + Compliance + Dropout

Dosing Regimen + Protocol Design + Data Analysis

=

Response / Effect Size → Efficacy endpoints

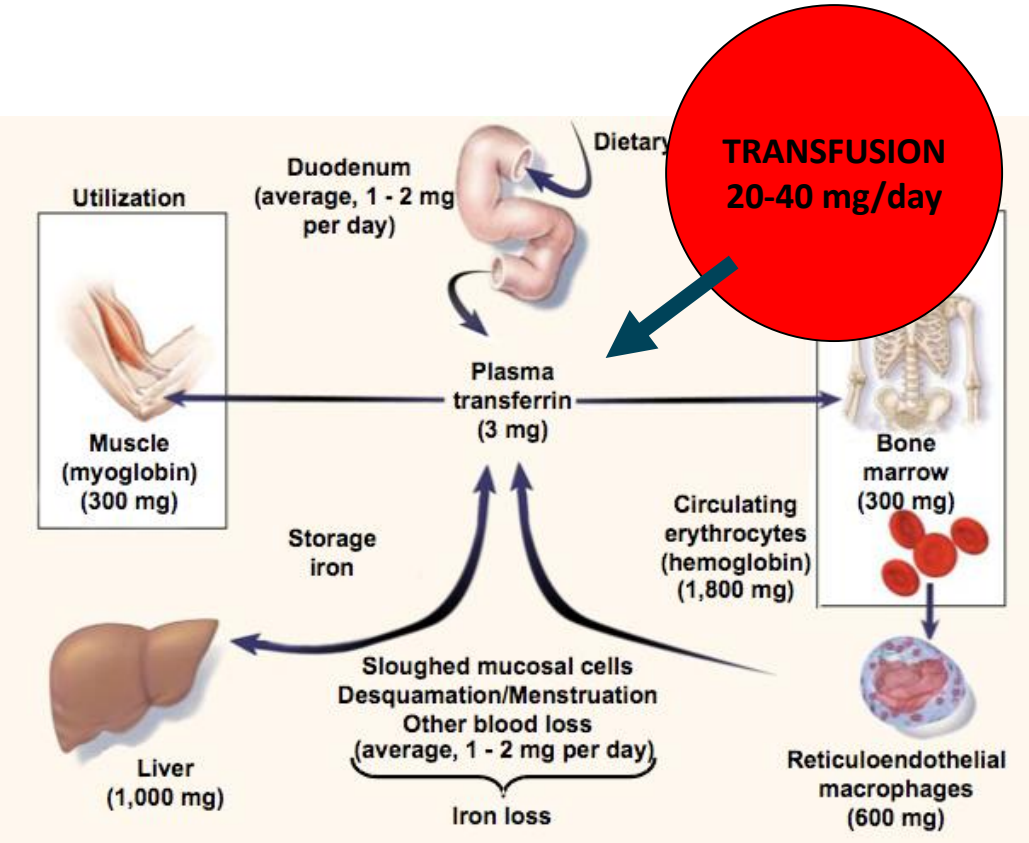
Response / Effect Size → Safety endpoints

# WHAT IS MCDA?

- A method to combine endpoints with different scales into a uniform 'response':
  - Utility function
  - Comparative weighting
  - Preference scores
- Not technically complex
- No inferential statistics (p-values)
- Probability-weighted utility scores
  - Highest score suggests the best decision/choice

# MCDA: STAGES

1. Establish the **decision context**
2. Identify the **endpoints or measures** of interest
3. Identify **objectives and criteria:**
   *- Identify criteria for assessing the consequences for each outcome*
   *- Organise criteria by clustering them under high-level and lower-level objectives in the hierarchy*
4. Assess the expected performance of each option against the criteria **('preference value')**:
   *- Describe the consequences of each outcome*
   *- Score the options on the criteria*
   *- Check the consistency of the preference values on each criterion*
5. Assign **weights** for each criterion to reflect their relative importance to the decision
6. Calculate **weighted scores** at each level in the hierarchy and calculate overall weighted scores
7. Examine the **results** and conduct **sensitivity analysis**




**Objectives:**

- To demonstrate the feasibility of a **model-based approach** for the evaluation of benefit-risk balance.

-To explore the implications of different **dosing regimens** on long-term response of iron chelation therapy (long term BRB)

# Iron Accumulation

Andrews NC. *N Engl J Med.* 1999;341:1986-1995.

# METHODS: ENDPOINTS AND PARAMETERS

**Treatment of interest: deferoxamine**

| | |
|---|---|
| Favourable Effects | Uncertainty of Favourable Effects |
| Unfavourable Effects | Uncertainty of Unfavourable Effects |

- **Favourable effects**
  - **Serum ferritin levels (PKPD model)**
    - *change from baseline (%)*
    - *percentage of responders (%)*
  - **Prevention of long-term disease complications (%)**
    - *Hypothyroidism (hazard model)*
    - *Diabetes mellitus (hazard model)*

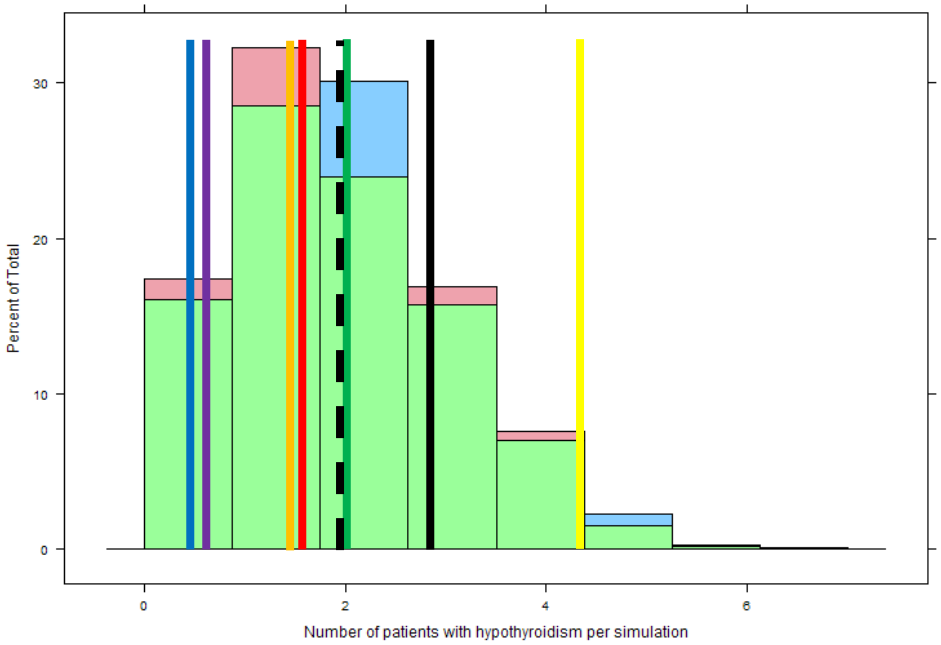
- **Unfavourable effects**
  - **Acute drug specific AEs (%)**
    - *Arthralgia/myalgia (very common and dose-dependent)*
    - *Anaphylaxis (rare and dose-independent)*

# Hypothyroidism

## Model performance in comparison with literature data

Borgna-Pignatti et al.
Belhoul et al.
Mehrvar et al.
Aydinoc et al.
Shamshirzar et al.
Kyriakou (Italy) et al.
Kyriakou (TIF) et al.

Dashed line: clinical data



# METHODS: CLINICAL TRIAL + FOLLOW UP

- Patient population: paediatric patients affected by transfusion-dependent haemoglobinopathies

- **Phase III randomised trial design**
- Sample size: 150 patients per treatment arm
- Age: 10 (2-17)
- Age groups: 2-6 years = 30
  6-12 years = 70
  12-17 years = 50
- Body weight: 32 (12-62)
- Gender: 50% males
- Baseline ferritin levels: 3000 (1000-8500)
- Number of samples per year: 5

- Duration: follow- up for **5 and 10 years**
- Treatment: iron chelator **deferoxamine**
- Dosing regimen: changes with each scenario (see options)

# EXTRAPOLATION AND SIMULATION SCENARIOS

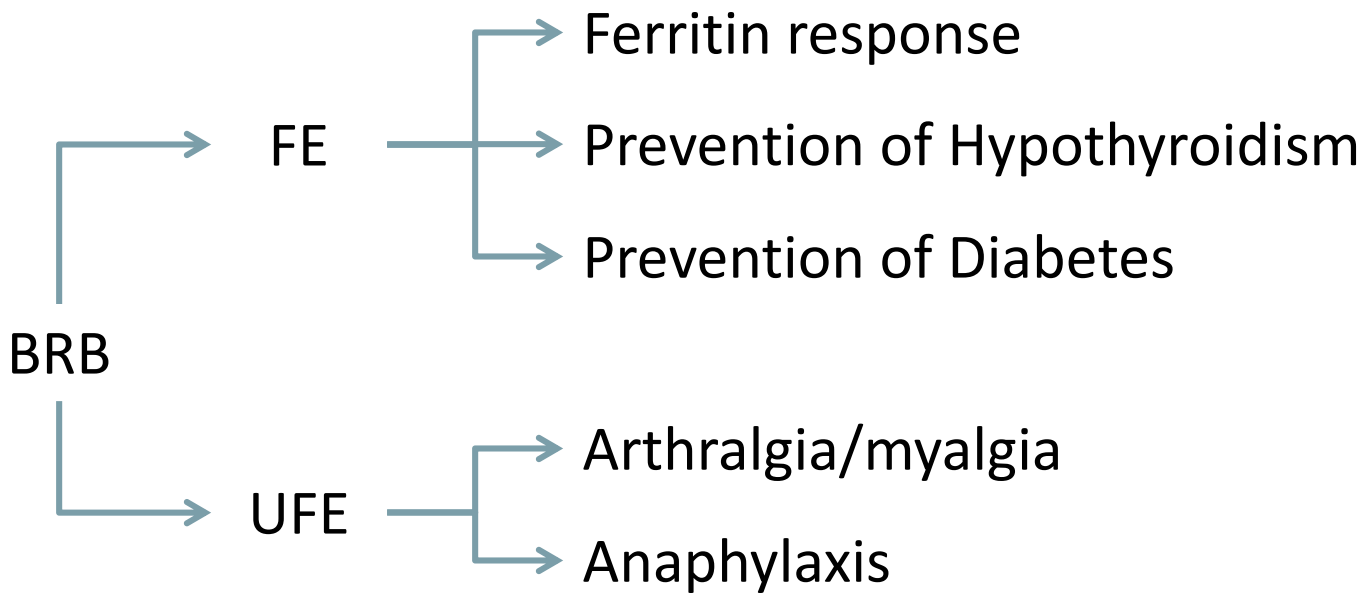
1- PKPD model describing the effects of transfusion and iron chelation on ferritin levels

2 – Covariate models describing the effects of compliance and dropout on treatment response

3 - Hazard models describing the effects of disease progression and chelation therapy on the incidence of co-morbidities

4 - Hazard models describing dose related and dose-unrelated adverse events

- **Scenario 1: FIXED DOSE REGIMEN**
  - Reference: fixed dose 45 mg/kg/day 5/7
- **Scenario 2: WEIGHT-BANDED DOSING REGIMEN**
- **Scenario 3: FERRITIN-GUIDED DOSING REGIMEN**
  - Individualised regimen based on serum ferritin levels



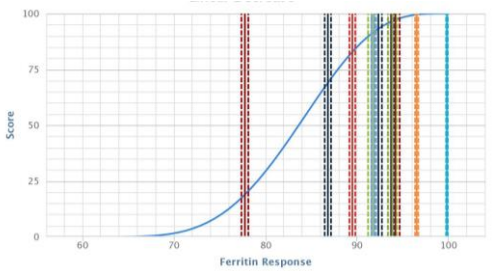

## Data

- Summary data for each endpoint are used as input for the MCDA software
- Mean and CI were used (250 simulations per individual)

# WEIGHT ELICITATION

## 1) Favourable effects vs. Unfavourable effects

FE




## 2) Favourable effects

Hypo

Ferritin

Hypo

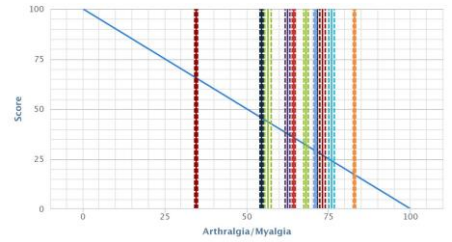
Diabetes

Ferritin

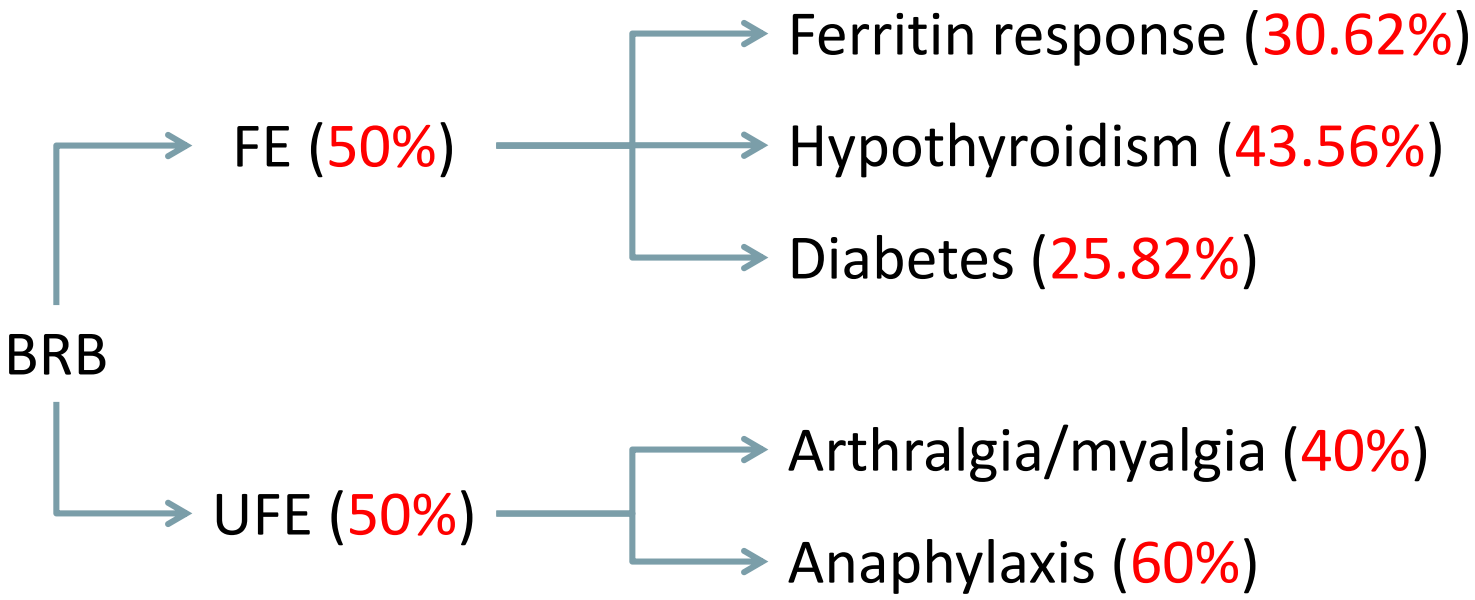
Diabetes

## 3) Unfavourable effects

Arth/Mya



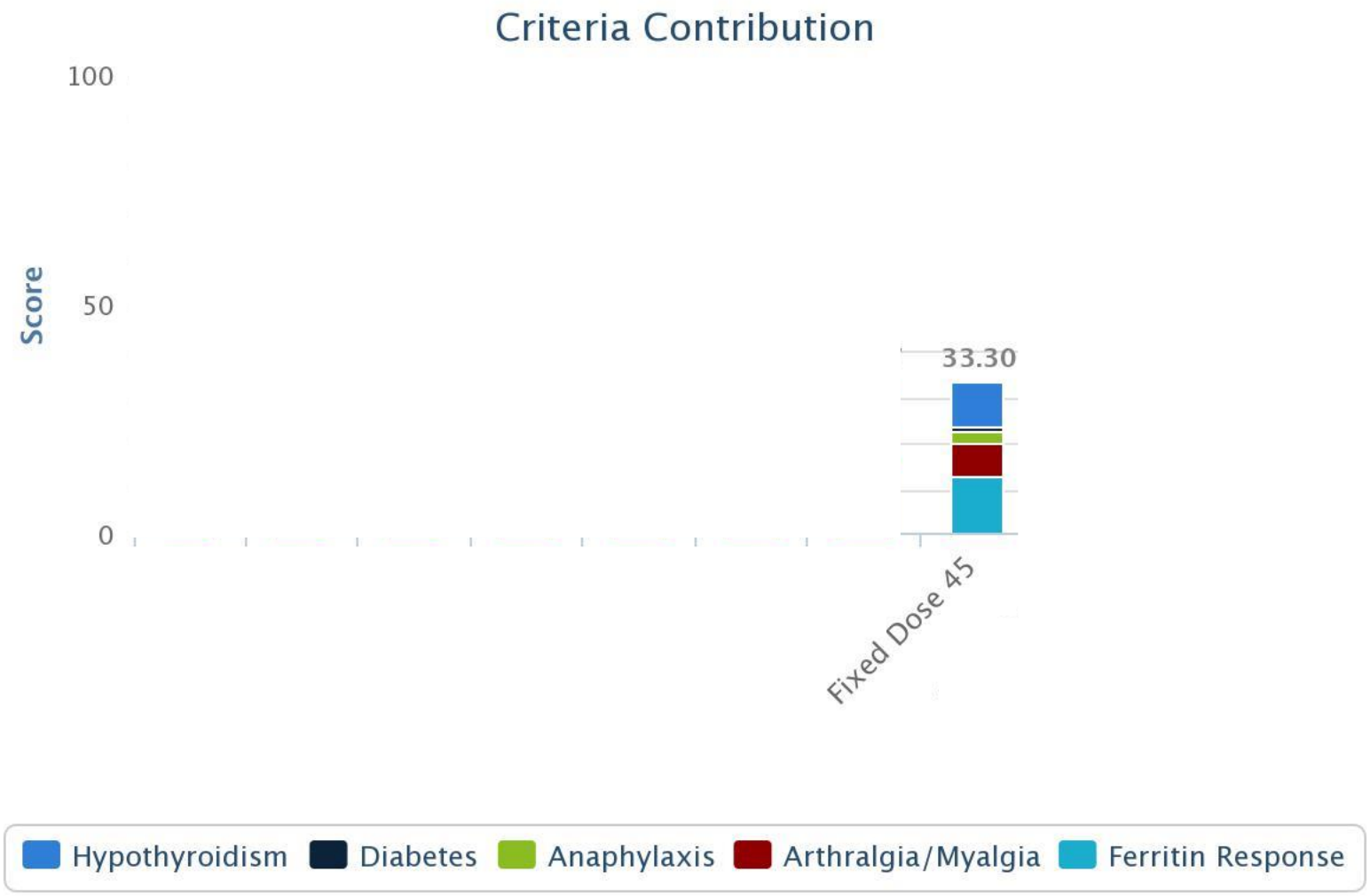
# Refined Value Tree



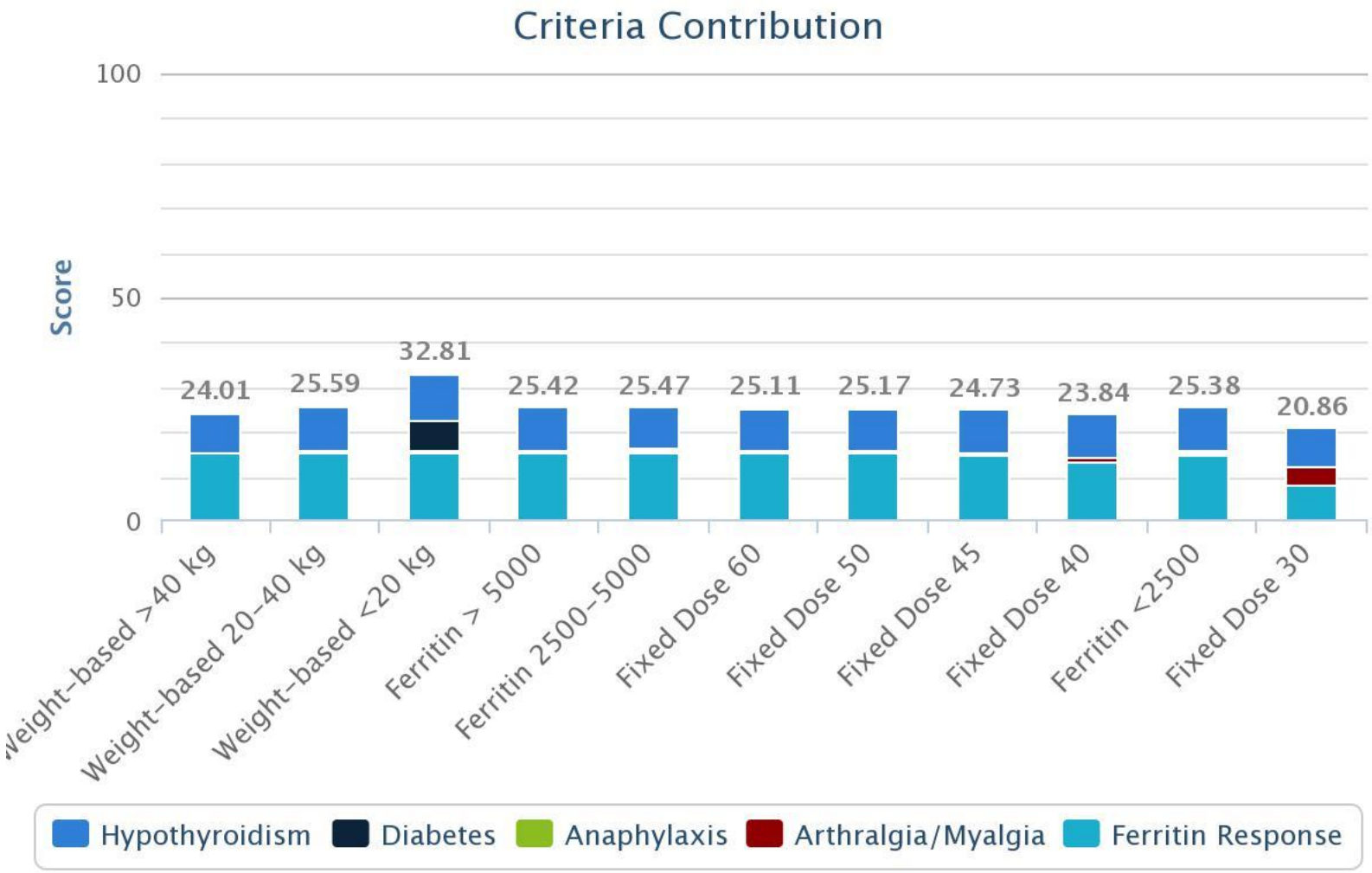

## Do the calculations!

$$U_i = \sum_{j=1}^{k} w_j S_{ij} = w_1 S_{i1} + w_2 S_{i2} + \cdots + w_k S_{ik}$$

# RESULTS: 1 YEAR FOLLOWUP (TYPICAL CLINICAL TRIAL)



# EXTRAPOLATION: 5 YEAR FOLLOW-UP



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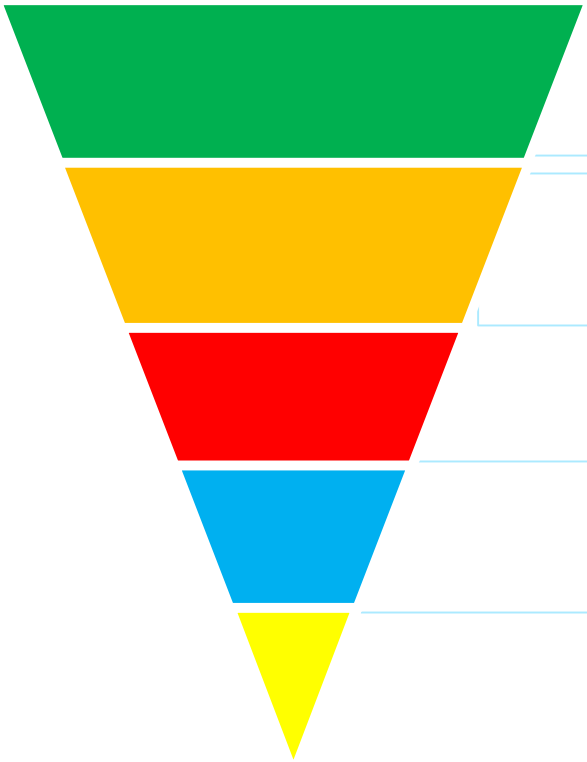

*Conclusions & recommendations*

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Extrapolation studies: Benefit-risk balance

# Conclusions

- **Extrapolation** must be considered in the context of evidence synthesis
- **Extrapolation can be used to replace or complement data**, especially when exploring scenarios for which clinical evidence may not be available or limited.
- **Drug-disease models** can and should be used in conjunction with **clinical trial and not-in-trial simulations** to extrapolate paediatric data
- **A (model-based) extrapolation** framework provides a robust basis for the **evaluation of benefit-risk balance** in paediatric diseases

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- **Models do not make decisions**, people do.

# Acknowledgments

**Experts:**

1. Paediatrician / ex-PDCO member
2. Paediatric haematologist
3. Paediatric haematologist
4. Paediatric haematologist
5. Paediatric haematologist/oncologist
6. Biostatistician
7. Clinical Pharmacologist
8. Paediatric Clinical Pharmacologist
9. Epidemiologist

DEferiprone Evaluation in Paediatrics