ICH E11A Pediatric Extrapolation

Pediatric Extrapolation Case Example: Development of a hypothetical TNF-alpha inhibitor "Drug X" for the treatment of polyarticular juvenile idiopathic arthritis (pJIA)

Training Material

ICH E11A Expert Working Group
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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

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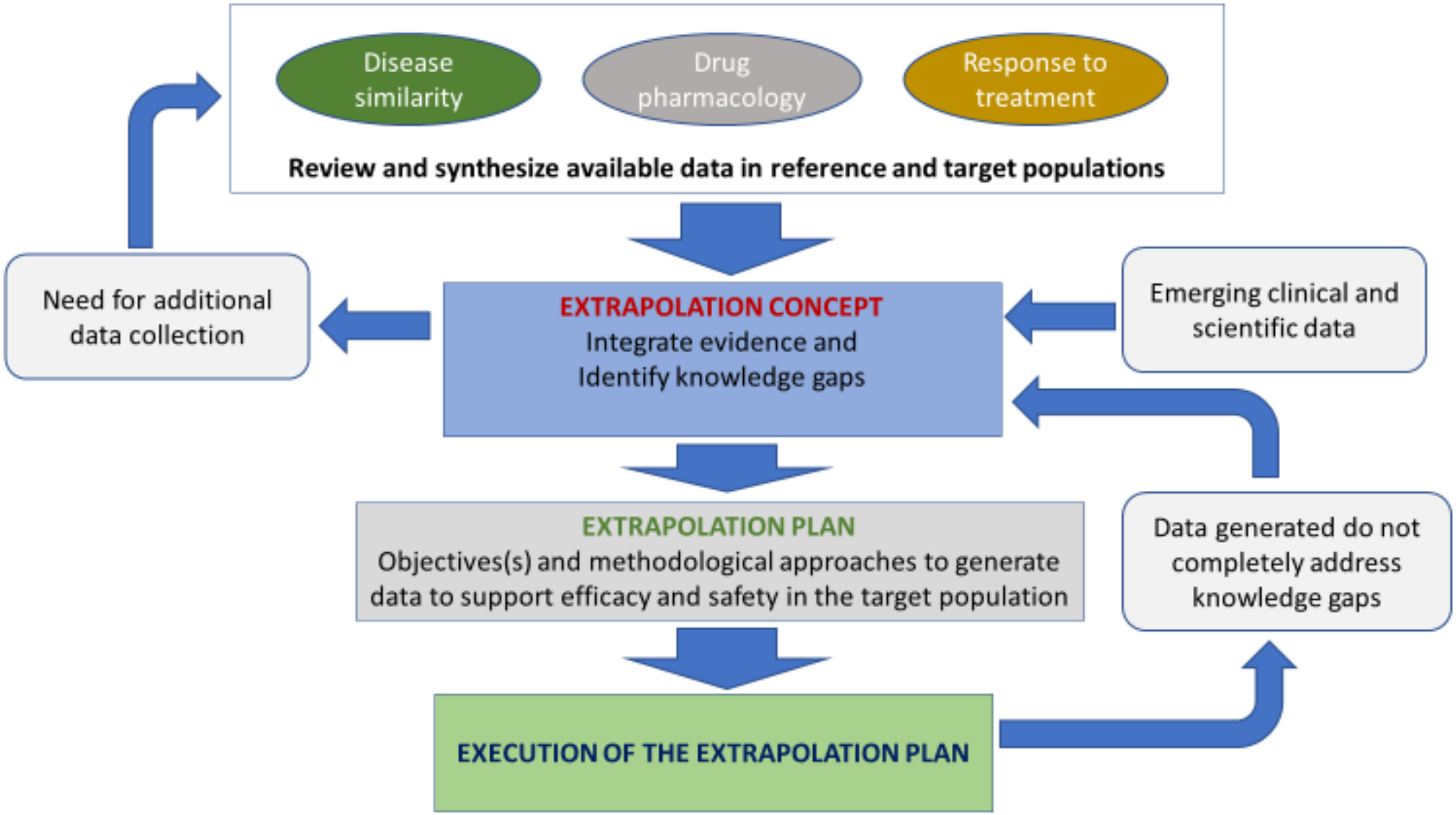
Teaching Objectives

- Illustrate the use of the pediatric extrapolation framework using a hypothetical case example
- This case example is a companion to the ICH E11A guideline
- Create a pediatric extrapolation concept using a question-based approach
- Create a pediatric extrapolation plan based on the need to fill specific gaps in knowledge

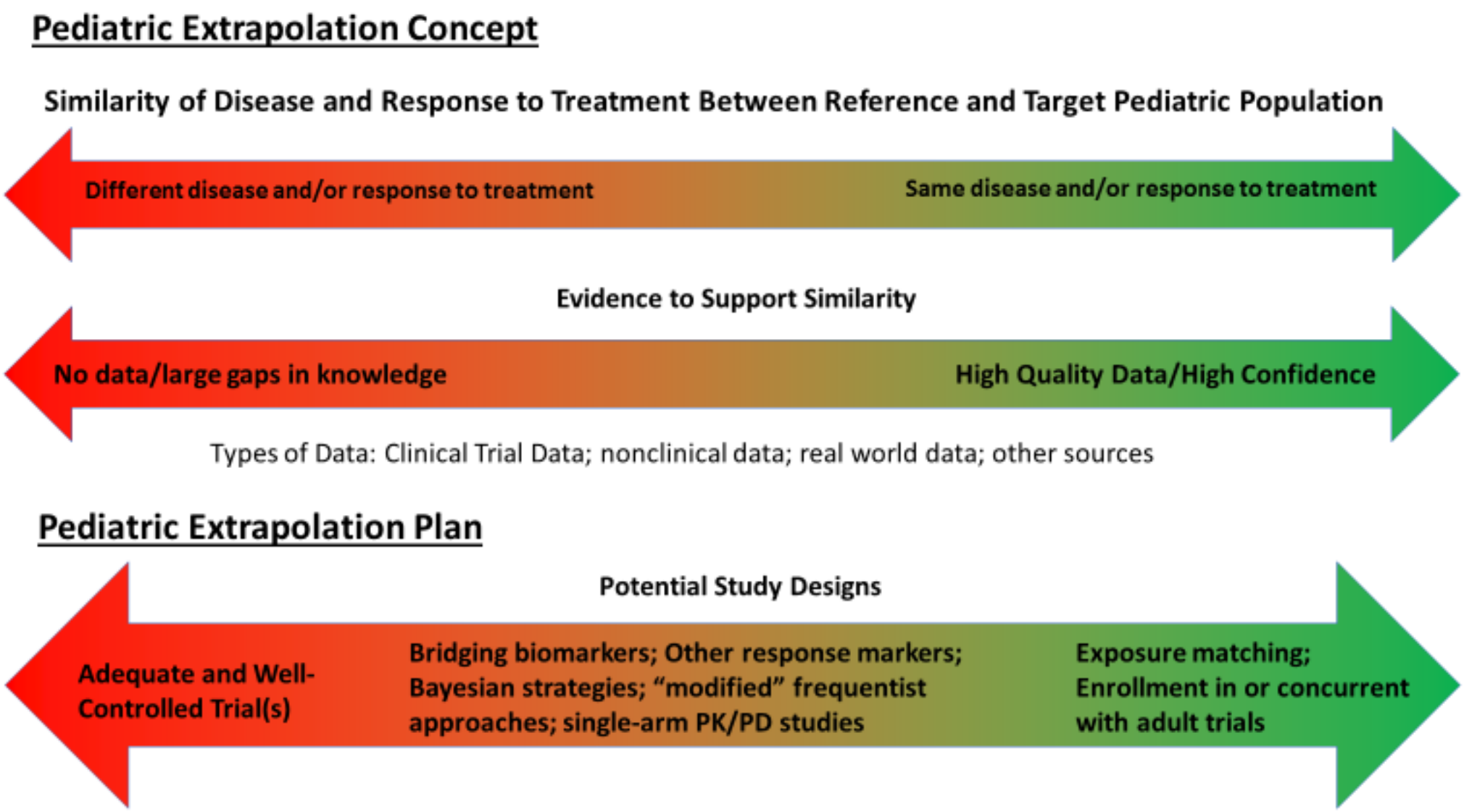
Caveats

- This hypothetical case example is not intended to provide specific regulatory guidance about the treatment of pJIA or rheumatoid arthritis (RA), and/or tumor necrosis factor-alpha (TNF-alpha) inhibitor drug development
- This case example reflects only one of many different approaches to pediatric extrapolation; other approaches may be applicable based on the disease, treatment, and the availability of existing knowledge
- This slide set is for illustrative purposes only and is not intended to be used as a template for regulatory submissions

Pediatric Extrapolation Framework (Fig. 2 section 2)



Pediatric Extrapolation Approach (Fig. 1 section 1.4)



Drug X: a new Tumor Necrosis Factor-alpha (TNF-alpha) inhibitor under development

- Drug X is a 2nd generation product in the class of TNF-alpha inhibitors
- Globally, TNF-alpha inhibitors have been approved in several indications in adult and/or pediatric populations
  - ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, plaque psoriasis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis (RA), ulcerative colitis, non-radiographic axial spondyloarthritis, and uveitis
- The mechanism of action of the TNF-alpha inhibitor class is well-established (see slide 13)
- Drug X is new monoclonal antibody (mAb) being developed for the treatment of RA in adults
- Drug X will be considered for the treatment of pJIA in the pediatric population 2 years of age and above (see slide 8)

Currently available data for Drug X*

- Data available so far in the development program for adult RA
  - Clinical adult data have established proof of concept and preliminary efficacy
- Adult data support that Drug X is similar with respect to efficacy and safety to other TNF-alpha inhibitors
- Nonclinical data support the planned studies down to 2 years of age
- TNF-alpha inhibitors have been approved for other pediatric indications, including pJIA (see previous slide)

*Drug X is hypothetical and the information on this slide and in the slide-deck is not representative of an actual TNF-alpha inhibitor development program.

Target Population: Polyarticular Juvenile Idiopathic Arthritis (pJIA)

- pJIA (a subset of JIA) is an autoimmune disease affecting children < 16 years of age, although uncommon in patients < 2 years of age
- Clinical presentation and diagnosis
  - Presence of ≥ 5 affected joints during the first 6 months of illness
  - Diagnosis is primarily based on clinical history and examination
  - Laboratory markers that may be helpful: RF, ANA, anti-dsDNA antibodies, ESR, CRP, HLA-B27
  - Most children with pJIA < 10 years of age are RF negative
- Prevalence
  - Approximately 3 per 10,000 (in US)
  - Affects ~ 25% of patients with JIA
  - More frequent in females than males (F:M approximately 3:1)
- Clinical course
  - Bone erosions and joint destruction occur if therapy is inadequate and can lead to contractures
  - Uveitis more common in patients who are ANA+ and younger in age at diagnosis
- Treatment
  - Treatment directed toward underlying inflammation and preventing joint destruction
  - First-line agents include nonbiologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate; non-steroidal anti-inflammatory drugs (NSAIDs) are used as adjunctive therapy
  - Second-line agents (biologic DMARDs) include TNF-alpha inhibitors

RF = rheumatoid factor; dsDNA = DNA double-stranded; ANA = antinuclear antibodies; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HLA = human leukocyte antigen

Martini A. 2019; Negrovic PA. 2018; Oberle EJ. 2014; Ringold S. 2019.

Reference Population: Rheumatoid Arthritis (RA)

- A symmetric, inflammatory, peripheral, autoimmune polyarthritis
- Clinical presentation and diagnosis
  - Presence of symmetric inflammatory polyarthritis, typically in the hands and wrists
  - Laboratory markers that may be helpful: RF, ACPAs, ESR, CRP
  - 70-80% of patients with RA are RF positive
- Prevalence
  - 0.5-1% of the population
  - More frequent in females than males (F:M approximately 2.5:1)
- Clinical course
  - Progressive inflammatory arthritis, leading to joint erosion and functional disability if untreated
- Treatment
  - Treatment directed toward underlying inflammation and preventing joint destruction
  - First-line agents include nonbiologic DMARDs such as methotrexate; NSAIDs
  - Second-line agents: TNF-alpha inhibitors, JAK inhibitors
  - Surgery to repair, replace, or fuse joints may help in certain situations

ACPAs = Anti-Citrullinated Peptide Antibodies
JAK = Janus Kinase

Scott DL. 2010.

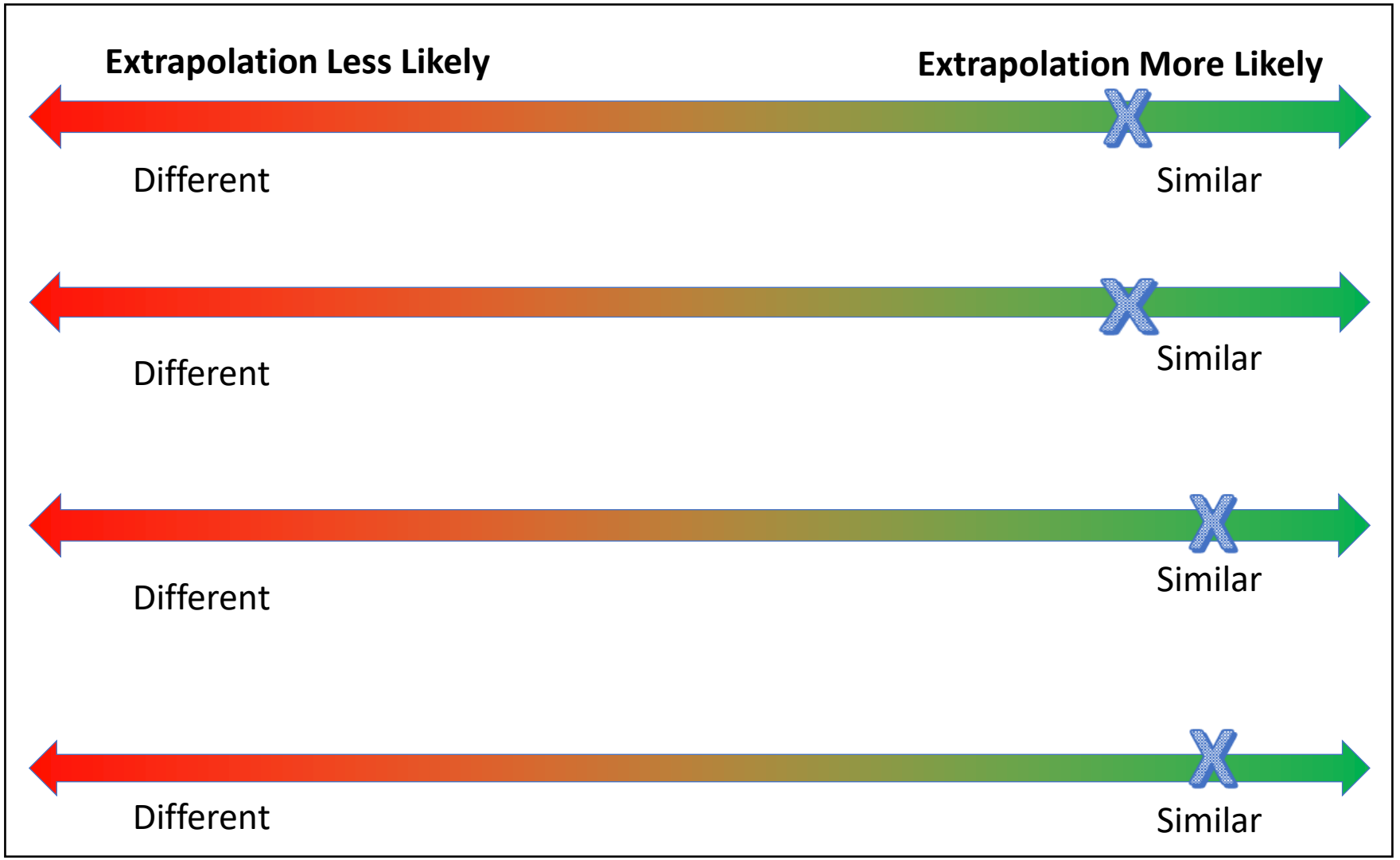
Similarities and Differences between pJIA and RA

Clinical Features and Pathogenesis	pJIA	RA
RF	Variable	Variable
ACPA	Negative in younger patients (pts.)	Positive
ANA	Positive (risk factor for uveitis) in younger pts.	Negative
HLA associations	HLA-DR1, -DR4	DRB1; A; B; and DPB1
Female : Male prevalence	3 : 1	2.5 : 1
Uveitis	Present (ANA +); younger age at diagnosis	uncommon
Joint involvement	≥ 5 joints; symmetric in younger pts.	Multiple joints; generally symmetric
Pathogenesis	Autoimmune activation with imbalance between pro-inflammatory Th1/Th17 and Treg cells	Complex autoimmune activation involving T and B cells, macrophage and dendritic cells
Age cut off	< 16 years	> 16 years
Treatments	Non-biologic DMARDs (1st line) Systemic biologics (2nd line)	Non-biologic DMARDs (1st line) Systemic biologics; JAK inhibitors (2nd line)

MHC = major histocompatibility complex; DRB1 = DR Beta 1; A = alpha; B = beta; DPB1 = DP Beta 1

Assessing Similarity of Disease between pJIA and RA (Section 3.1.1)

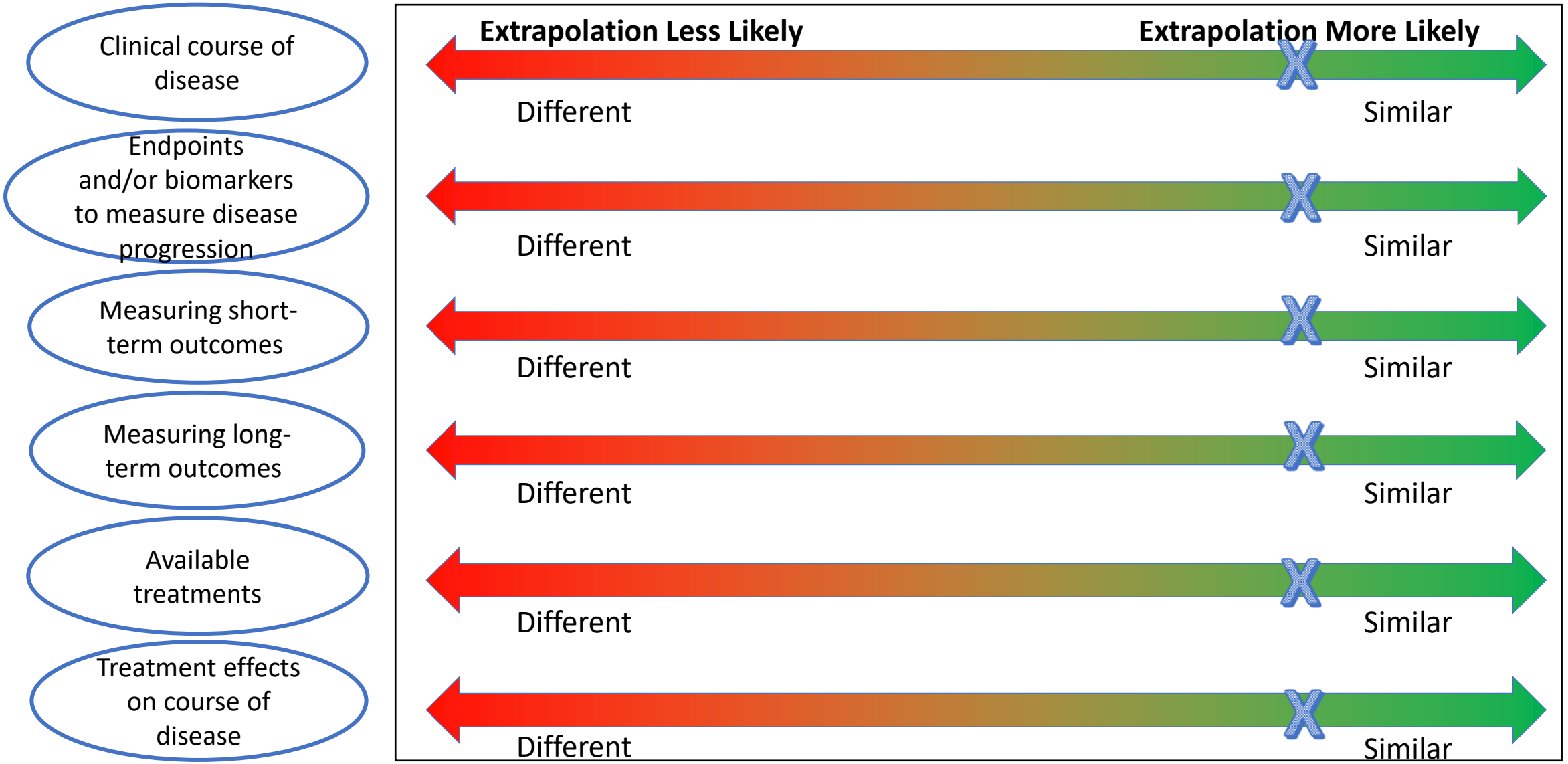
- Manifestations of disease/ Diagnostic criteria
- Measurements used to define disease
- Subtypes of disease (e.g., defined by severity, genetics or molecular markers)
- Other factors that define the disease (e.g., genetic/ epigenetic)



In other scenarios if no data are available, there may be a need to collect data to assess similarity of disease.

FDA, United States-CERSI Workshop on Accelerating Drug Development for pJIA - October 2019.

Assessing Similarity of Disease between pJIA and RA (Section 3.1.1)



In other scenarios if no data are available, there may be a need to collect data to assess similarity of disease. *FDA, United States-CERSI Workshop on Accelerating Drug Development for pJIA - October 2019.*

TNF-alpha inhibitors: Pharmacology

- Tumor necrosis factor (TNF) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses
- TNF in RA and pJIA
  - Elevations in TNF are found in synovial fluid of patients with RA and pJIA
  - TNF plays a role in pathologic inflammation and joint destruction in RA and pJIA
- TNF alpha inhibitors
  - Bind to TNF-alpha and blocks its interaction with p55 and p75 cell surface TNF receptors
  - There are differences in structure and mechanism of action among anti-TNF agents which may result in minor differences in their effects
- ADME for Drug X
  - Intravenous administration (mg/kg dosing)
  - Mean half-life ~ 2 weeks
  - Mean volume of distribution ~ 5L
  - Linear clearance with no evidence of target-mediated drug disposition (TMDD) or time dependent changes
  - Most influential covariate for exposure was body weight (BW)
  - Pharmacokinetic (PK) considerations for the pediatric population: Allometric BW scaling for clearance and volume; Target levels are not expected to influence PK due to the absence of TMDD

Singh et al. 2021.

ADME = Absorption, Distribution, Metabolism and Excretion

TNF-alpha inhibitors: Similarity of response to treatment

- Clinical endpoints used in adult RA clinical trials based on clinical disease activity improvement (ACR 20%, 50%, 70% improvement)
  - ACR measures joint swelling and tenderness and improvement in other clinical parameters (e.g., global disease activity, pain, disability/functional, acute phase reactants)
- Clinical endpoints in pJIA trials also based on similar clinical disease activity improvements (pACR 30%, 50%, 70%, 90%)
- In previous programs for TNF-alpha inhibitors, clinical response between children with pJIA and adults with RA were comparable at similar exposures after adjusting for relevant covariates

ACR = American College of Rheumatology
pACR = pediatric American College of Rheumatology

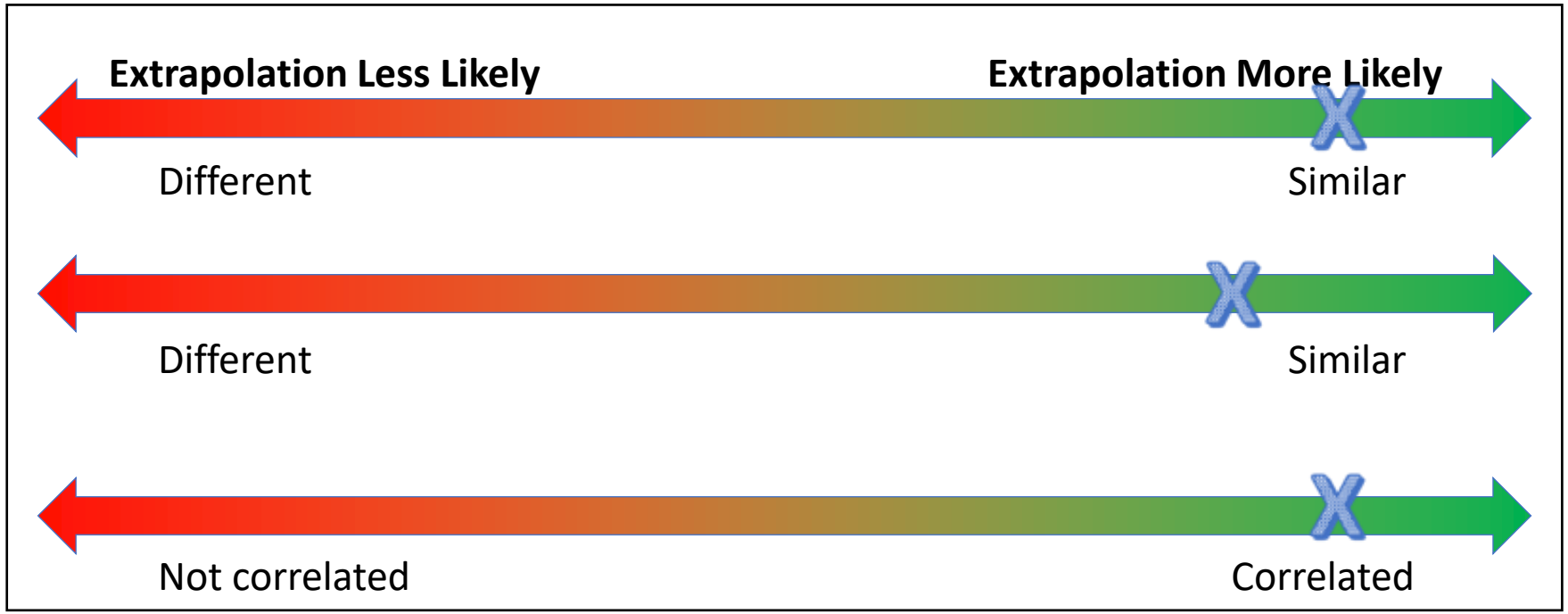
Singh et al. 2021.

Assessing Similarity of TNF-alpha inhibitor Pharmacology and Response To Treatment in pJIA and RA (Section 3.2)

ADME properties

Endpoints and/or biomarkers to measure response*

Relationship between different response endpoints and/or biomarkers



In other scenarios if no data are available, there may be a need to collect data to assess similarity of pharmacology and response to treatment.

*For this hypothetical case example, clinical endpoints were available to measure response; No biomarkers were evaluated to measure clinical response.

Examples of Sources and Types of Existing Data in pJIA and RA to Support the Extrapolation Concept (Section 3.4)

	Nonclinical Data	RWD	Other Sources of Data	Clinical Data (in a Different Disease)	Clinical Data (in the Same Disease)
Similarity of Disease	1. Nonclinical disease models	1. Disease registries 2. Health records (e.g., EHR) 3. Health claims databases	1. Society guidelines 2. Consensus documents 3. Public workshops	N/A	1.Natural history 2. Pathophysiology of disease 3. Clinical trials (TNF-alpha inhibitor class & other MOAs)
Similarity of Drug Pharmacology	1. ADME/PK from animal models	No Data	No Data	1. PK, PK/PD and clinical data (TNF-alpha inhibitor class)	1. PK, PK/PD and clinical data (TNF-alpha inhibitor class & other MOAs) 2. Adult PK, PK/PD and clinical data for Drug X
Similarity of Response to Treatment	1. Mechanistic data	1. Disease registries 2. Health records 3. Health claims databases	1. Society guidelines 2. Consensus documents 3. Public workshops	1. PK, PK/PD and clinical data (TNF-alpha inhibitor class)	1. PK, PK/PD and clinical data (TNF-alpha inhibitor class) 2. Adult PK, PK/PD and clinical data for Drug X

N/A = Not applicable to establish extrapolation concept for pJIA and RA (see Slides 8 & 9) - May be applicable in other scenarios
RWD = real-world data; EHR = electronic health records; MOA = mechanism of action; PD = pharmacodynamic

Safety Considerations for TNF-alpha inhibitor class (Section 3.5)

- The safety profile of TNF-alpha inhibitor class is well characterized in adults and children
- Adverse reactions in TNF-alpha inhibitor class are generally similar in frequency and type
  - Serious infections and risk of malignancies (including lymphomas in pediatric patients), and hypersensitivity reactions are reported
  - No major differences in common adverse event profiles across TNF-alpha inhibitors
- Long-term safety of TNF-alpha inhibitors is well characterized
  - Development of immunogenicity, serious infections, and malignancies
  - Diminished effectiveness over time in RA
- In clinical trials with pediatric patients 2 - 4 years of age, safety profile is generally similar to older pediatric patients

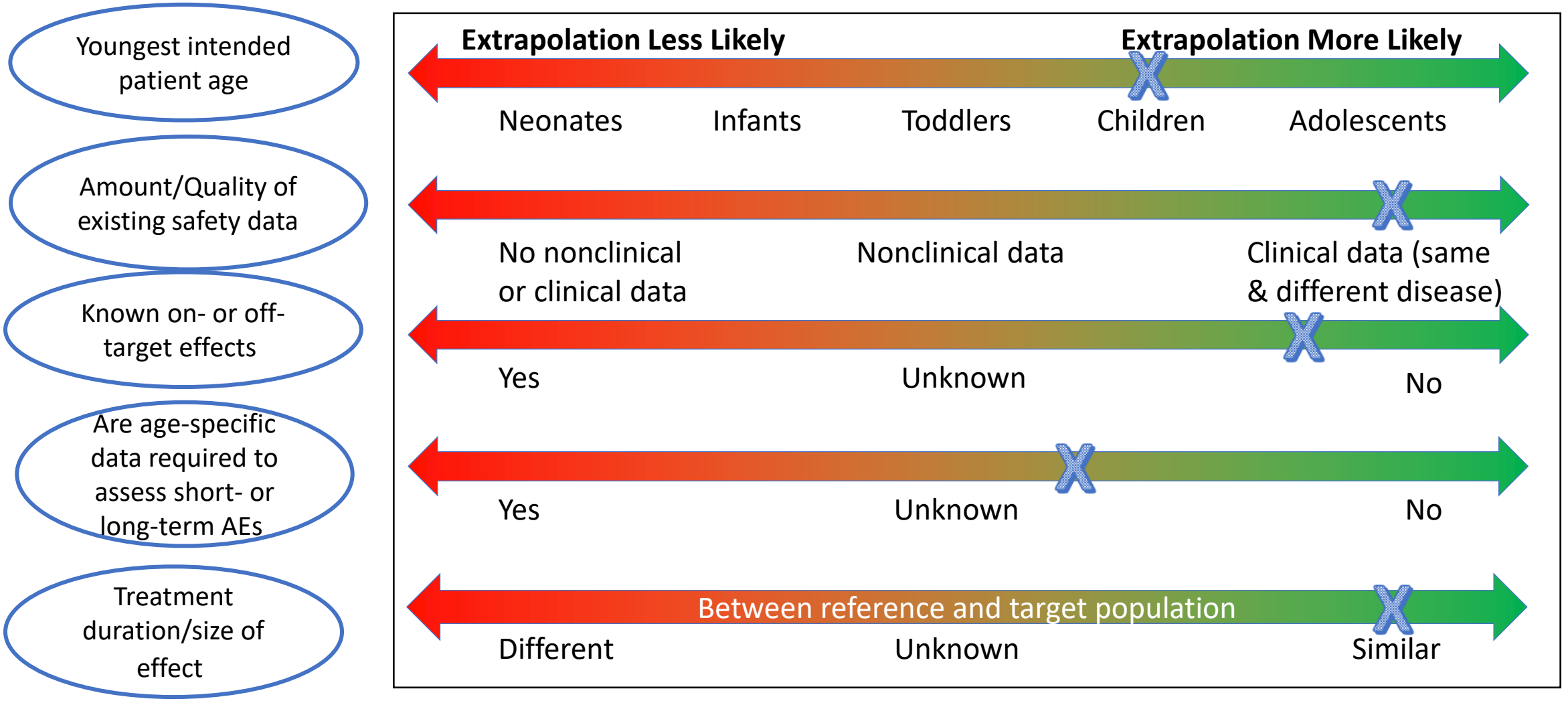
Li J, et al. 2021.

Safety Considerations for Drug X in pJIA (Section 3.5)

- The plan is to study Drug X for pJIA down to 2 years of age
- Robust safety data are available from the reference population (adults with RA) for Drug X and similar to those treated with marketed TNF-alpha inhibitors
- There are no known on- or off-target effects of Drug X relevant to pediatric safety - Therefore, no PD marker to predict a specific toxicity in children is needed
- Long-term safety for Drug X in RA and pJIA is unknown
- Duration of treatment and treatment effect size in RA and pJIA are expected to be similar
  - Both are intended to be used chronically
- Target drug exposures are expected to be similar between RA and pJIA
- The predicted/known therapeutic window for Drug X is expected to be similar to other TNF-alpha inhibitors pending confirmation in adult phase 3 trials
- There is no other nonclinical data that can be leveraged to the pediatric population

Randell RL, Becker ML. 2021.

Extrapolation of Safety (Section 3.5.1)



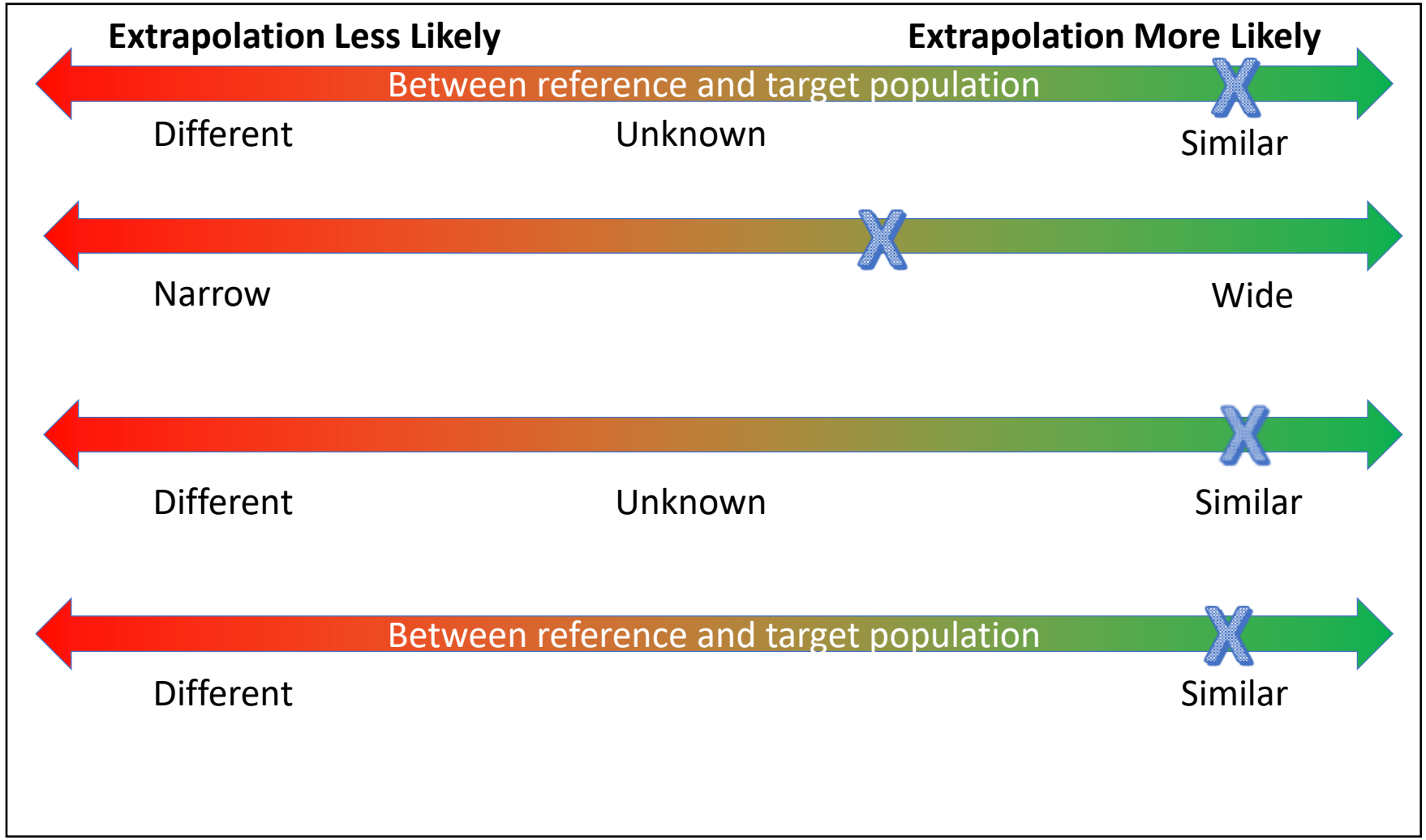
Extrapolation of Safety (Section 3.5.1)

Expected drug exposure

Predicted/known therapeutic window

Other relevant nonclinical data

Other factors (e.g., unique background therapy)



Integration of Evidence (Section 3.6)

- **Body of evidence and clinical relevancy**
  - Large body of evidence available on similarity of disease and clinical management for RA and pJIA
  - Available evidence for TNF-alpha inhibitors in RA and pJIA suggests similarity in nonclinical, PK, safety and efficacy in adults and pediatric patients
  - For Drug X: nonclinical data, PK (effective exposures, preliminary exposure-response), safety and efficacy data in adult patients with RA are similar to other TNF-alpha inhibitors for RA
- **Strengths and limitations of the evidence**
  - Data to support similarity of disease and response to treatment include nonclinical data, RWD, clinical data, and other sources of data
  - Large quantity of data available for TNF-alpha inhibitors in adult and pediatric patients in RA and pJIA
  - Few, if any, limitations in the available evidence
- **Consistency of findings**
  - Consistency between nonclinical and clinical findings for other TNF-alpha inhibitors and Drug X
  - Consistency in efficacy findings in adult patients treated with other TNF-alpha inhibitors and Drug X
  - Consistency in overall safety findings between adult and pediatric patients treated with other TNF-alpha inhibitors

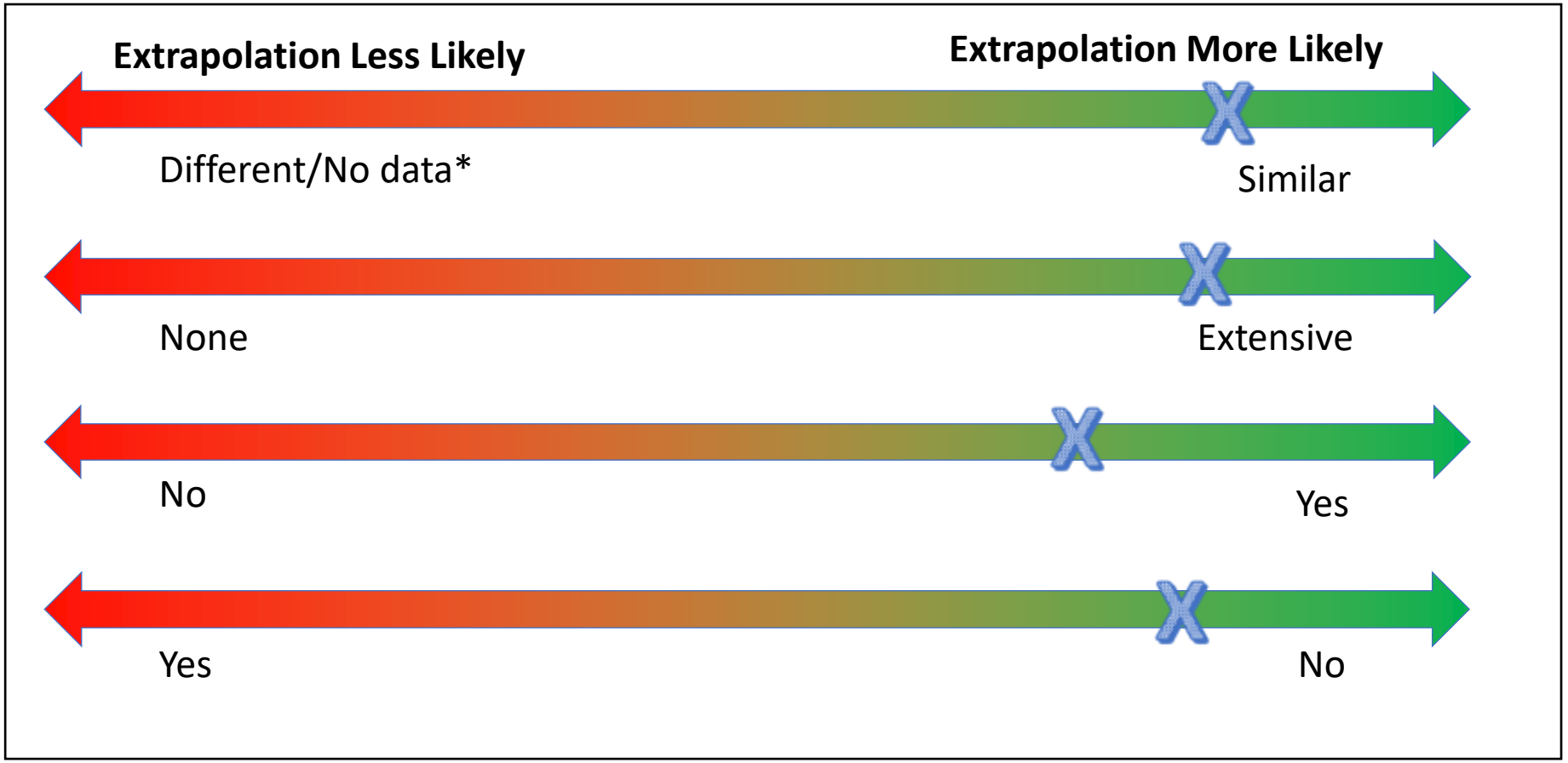
Integration of Evidence (Section 3.6)

Body of evidence and clinical relevance

Robustness of the evidence

Consistency of findings across the data sources

Do the differences in the data affect the assessment of similarity



*If no data is available, there may be a need to collect additional data to refine/revise the Extrapolation Concept.

Knowledge Gap Identification for Drug X in pJIA (Section 3.6)

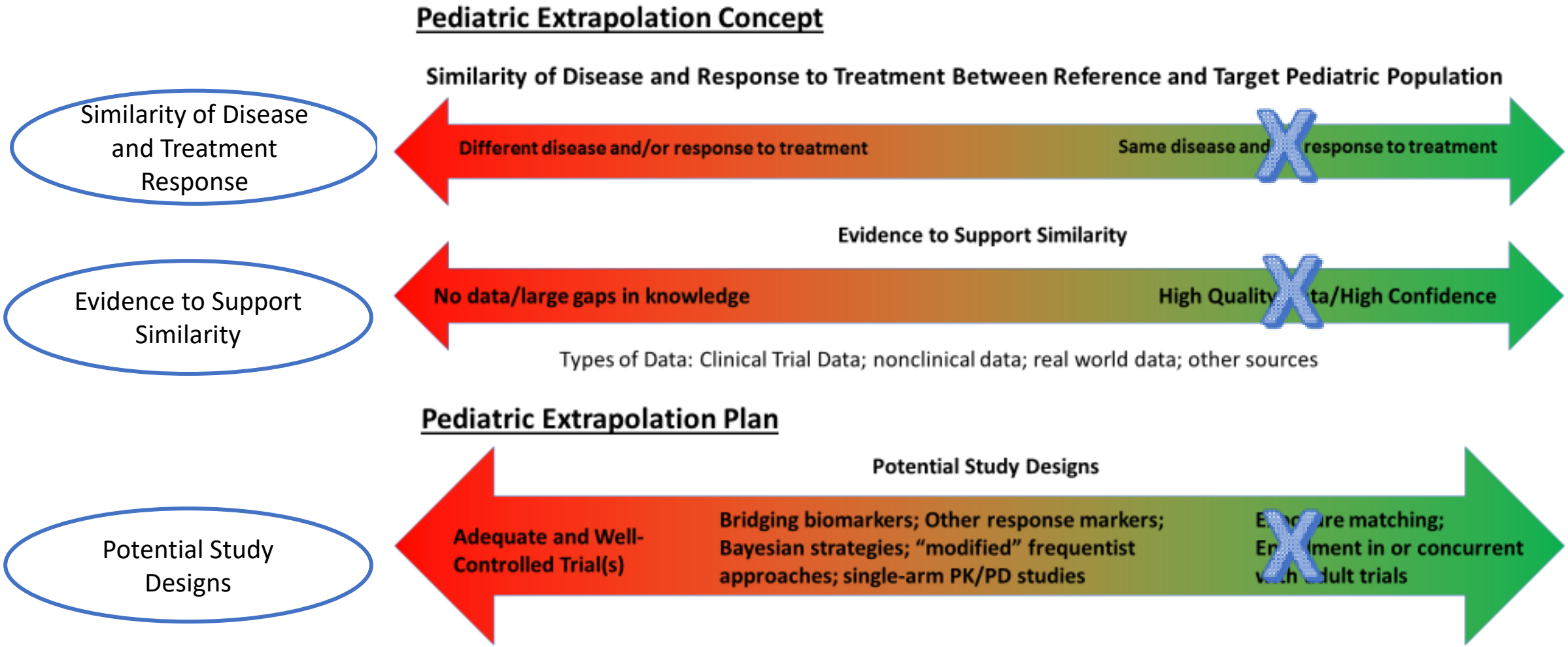
	Disease	Drug Pharmacology	Response to Treatment	Safety
Identified gaps in knowledge	No	No	Yes [Dosing in pediatric patients]	Yes [Long-term safety concerns in class, e.g. malignancy, new autoimmune disease]
Do these gaps require additional data generation to finalize Extrapolation Concept	N/A	N/A	No	No
How will gaps be addressed in the Extrapolation Plan	N/A	N/A	1. PK data in pediatric patients to support exposure matching	1. Leverage existing data in TNF-α inhibitor class 2. Evaluate need for long-term safety data

Green = No action required; Red = Action required; N/A = Not applicable because no gaps were identified (may be applicable in other scenarios)

Presentation of the Extrapolation Concept for pJIA (Section 3.7)

- Overall assessment of the evidence of similarity of disease and response to treatment in pJIA and RA
  - There is strong evidence that pJIA and RA are similar diseases
  - There is strong evidence that Drug X is likely to behave similarly in pJIA and RA patients
- An assessment of the gaps in knowledge
  - Dosing of Drug X in pediatric pJIA patients
- Overall assessment of available safety information for TNF-alpha inhibitors, including Drug X
  - There is considerable short- and long-term safety data with the TNF-alpha inhibitor class in both pediatric and adult patients
  - Drug X behaves similarly to other TNF-alpha inhibitors in RA
  - There is strong evidence that Drug X is likely to have a similar safety profile in pJIA and RA patients
  - Potential rare and very rare adverse events for Drug X in pediatric patients are unknown
  - Long-term safety of Drug X in pediatric patients is unknown

Pediatric Extrapolation Concept for Drug X in pJIA



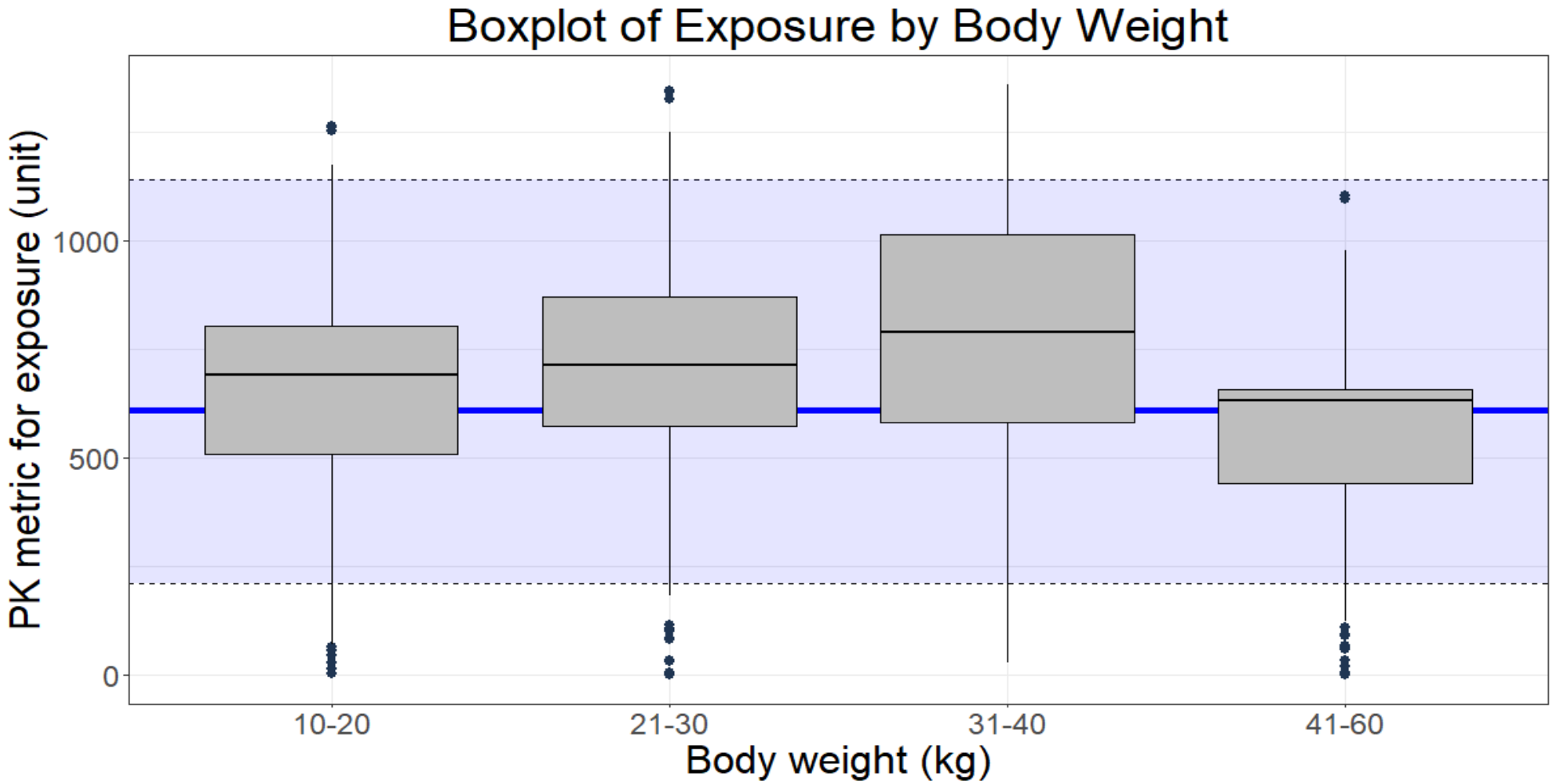
Pediatric Extrapolation Plan for Drug X in pJIA (Sections 4.1 & 4.2)

- Study Design: exposure (PK) matching
  - Modeling and simulation strategies will be applied to support the initial dose selection in the exposure matching study in the target population
  - The target exposure metric will be based on the exposure range associated with treatment response (efficacy and/or safety) and will be derived from established exposure-response relationships or observed data in the reference population
- Number of patients
  - The availability of patients in a specific body weight/age range
  - The adequacy of the sample size to demonstrate precision in key PK parameters in the pediatric population such as clearance and volume of distribution
  - The adequacy of the sample size to match the pre-specified target exposure range (e.g., the interquartile range for the PK metric(s) in the reference population)
  - Justification of the selected sample size (feasibility)
- Justification of the proposed posology in pJIA patients
  - Graphical and tabular presentation of predicted exposures in the pJIA population compared to the adult population will be provided

Use of Secondary Response Endpoints in Exposure (PK) Matching Studies

- Although exposure is the primary endpoint, an assessment of response (e.g., biomarker and/or clinical endpoint) may often be included as a secondary endpoint
- The choice of this secondary endpoint should be justified in the extrapolation plan and supportive of the extrapolation of efficacy from the reference to the target population
- Caution should be exercised in the analysis of this secondary response endpoint as the sample size will have been justified based on the primary exposure metric and may be inadequate to confirm response similarity

Sample Graphical Presentation of Exposures of Drug X in Pediatric Patients Compared to Adults



Exposures of Drug X in pediatric patients (boxes) and reference range from the adult population (shaded area).

Adapted from EMA Modelling & Simulation Questions & Answers; https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers#paediatrics-section

Extrapolation Plan for Drug X: Safety (Section 5.1)

- Extrapolation of available safety data from the following patient populations can be considered
  - Adult patients treated with Drug X in RA
  - pJIA patients treated with other TNF-alpha inhibitors
  - Adult and pediatric patients treated for other indications with other TNF-alpha inhibitors
- Remaining gaps in knowledge
  - Confirmation of long-term safety of Drug X in pediatric patients
  - Confirmation of short-term safety of Drug X in pJIA patients compared to RA patients
- Plan
  - Collection of safety data in pediatric patients studied
  - Independent substantiation of safety in pediatric patients through controlled safety data collection not needed
  - Post-approval surveillance for long-term safety concerns in class (e.g., malignancy, new autoimmune disease)

References

- European Medicines Agency M&S Q&As: #paediatrics-section https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers (Accessed 24 May 2022).
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Contact

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