EMA EFPIA workshop

Breakout Session 3

Evidence Synthesis in Drug Development for

Special Populations, Ethnic Groups and Rare Diseases

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LEADING STATEMENTS

1. An **evidence-based approach is often unsuitable** for the evaluation of pharmacokinetics, pharmacodynamics, safety and efficacy in special populations, ethnic groups and rare diseases.

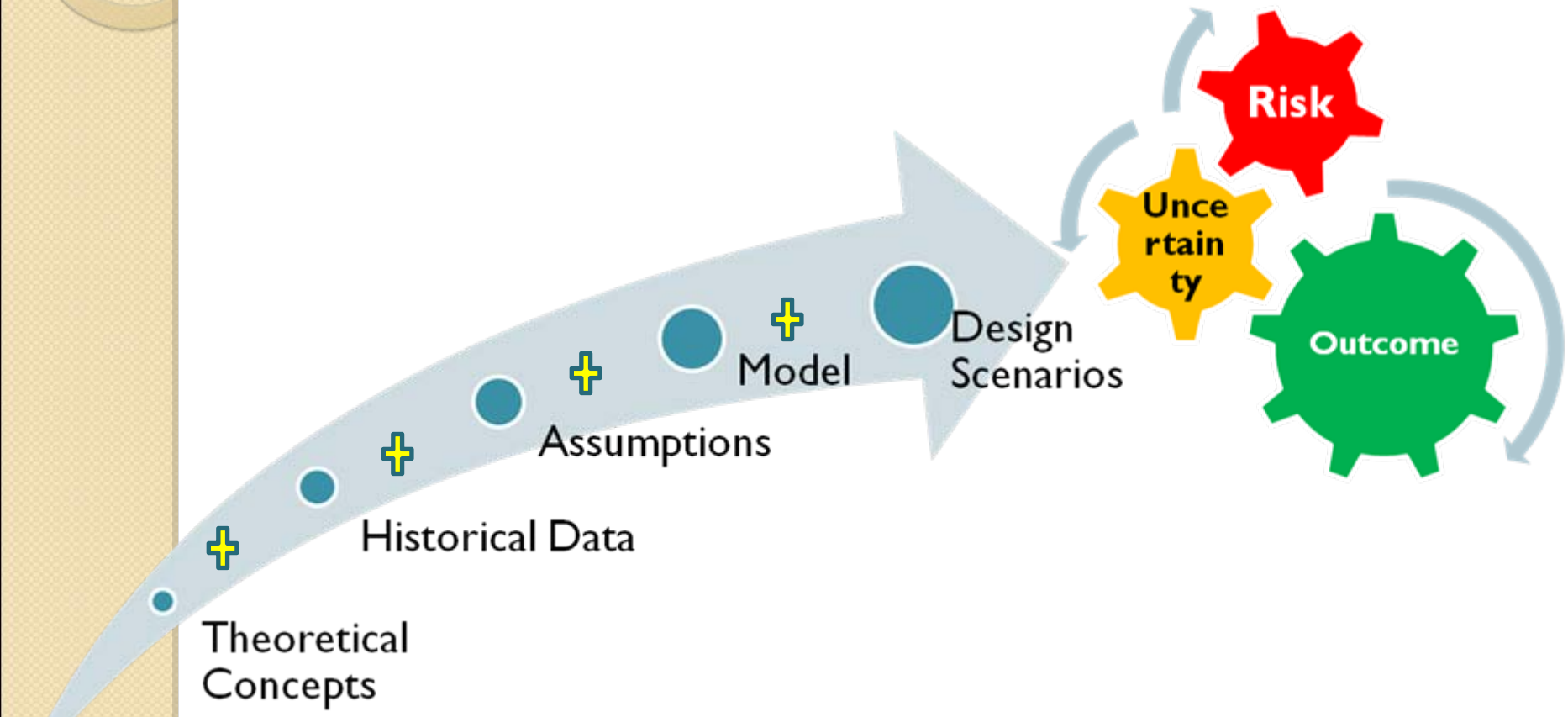
2. Inferential methods (M&S) should underpin evidence synthesis and knowledge integration in the development of drugs for special populations, ethnic groups and rare diseases

3. Inferences are required to support evidence synthesis during the **design stage (i.e., protocol optimisation)**, as well as during the **analysis and interpretation** of existing or new evidence.

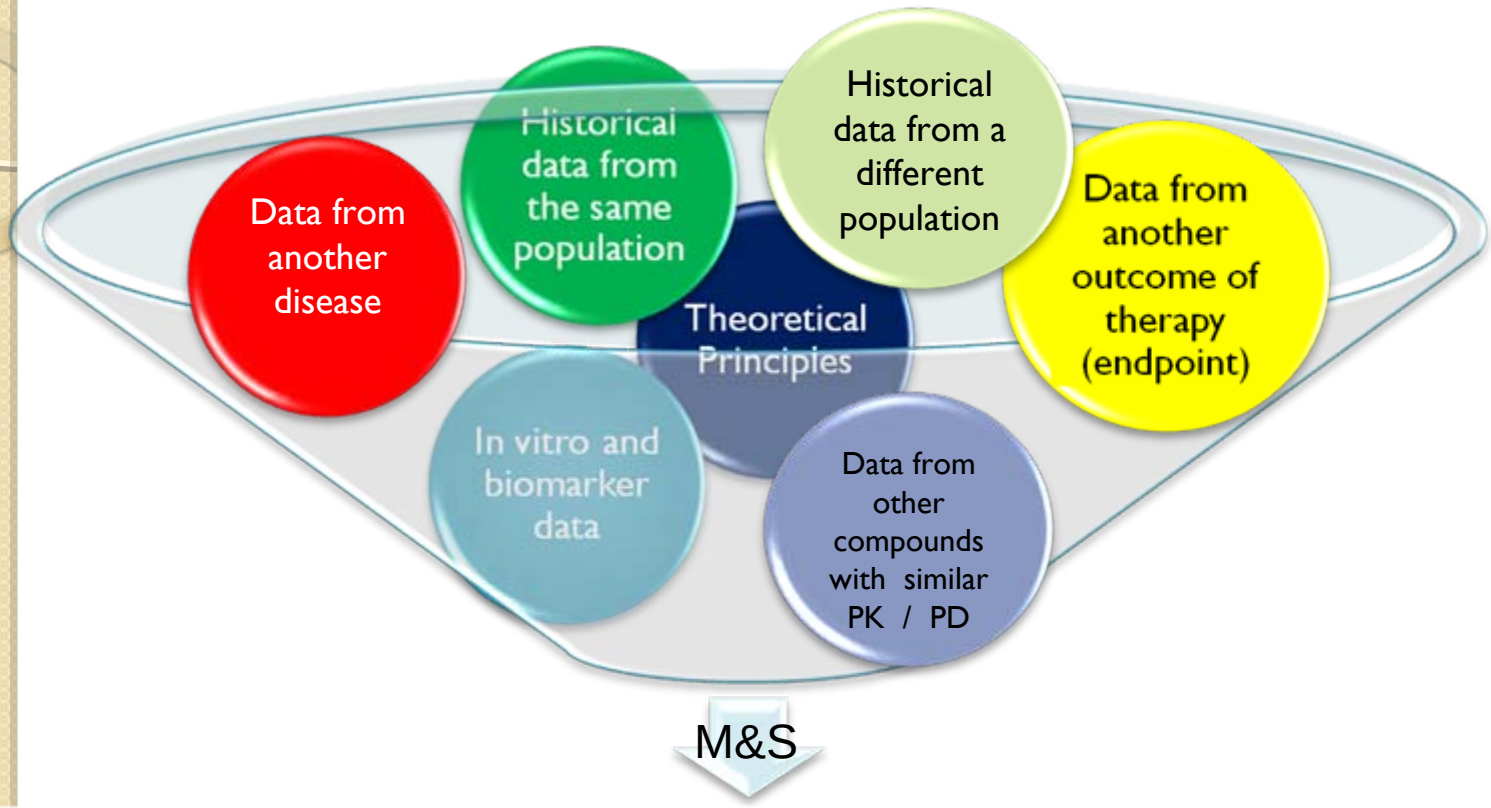
4. The **consequences of M&S assumptions** must be assessed**.** Assumptions can be **violated** (this should be addressed accordingly e.g. by additional evidence or by a better model), **mitigated** (e.g., by label restriction, dose titration) or **pertain as risk** to patients and other stakeholders (e.g., regulator/sponsor).

Evidence synthesis in the development of drugs for special populations, ethnic groups and rare diseases

TO ADDRESS CLINICAL, SCIENTIFIC OR REGULATORY QUESTIONS BY INFERENTIAL METHODS ONE MUST CONSIDER THE FOLLOWING COMPONENTS:

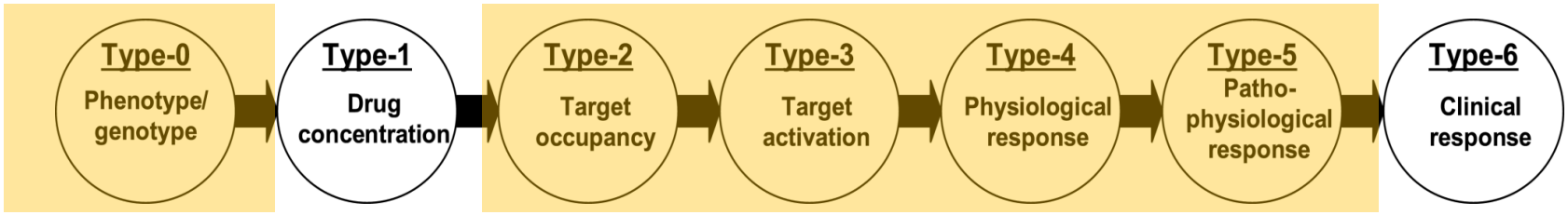


Evidence synthesis in the development of drugs for special populations, ethnic groups and rare diseases

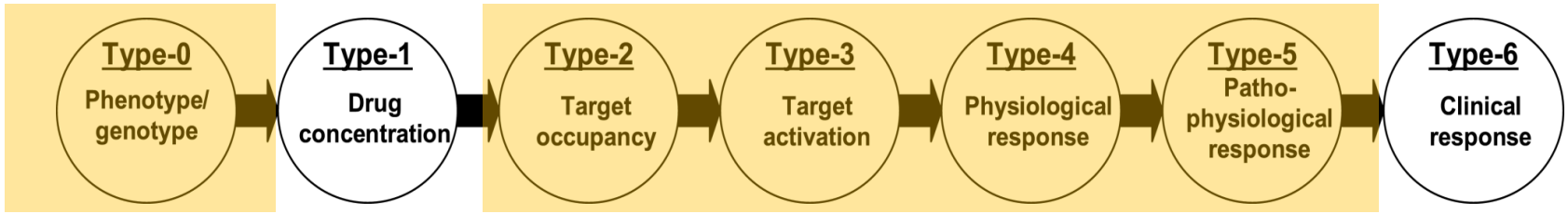


ASSUMPTIONS: which biological, pharmacological and clinical aspects need to be considered when extrapolating across populations?

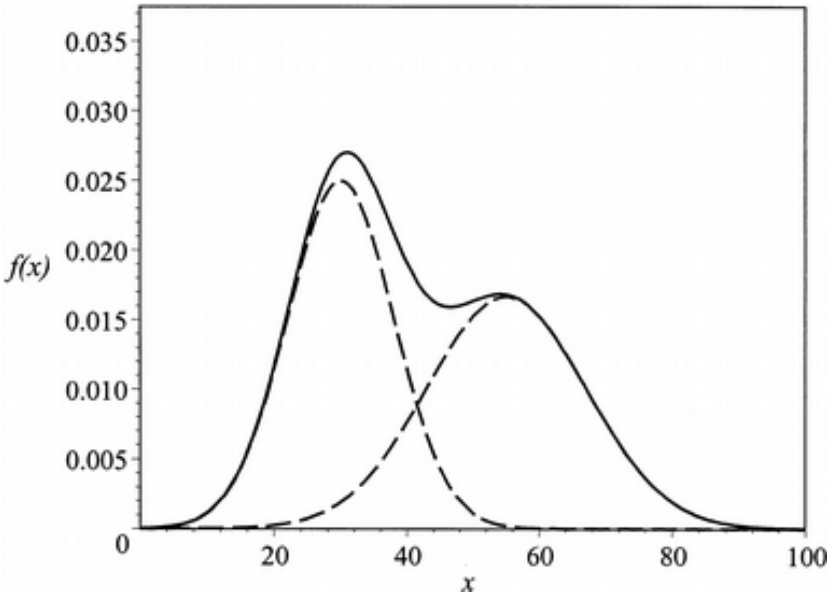
Within groups or populations but different stratification factors:



Across endpoints or diseases:



ASSUMPTIONS: which statistical aspects need to be considered when extrapolating across populations ?



VARIABILITY : Across age groups, ethnicities, endpoints and diseases

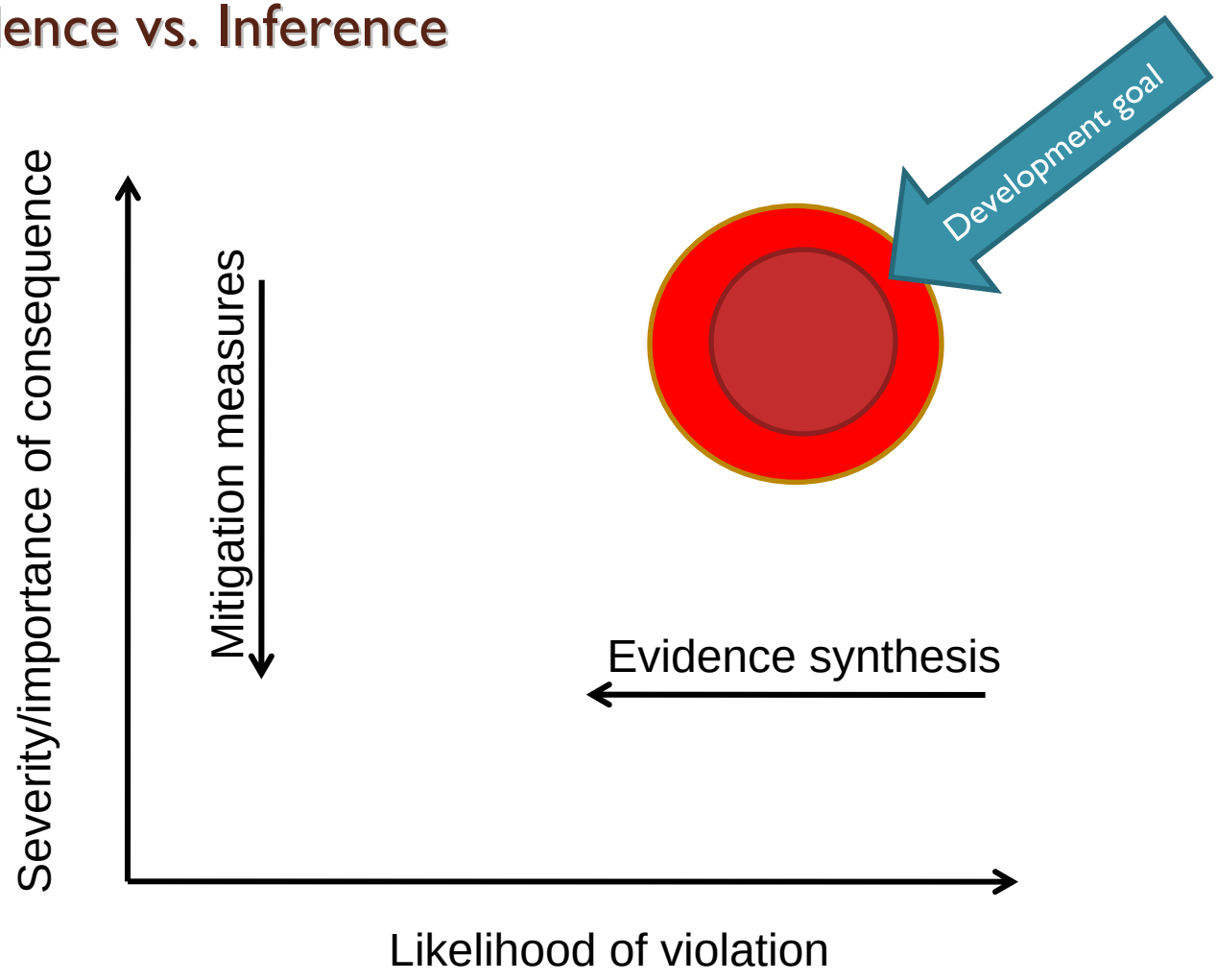
HOMOGENEITY : Across age groups, ethnicities, endpoints and diseases

EFFECT SIZE : Across age groups, ethnicities, endpoints and diseases

UNCERTAINTY: due to sparseness of evidence, model misspecification, bias or lack of knowledge.

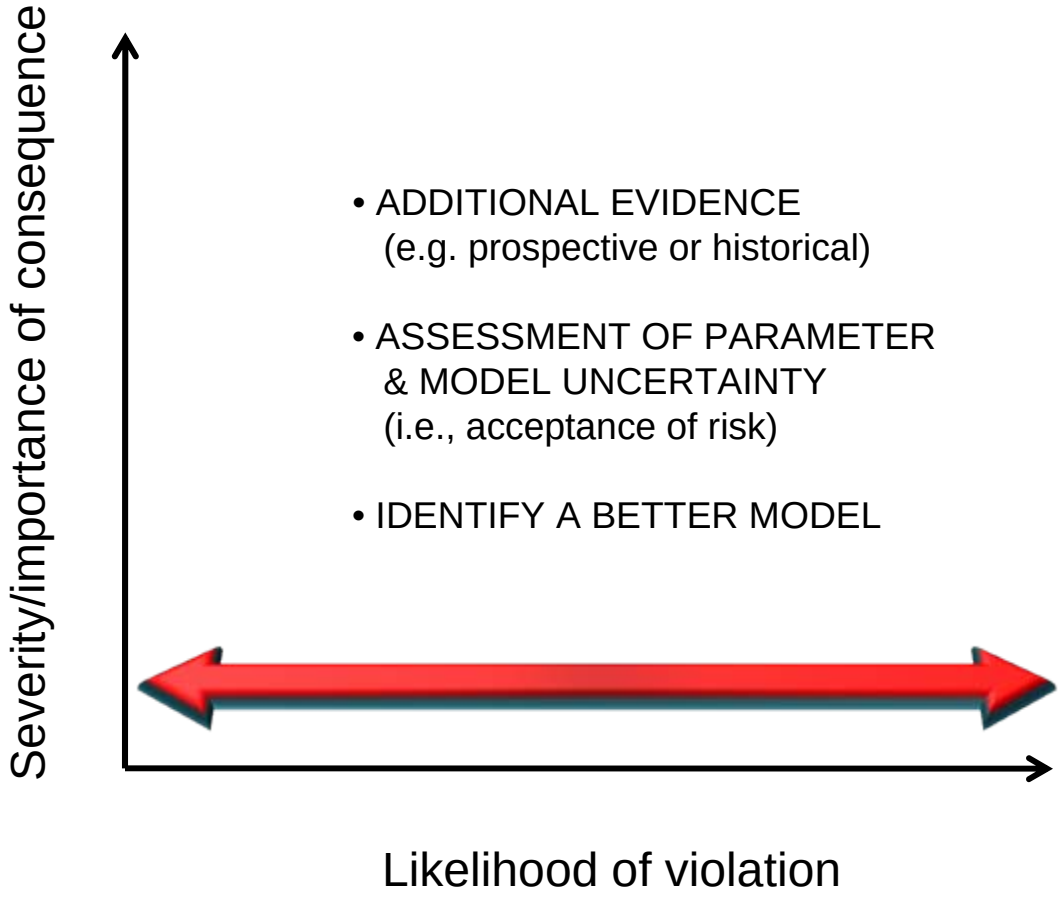
Impact of Assumptions

Evidence vs. Inference

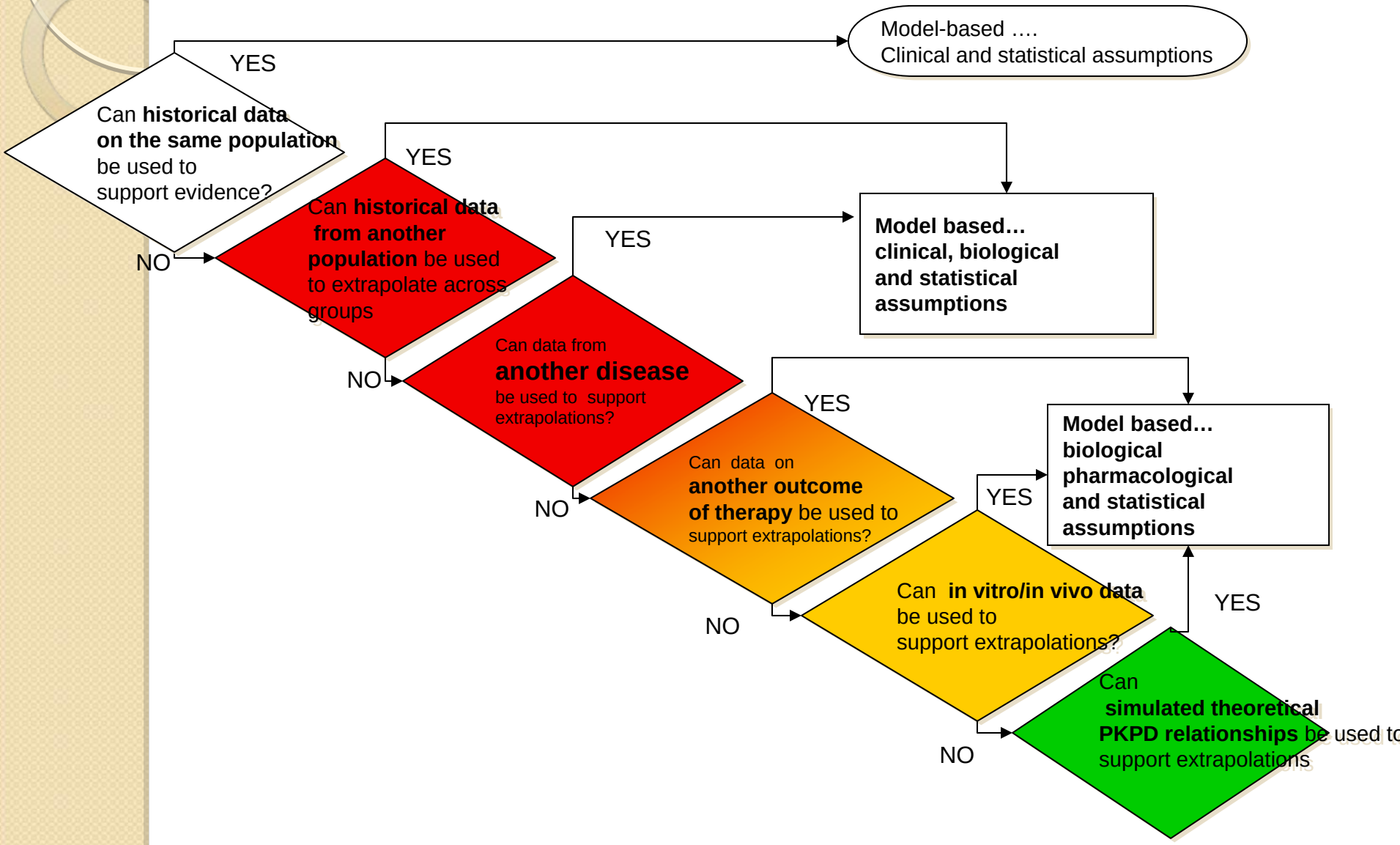


Impact of Assumptions

Evidence vs. Inference



CHALLENGE: framework to handle M&S assumptions



CHALLENGE: framework to handle M&S assumptions

Assumption	Probability to violate	Clinical Consequences	Impact of M&S on development programme
PK properties	Definitely Likely Unlikely Improbable	Minor Major Unknown	Reduce trial burden Reduce sampling frequency
PD properties	Definitely Likely Unlikely Improbable	Minor Major Unknown	Incorporation of biomarkers Better dose rationale
Disease	Definitely Likely Unlikely Improbable	Minor Major Unknown	Population selection Stratification Different recommendation (e.g., contraindication)
Patient population	Definitely Likely Unlikely Improbable	Minor Major Unknown	Estimation of covariate effects Define appropriate inclusion criteria
Statistical aspects	Definitely Likely Unlikely Improbable	Minor Major Unknown	Reduce sample size Higher statistical power Eliminate need for a study

Case Studies

We we will illustrate how M&S can be used as a management tool for evidence synthesis and how assumptions can be managed during drug development for special populations, ethnic groups and rare diseases. In these examples, focus will be given to the following ASSUMPTIONS :

1.Use of historical data from a reference population under the assumption of ***scalable ADME processes***

2.Use of data from another disease (indication) under the assumption of ***comparable pathophysiology and PKPD relationship across populations***

3.Use of historical data from a reference population under the assumption of ***similar parameter-covariate relationships, no model misspecification***

4.Use sparse data under the assumption of ***no model uncertainty and parameter precision***