Predicting the population health effects of changing tobacco exposures: Statistical models for regulatory compliance

70th Tobacco Science Research Conference
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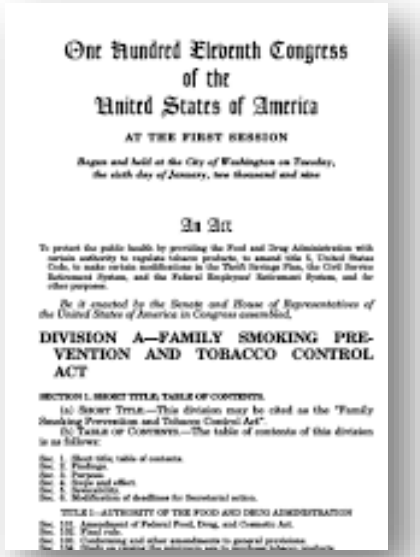
FAMILY SMOKING PREVENTION AND TOBACCO CONTROL ACT (FSPTCA)

A tobacco product may be designated as an MRTP if, among other conditions, the applicant has demonstrated that

"a measurable and substantial reduction in morbidity or mortality [...] is reasonably likely in subsequent studies."



One Hundred Eleventh Congress
of the
United States of America

AT THE FIRST SESSION

An Act

DIVISION A—FAMILY SMOKING PREVENTION AND TOBACCO CONTROL ACT

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MRTP CONSIDERATIONS

- Reductions in morbidity and mortality are expected and hoped for
- Unintended consequences may also occur

REGULATORY IMPORTANCE

- Policy makers must consider
  - Intended, beneficial consequences; and
  - Potential for unintended, harmful consequences
- Policy makers must assess the magnitude and likelihood of both

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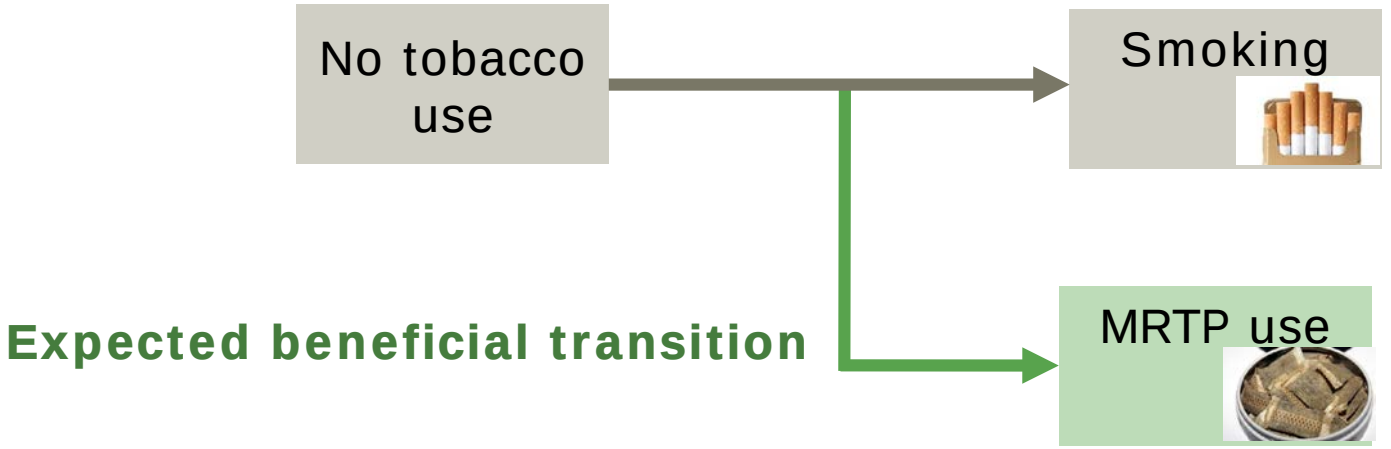
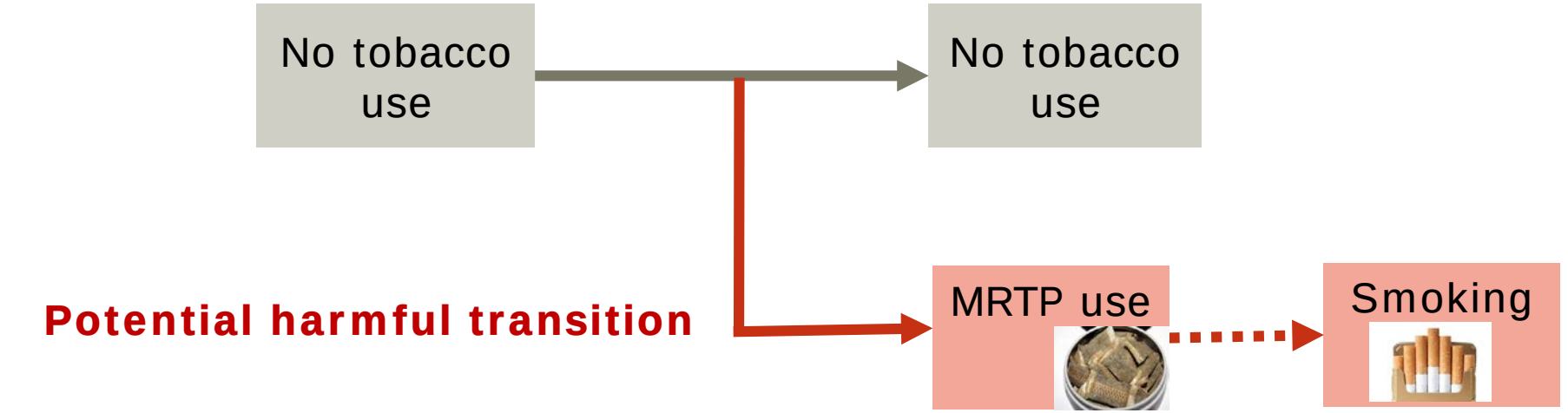
INTRODUCTION OF AN MRTP TO 'NEVER TOBACCO USERS'





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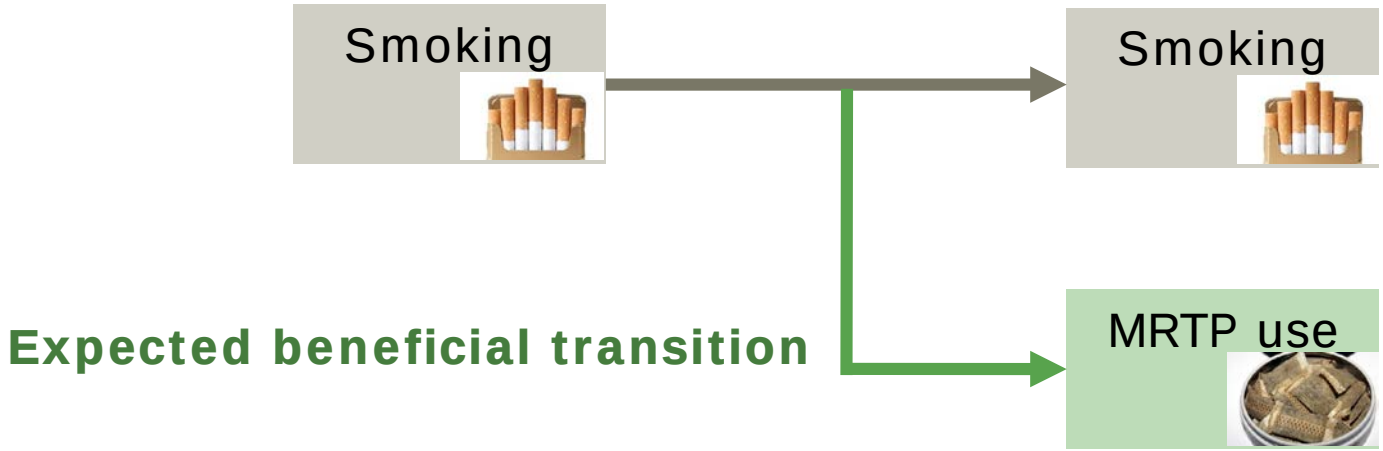
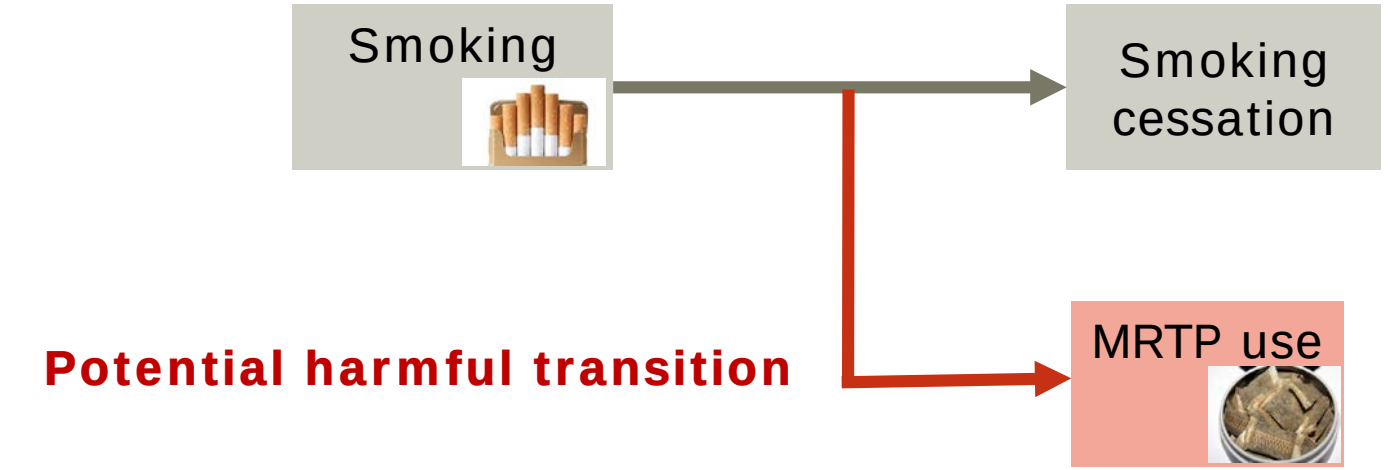
INTRODUCTION OF AN MRTP TO CURRENT SMOKERS





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The proposed MRTP is a new product

Risks are unknown
Population-level effects cannot be directly estimated

"Statistical thinking will one day be as necessary for efficient citizenship as the ability to read and write."

H.G.Wells

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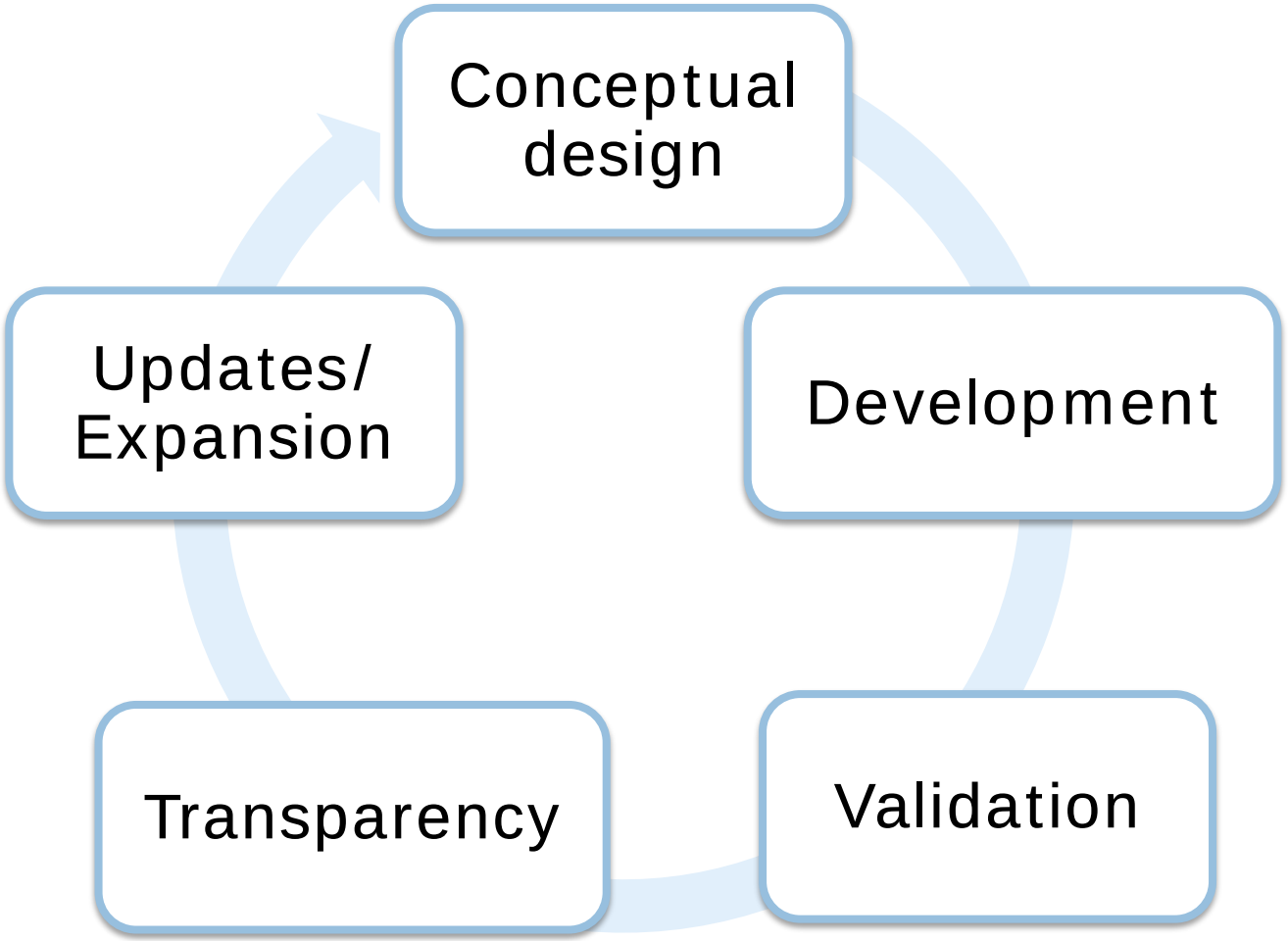
REQUIREMENTS FOR A STATISTICAL MODEL IN THE REGULATORY CONTEXT



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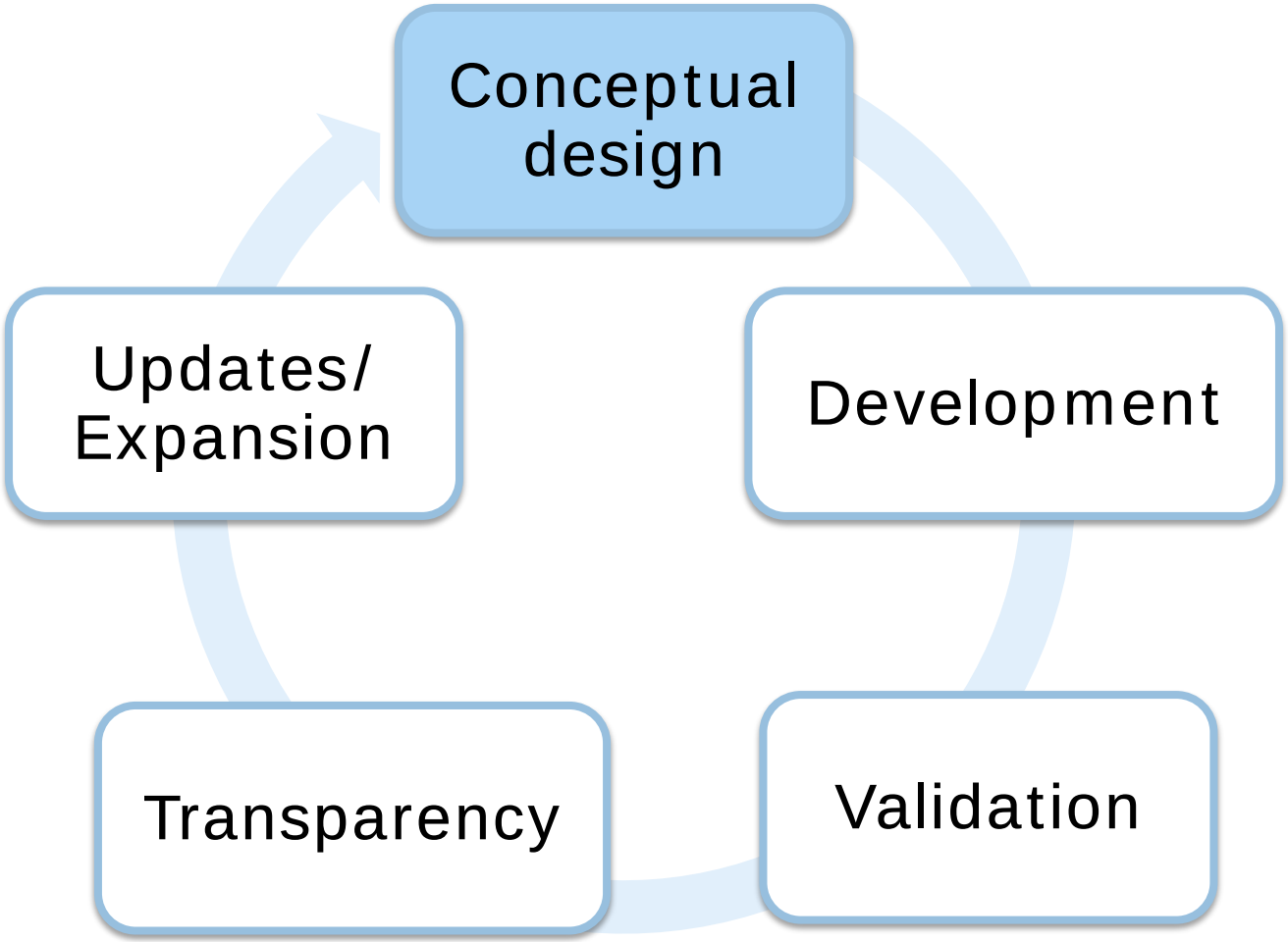

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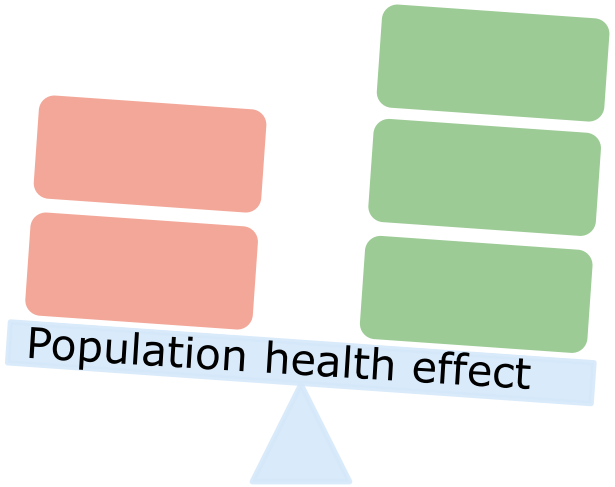
ADHERENCE TO FSPTCA GOAL

- Tipping point analyses

Harmful changes in exposure patterns

Beneficial changes in exposure patterns



REGULATORY IMPORTANCE

- Policy makers can weigh risks and benefits using a scientifically valid approach
- Health impacts of alternative policies can be assessed
- Model results may support selection of one policy over another

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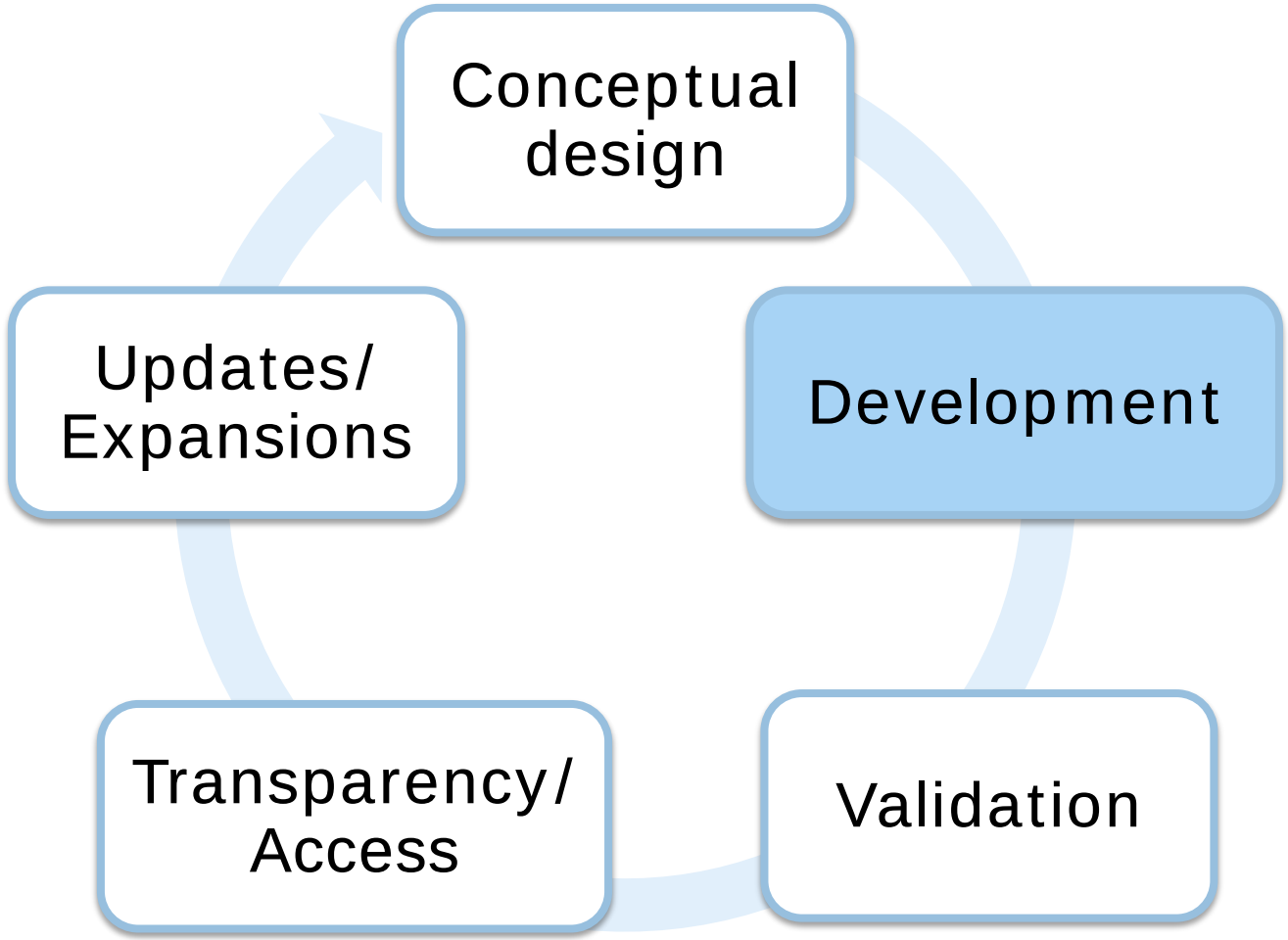

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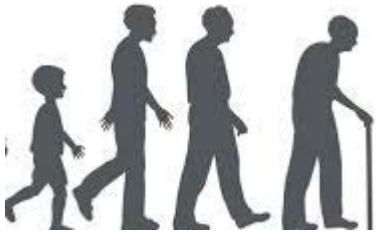
STUDY POPULATION AND TIME VARIABLES

Approach 1: Follow one birth cohort as it ages



- All cohort members have the same age; age is the only time variable
- Follow-up occurs until all cohort members have died
- Multiple exposure transitions can occur throughout follow-up
  - Base case: Exposure to cigarettes, no MRTP use
  - Counterfactual scenario: Exposure to cigarettes and/or MRTP

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ADVANTAGES

- Relatively few input values
  - o Clear definition of underlying assumptions
- Complete follow-up
  - o Exposure histories are known
  - o All deaths are accounted for
- Easy investigation of relevant questions
  - o Tipping point analyses

REGULATORY IMPORTANCE

- Clarity of assumptions
- Answers to relevant questions

Switching to MRTP use…

…among base case smoking quitters

…among base case continuing smokers

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DISADVANTAGE

- No direct predictions for cross-sectional populations

REGULATORY IMPORTANCE

- Results can provide evidence of the effects of introducing a MRTP to a cross-sectional population
- Results do not provide direct estimates

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STUDY POPULATION AND TIME VARIABLES

Approach 2: Follow a cross-sectional population over time

- Cross-sectional population of mixed ages and tobacco exposures is followed into the future
- New members may be added during follow-up
- Two time variables, age and calendar year
- Follow-up occurs to a pre-specified age or the end of follow-up
- Multiple exposure transitions can occur throughout follow-up

THEORETICAL ADVANTAGE

- Conceptually appealing
  - In theory, direct predictions are possible for the modeled cross-sectional population

REGULATORY IMPORTANCE

- Approach is flawed
- Invalid predictions are not useful

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DISADVANTAGES

- Large number of birth cohorts
- Input values
  - o For all birth cohorts
  - o Stratified by two time variables
  - o Impossible to obtain
- Follow-up must be short
  - o Tobacco-related mortality may occur after the end of follow-up
  - o Artificially low mortality risks
- Survivor bias
- No tipping point analyses

REGULATORY IMPORTANCE

- Low validity and generalizability
  - o Input values
  - o Incomplete follow-up
  - o Survivor bias
- No valid assessment of
  - o MRTP initiation/gateway effect
  - o Switching to MRTP use/dual use
  - o Tipping points

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EXPOSURE TRANSITIONS AND TRANSITION PROBABILITIES

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EXPOSURE TRANSITIONS

- Model must allow for comparisons between
  - o Counterfactual scenario
  - o Base case
- Model must allow for the most commonly observed exposure transitions

REGULATORY IMPORTANCE

- Transitions address research questions pertinent to regulatory requirements
- Transitions are relevant to the population affected by the regulation

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TRANSITION PROBABILITIES

- Throughout follow-up, survivors should be distributed into age and exposure categories
- Model users should be able to specify probabilities of shifts between exposure categories
- These transition probabilities should be age-specific

REGULATORY IMPORTANCE

- Transition probabilities are easily modifiable to evaluate different scenarios

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RISK TO THE POPULATION RESULTING FROM DIFFERENT EXPOSURE SCENARIOS

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RISK ESTIMATION

- Smoking: Risk estimates should
  - o Be based on the literature
  - o Account for key predictors of the outcome measure
- MRTP use:
  - o Risks are unknown
  - o Adjustment factors such as an excess relative risk (ERR) can be used to reduce smoking-specific risks

REGULATORY IMPORTANCE

- Model input values can be substantiated
- Model results are relevant to the population affected by the regulation

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MODEL OUTPUT

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REPORTABLE RESULTS

- Counterfactual vs. base case
  - Survivors or deaths
  - (Quality of life adjusted) life expectancy
  - Age-dependent
- Tipping points

REGULATORY IMPORTANCE

- Population-level impact of changing exposure patterns
  - Mortality
  - Morbidity (Surrogate)
  - Subpopulations of different ages
- Expected benefits vs. potential harm of changing exposure patterns

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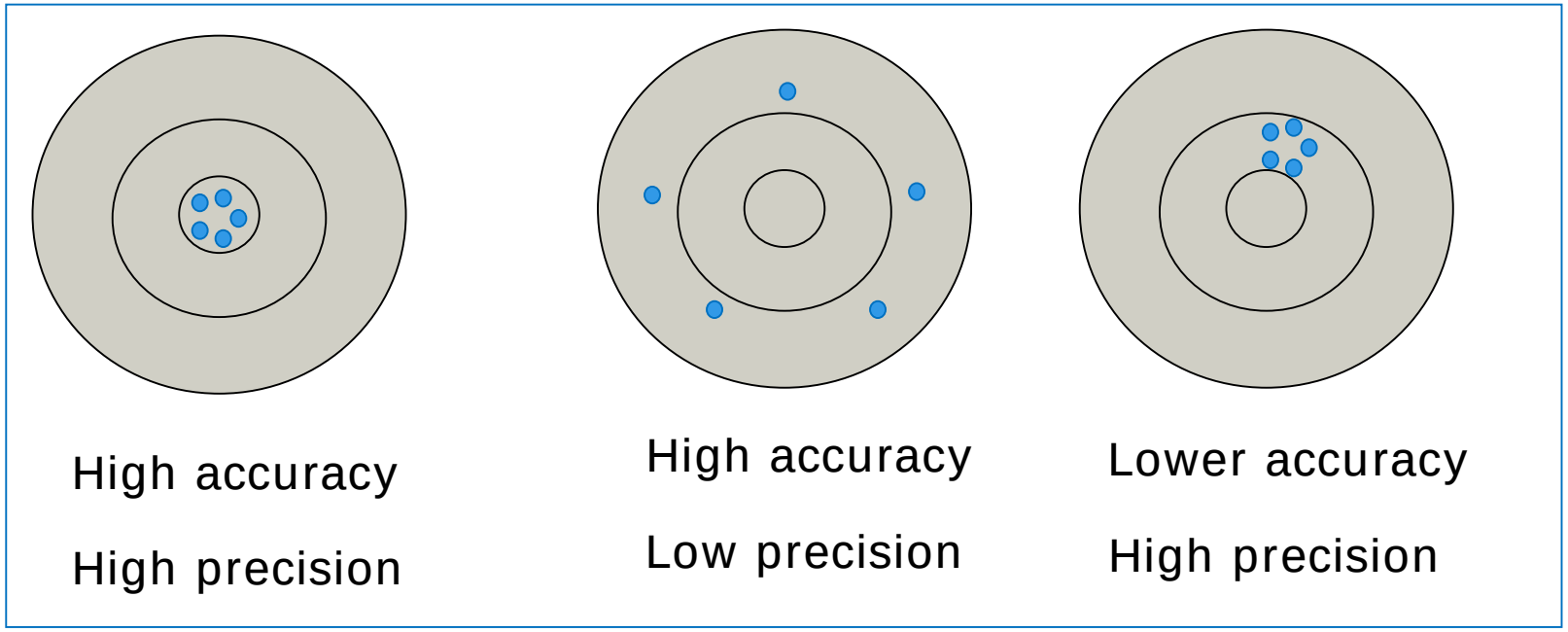
PRECISION (VARIABILITY) OF THE RESULTS



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INCORPORATING UNCERTAINTY, ESTIMATING VARIABILITY

- Model should accept input as
  - Fixed; or
  - With a degree of uncertainty
- Variability in the output measures should be estimated
  - E.g., by using Markov Chain Monte Carlo (MCMC) techniques

REGULATORY IMPORTANCE

- Uncertainty in model input is taken into account
- Variability of model results is estimated
- Sensitivity analyses
  (model user generates results for a range of input values)
  can be informative, but do not replace variability estimates

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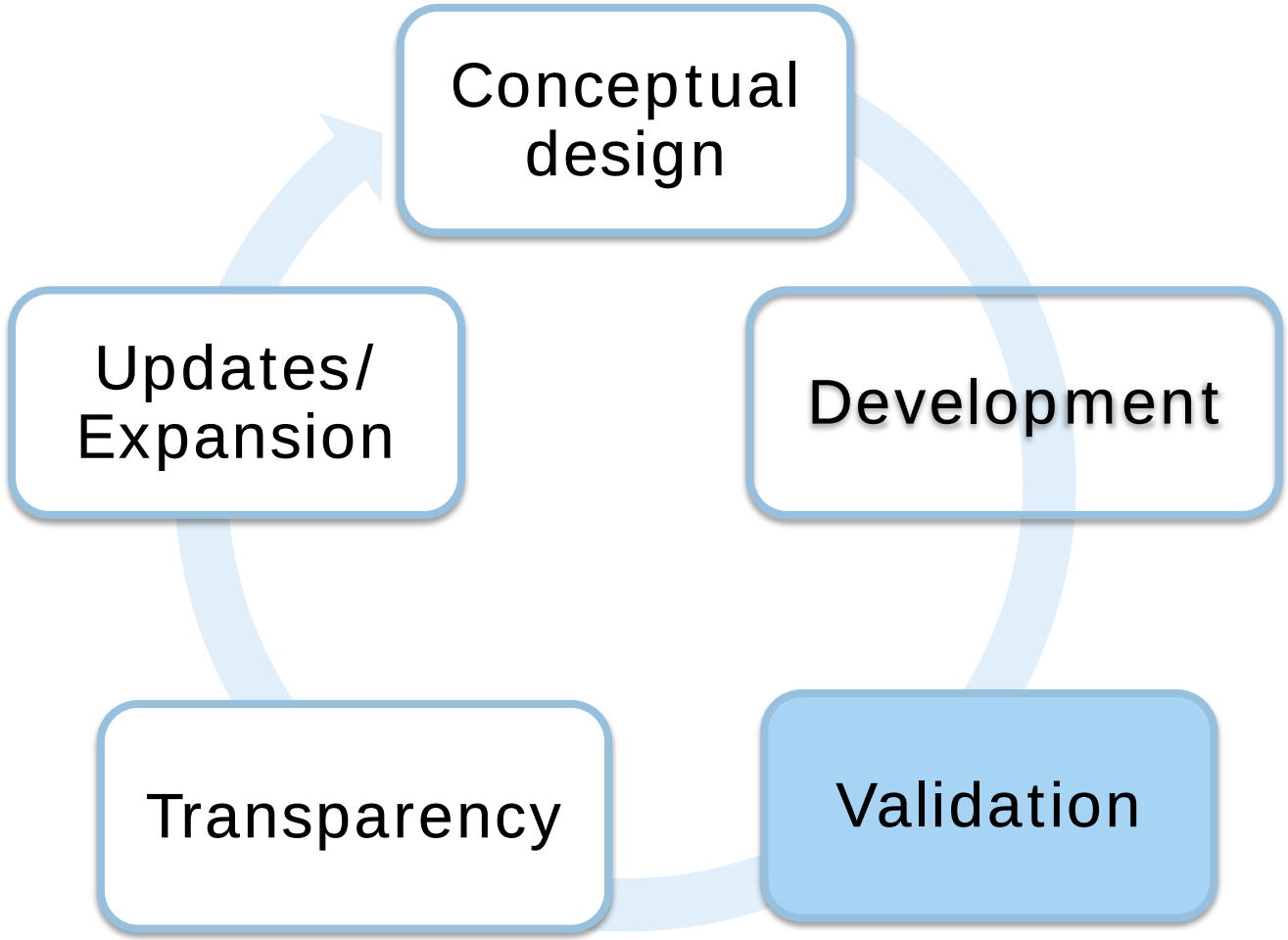

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SORTING PROCESS AND CALIBRATION

- Sorting of population into age and exposure categories must be validated
- Model must be calibrated
  - Use data from actual populations as input for a base case and counterfactual scenario
  - Compare model results to survival data from the actual populations

REGULATORY IMPORTANCE

- Close correspondence between model results and observations from the population
  ➔ Model is well calibrated
- Predictions based on the scenarios being tested may be considered valid

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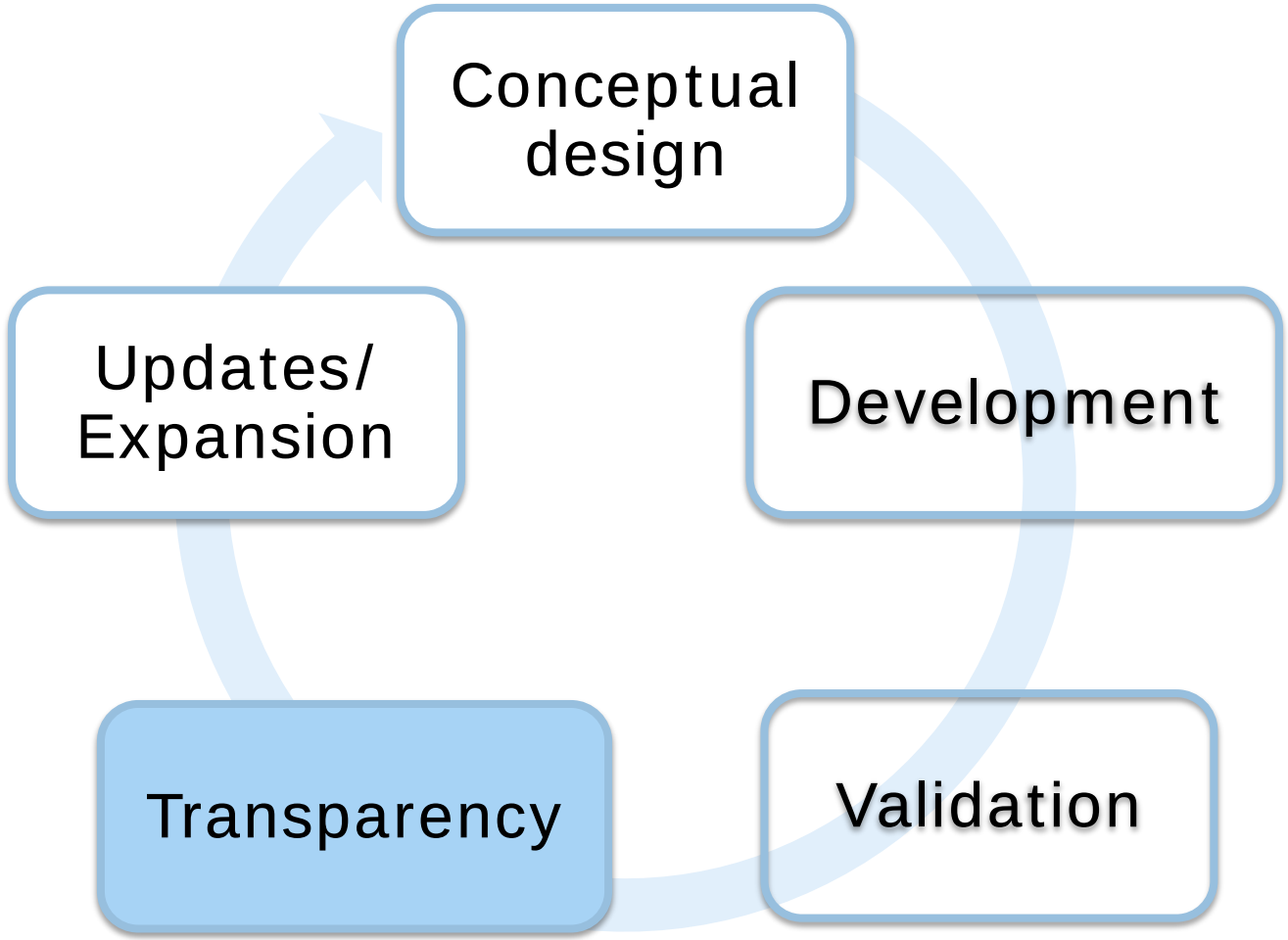

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CRITICAL REVIEW AND ACCESS

- Methods, assumptions, input data must be be clearly documented and available for peer and stakeholder review
- To facilitate this, set up and operation of the model must be user-friendly

REGULATORY IMPORTANCE

- Policy makers are able to assess
  - Validity of methods and assumptions
  - Relevance of methods and assumptions to regulatory goals

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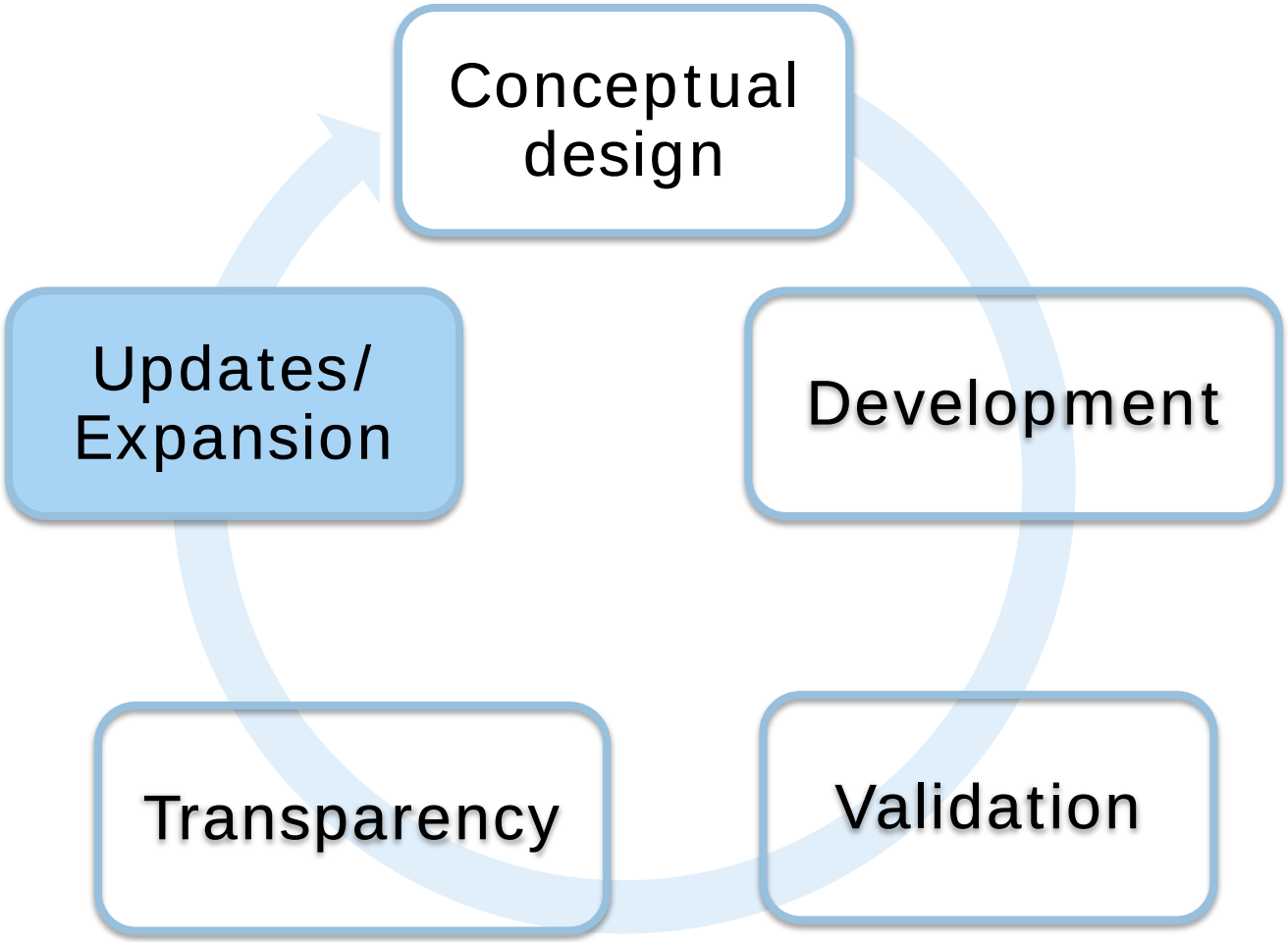

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UPDATES/EXPANSIONS

- The model should be flexible enough to allow for the easy incorporation of new study questions or data

REGULATORY IMPORTANCE

- Incorporation of post-market surveillance data
  - E.g., update transition probabilities to monitor potential adverse, unexpected consequences
- Expandability
  - E.g., allow comparison of a base case with two products to a counterfactual scenario with three or more products

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THANK YOU!

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CONTACT INFORMATION

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The dynamic population modeler described here was developed independently of the sponsors.

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