Aligning Bayesian Trial Designs with Expert Opinion: Some Rules of the Road

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Disclaimer

This presentation reflects the views of the authors and should not be construed to represent the policies of the U.S. FDA.

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Outline

- Legal Framework for Pediatric Studies
- The Statistician as Translator
- Phases for Designing a Bayesian Trial
- Bridging the Gap Between Expert Opinion and the Prior
- Conclusions

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- Legal Framework Driving Pediatric Studies
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Legal Framework Driving Pediatric Studies

- Goal: Ensure availability of safe and effective drugs, at proper doses, for pediatric populations (birth to < 17 years of age)
- Largely driven by legal mandates and incentives
  - Mandate to conduct trials: Pediatric Research Equity Act (PREA)
    - All new active ingredients, new indications, new dosage forms, new dosing regimens, new routes of administration
    - Some exceptions, such as orphan products, adult-related conditions
  - Incentive to conduct trials: Best Pharmaceuticals for Children Act
    - Offers pediatric exclusivity and extensions of adult exclusivity

Pediatric Extrapolation as a Legal Mandate

- Goals
  - Minimize pediatric enrollment due to lack of informed consent by subjects
  - Rapid availability of safe and effective pediatric therapies
- Legal mandate
  - **Extrapolate** pediatric effectiveness from studies in adults if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients (PREA)

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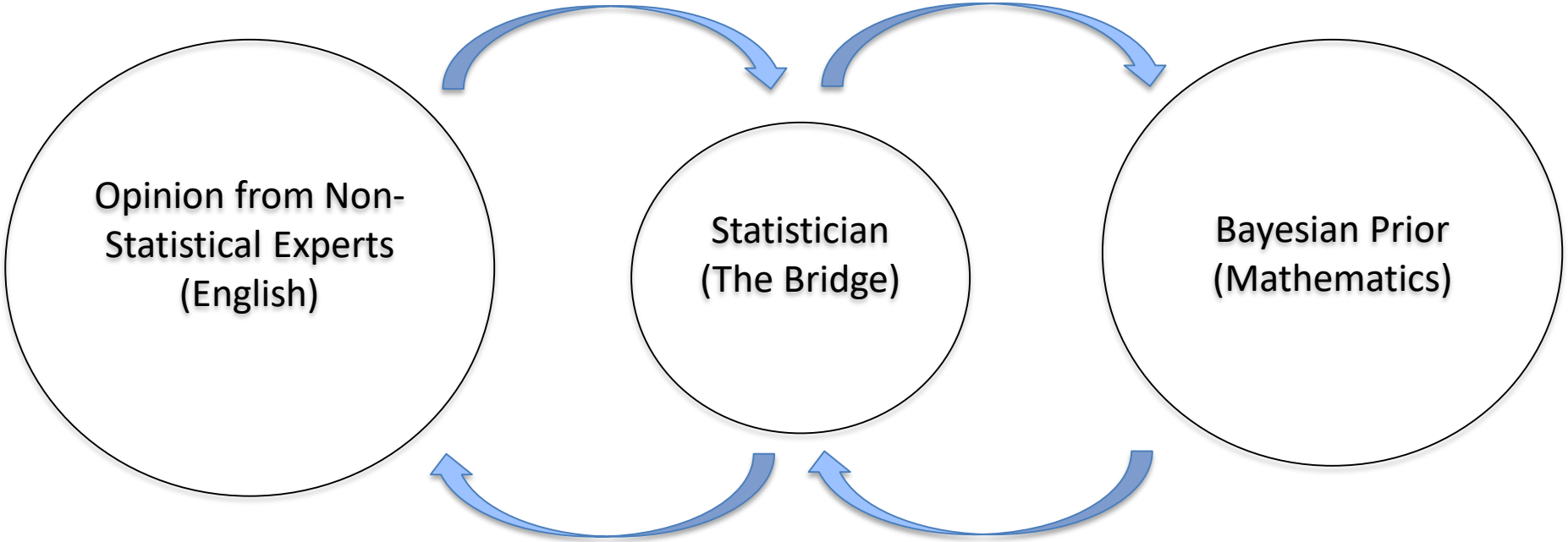
The Statistician as Translator



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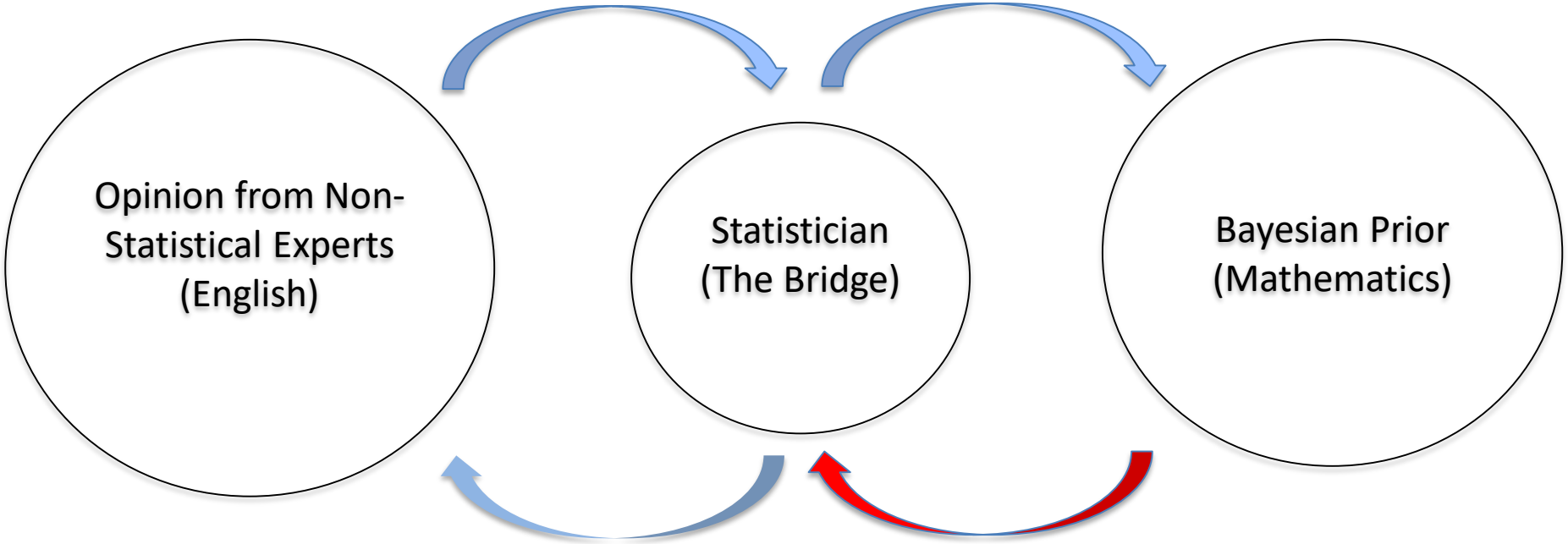

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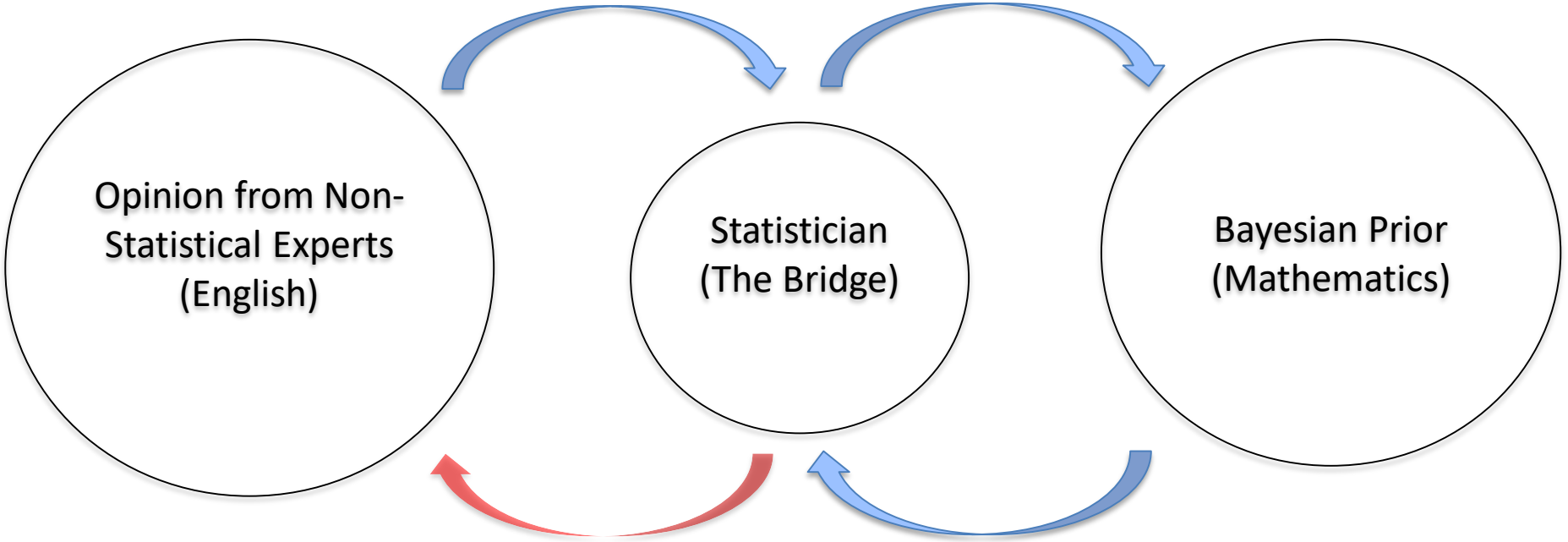

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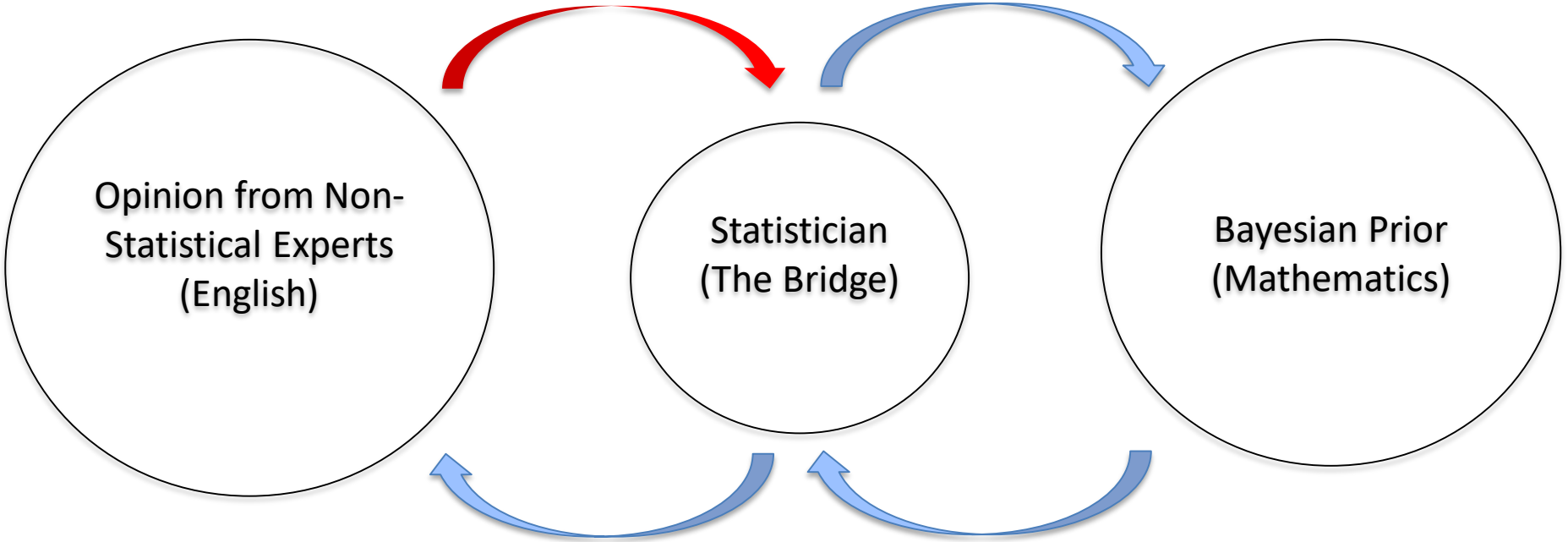

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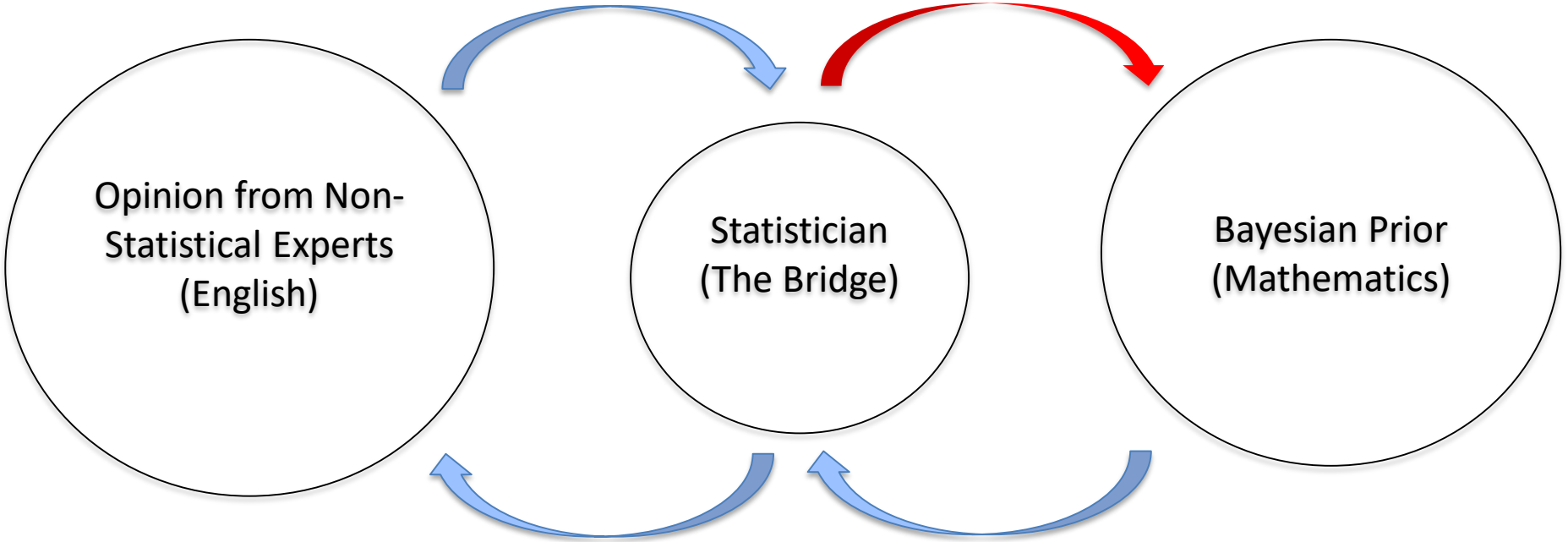

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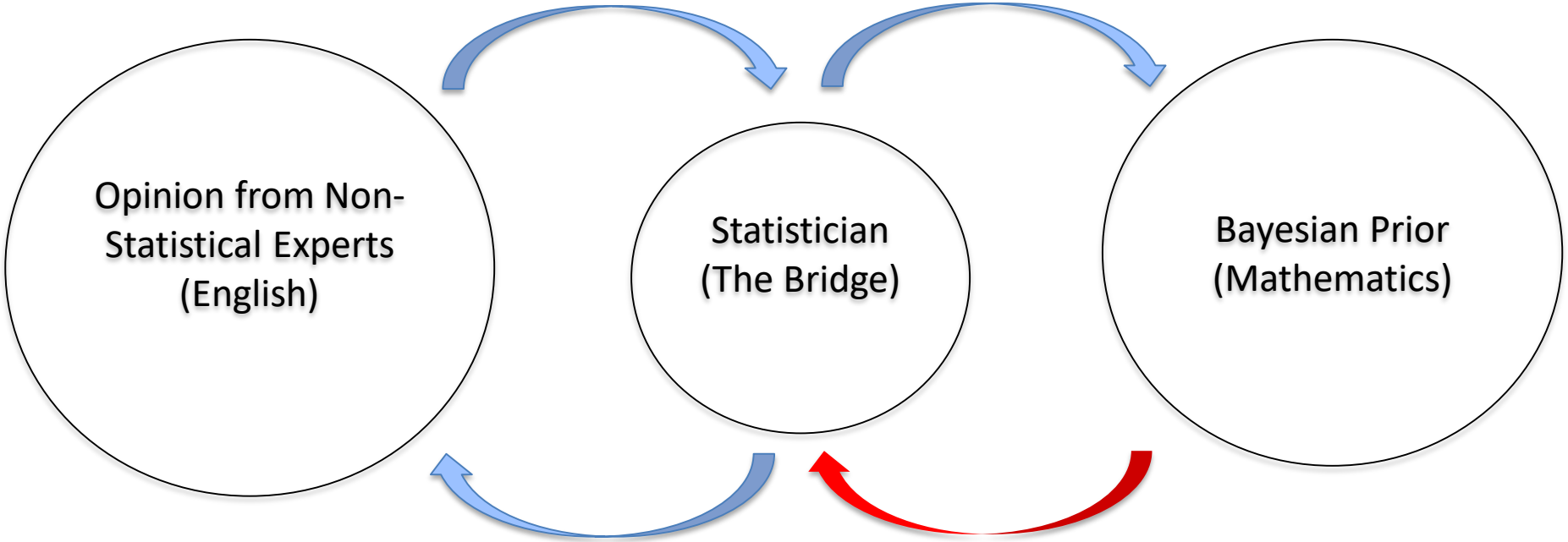

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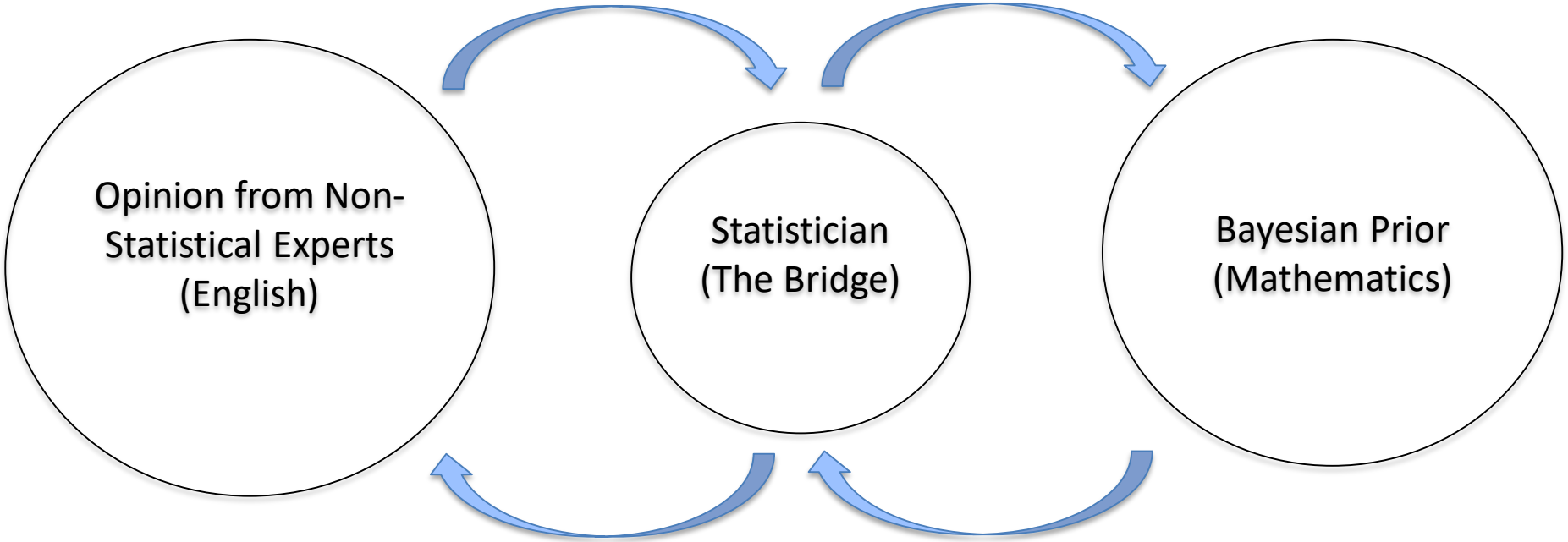
Bayesian Design as an Iterative Process



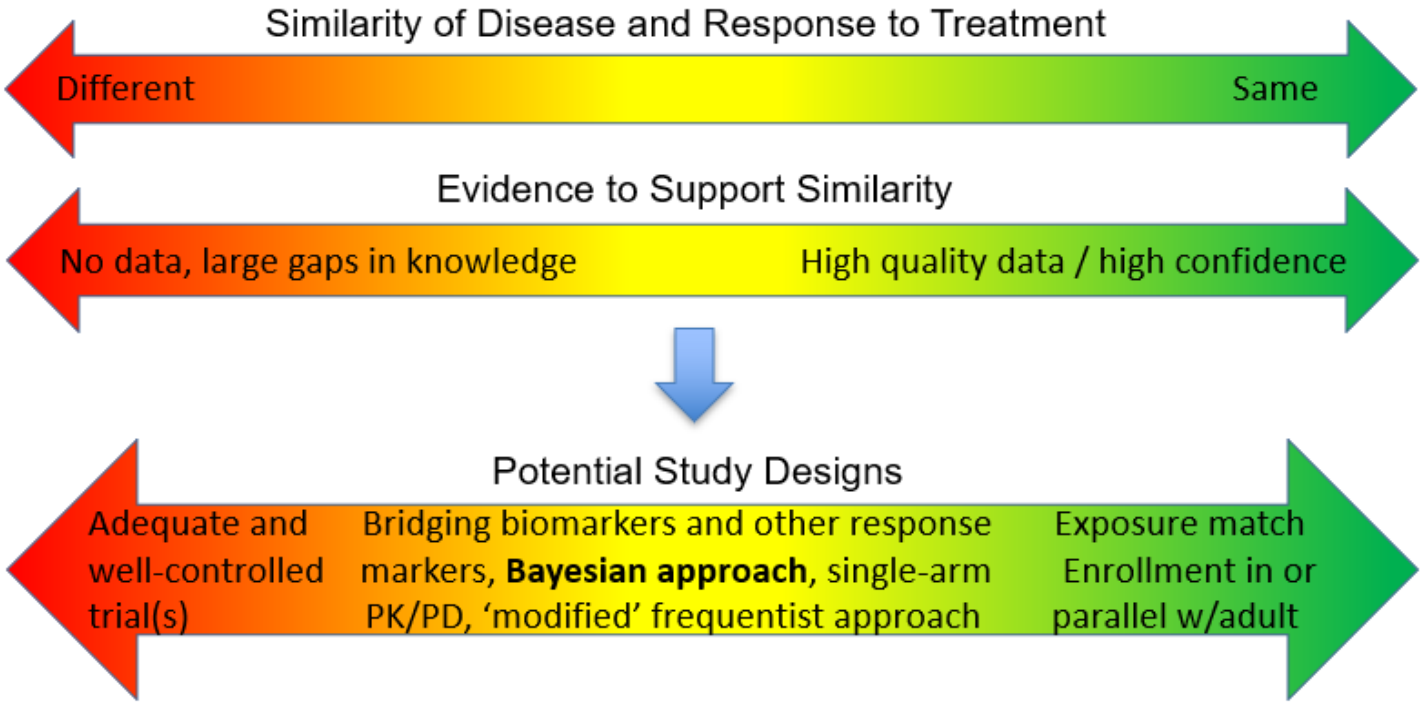
Phases for Designing a Bayesian Trial

1. Develop Pediatric Extrapolation Concept and Plan
2. Establish Minimum Design Requirements
3. Converge to ‘Optimal’ Feasible Design

Phases for Designing a Bayesian Trial

1. Develop Pediatric Extrapolation Concept and Plan
   - Mandated by PREA
   - Purpose: Determine appropriate study design(s)
     - Bayesian approach may be an option
   - Discussants: Statisticians, clinicians, pharmacologists, (epidemiologists), (patients)

Framework for Pediatric Extrapolation



Source: modified from draft FDA Guidance E11A Pediatric Extrapolation

Phases for Designing a Bayesian Trial

2. Establish Minimum Design Requirements
   - When: After extrapolation framework, but before simulations
   - Discussants: Statisticians, clinicians, pharmacologists, (epidemiologists), (patients)
   - What to discuss: ‘Outwardly facing’ concerns
     - Success criteria
     - Power
     - Type 1 error
     - Bias

Phases for Designing a Bayesian Trial n

3. Discuss ‘Optimal’ Feasible Design
   - When: After simulations available
   - Discussants: Statisticians, clinicians, pharmacologists, (epidemiologists), (patients), resource administrators
   - What to discuss: prior adjustment to provide analysis with ‘best’ characteristics including
     - Sample size
     - Success criteria
     - Power
     - Type 1 error
     - Bias

Phases for Designing a Bayesian Trial

- ‘Optimal’ Design (continued)
  - As set of tables to be picked through
    - appropriate if minimal number of ‘control’ parameters in prior
  - As solution to a linear or non-linear programming problem
    - may be appropriate if multiple ‘control’ parameters in prior or comparing multiple forms of priors
    - evaluating too many control parameters or forms of priors will invoke curse of dimensionality
    - elicitation of tradeoff functions from team would be necessary

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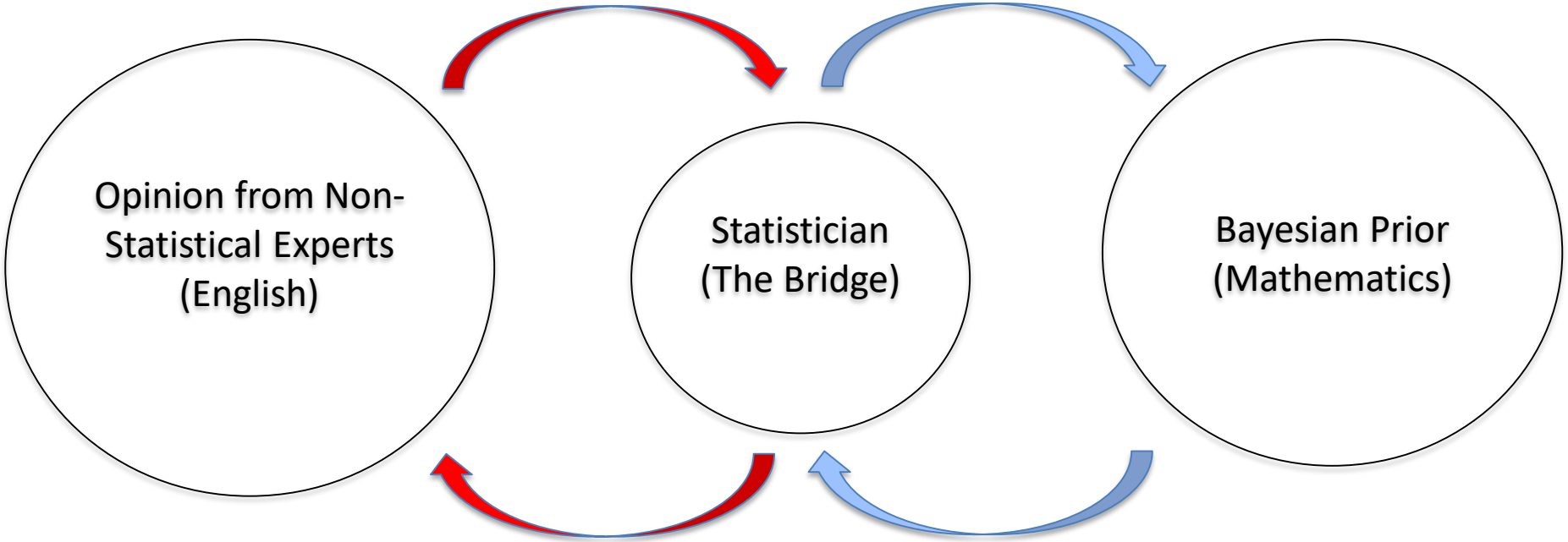
Bayesian Design as an Iterative Process



Methods to Elicit Expert Opinion

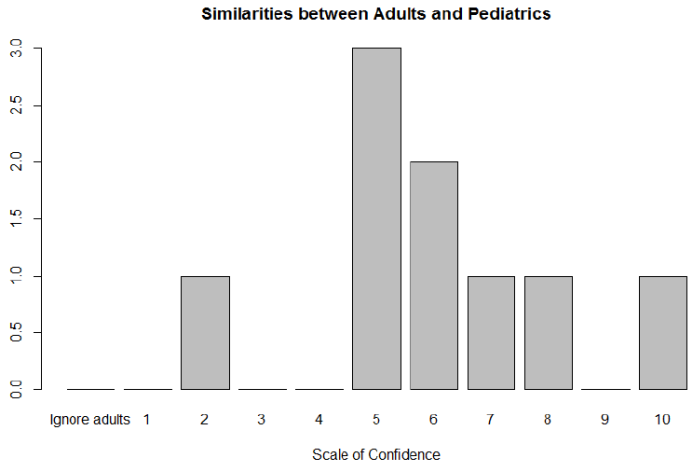
- Informal, wide-ranging discussions
- Cooke Protocol: aggregate separate opinions according to measured expertise of participants
- Sheffield Protocol: separate opinions followed by consensus
- Probabilistic Delphi: multiple rounds of judgement, with controlled, anonymous interactions

after O'Hagan A. 2019. https://doi.org/10.1080/00031305.2018.1518265

A Problematic Elicitation and Identifiability

Expert Elicitation Results

- 10 responses



Weight in Mixed Prior	
Adult Prior	0.60
Skeptical Prior	0.40

- Average similarity = 6
- Median similarity = 6 --> a=P(applicability of adult results)

from Ye J, Travis J. 2017. Pediatric Trial Design and Modeling: Moving into the Next Decade - | FDA

A Problematic Elicitation and Identifiability

- Correspondence between ‘similarity’ and mathematical construct
  - Weight on prior? Percentage of data borrowed from adults?

Weight on Adult Data in Mixed Prior	0	.25	.50	.75	.90	1.0
ELIR Percentage of Total Events Borrowed From Adults	0.0%	84.8%	92.8%	95.2%	96.0%	96.4%

*after: Updated Information: November 8, 2022: Meeting of the Pulmonary-Allergy Drugs Advisory Committee Meeting Announcement - 11/08/2022 | FDA

A Problematic Elicitation and Identifiability

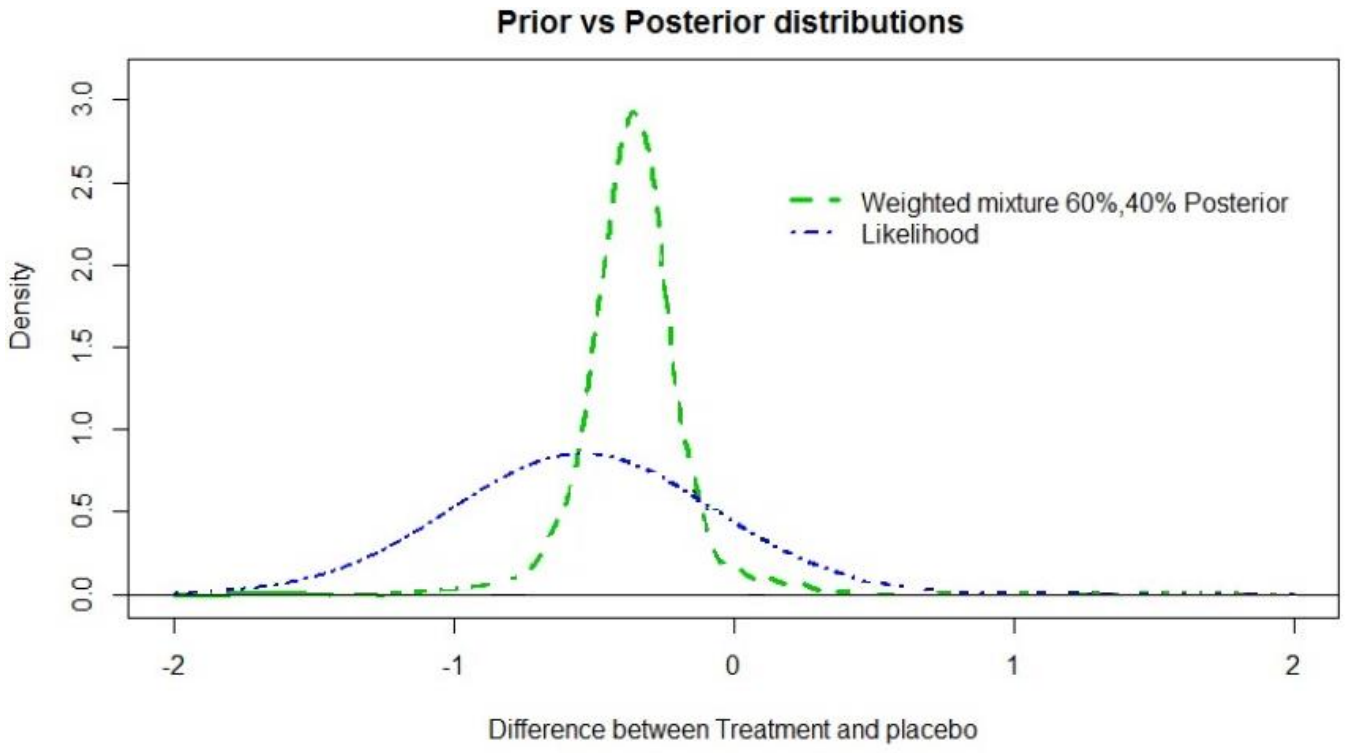
- Different statisticians may interpret same elicited result for similarity as applicable to different mathematical quantities, i.e., we have a 1:N mapping
- Even ‘borrowing’ exhibits a 1:N mapping*
- The 1:N mappings between ‘similarity’ or ‘borrowing’ and their mathematical counterparts can result in grossly different assessments of whether the prior aligns with expert opinion

* Pennello G, Thompson L. 2007. https://doi.org/10.1080/10543400701668274
Travis J, Rothman M, Thomson A. 2023 https://doi.org/10.1080/10543406.2023.2170405

A Problematic Elicitation and Identifiability

- Moral: Ensure linguistic ‘identifiability,’ i.e., 1:1 mapping between language and math
- Identifiability may involve language for a single measure or, at minimum, language for a class of measures which yield similar results

A Problematic Elicitation and Identifiability



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Conclusion: Aligning Bayesian Trial Designs with Expert Opinion

- The added value of the Bayesian approach is incorporation of expert opinion into the statistical model
- Unless expert opinion and the prior are meticulously aligned, the Bayesian approach will be a liability rather than an advantage
- The statistician is responsible for this alignment, as the only person with detailed understanding of both the underlying mathematics and the spoken language

Conclusion: Aligning Bayesian Trial Designs with Expert Opinion

- Avoiding misalignment: Some rules of the road
  - Establish a common, accurate and precise language
    - avoid jargon
    - adopt familiar terminology where jargon is unavoidable
    - ensure any prior characteristic under discussion is ‘identifiable’ from English and, conversely, that the English is identifiable from the prior(s) characteristic
    - implement appropriate methods for elicitation

Conclusion: Aligning Bayesian Trial Designs with Expert Opinion

- Avoiding misalignment: some rules of the road (continued)
  - Only discuss needed characteristics, avoiding excessive details of the modeling
    - simplify rather than complicate the discussion
    - facilitate ‘optimization’ of the design in face of tradeoffs