Bayesian applications in rare disease clinical trial research

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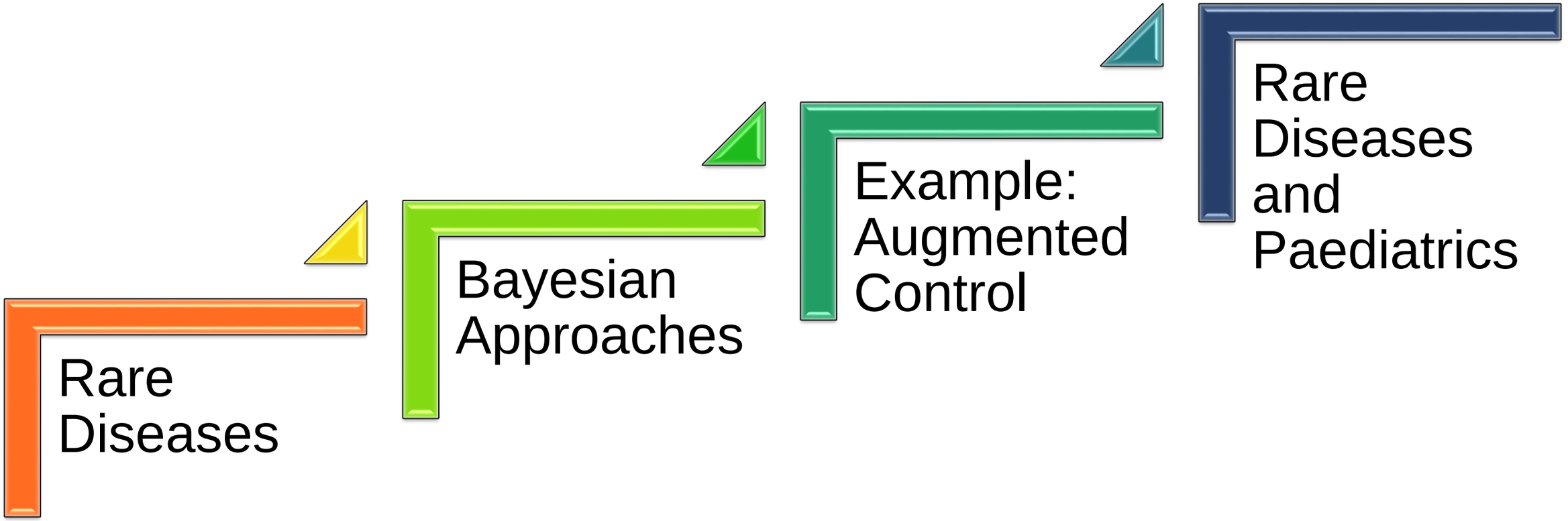
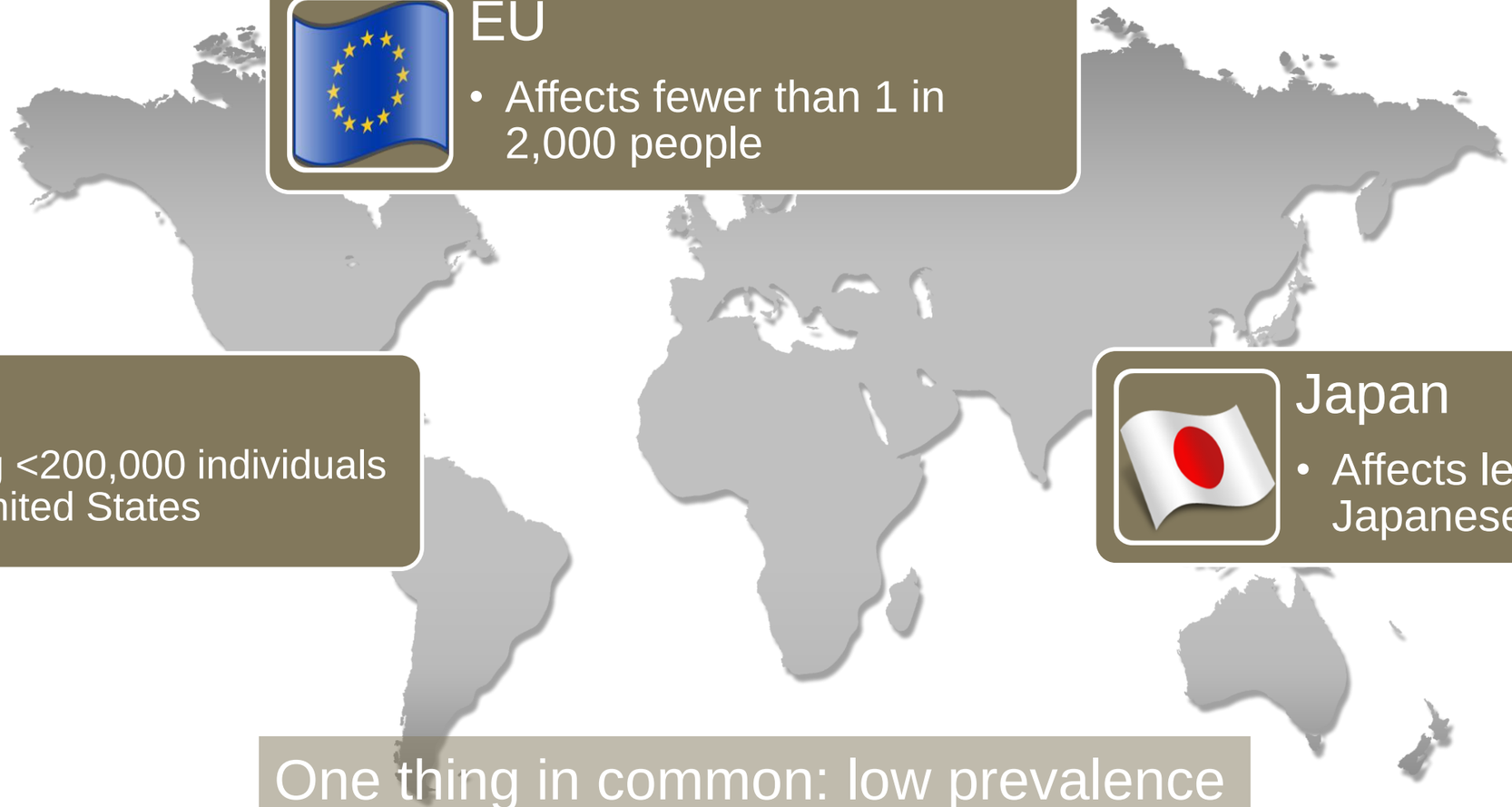
Bayes-Pharma, 24 May 2019

Lilly

Outline



What Makes a Disease Rare?



EU

- Affects fewer than 1 in 2,000 people

USA

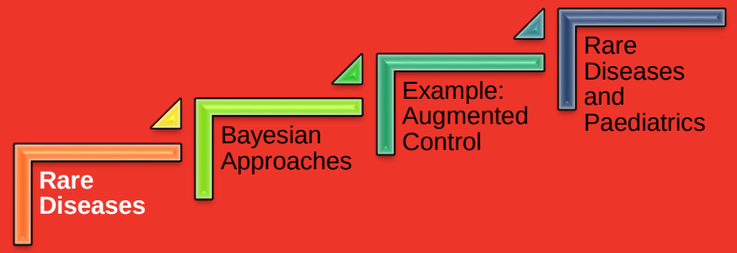
- Affecting <200,000 individuals in the United States

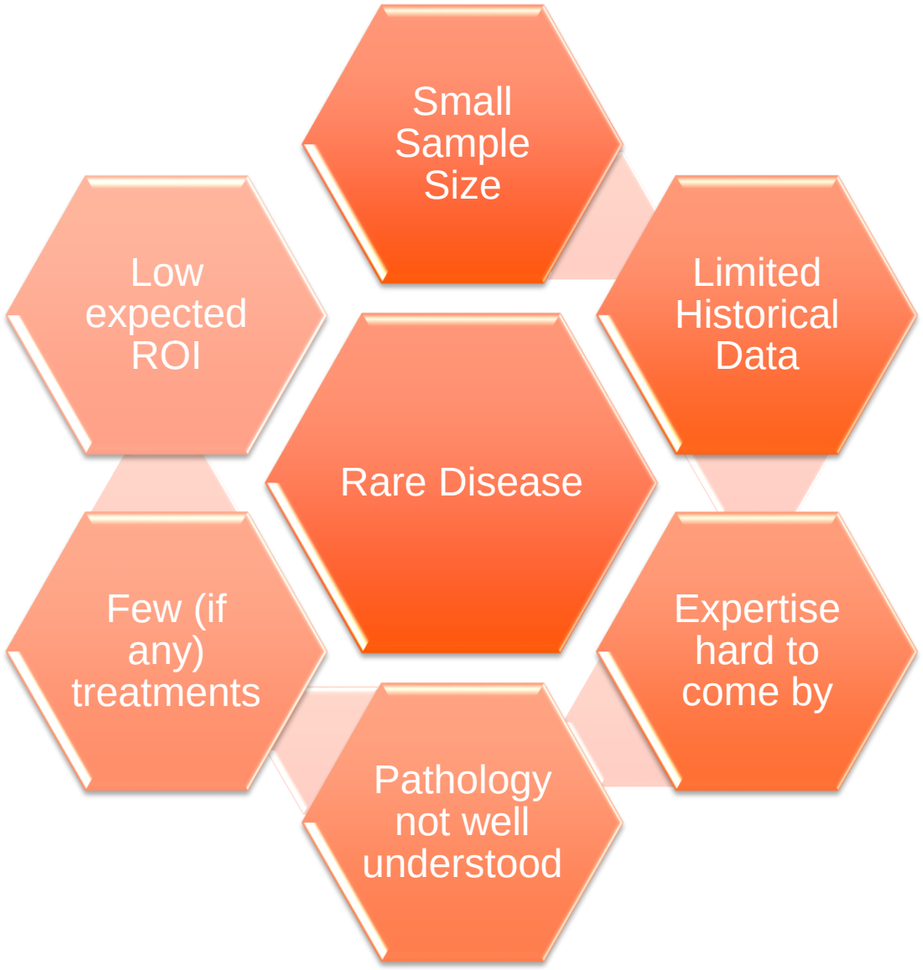
Japan

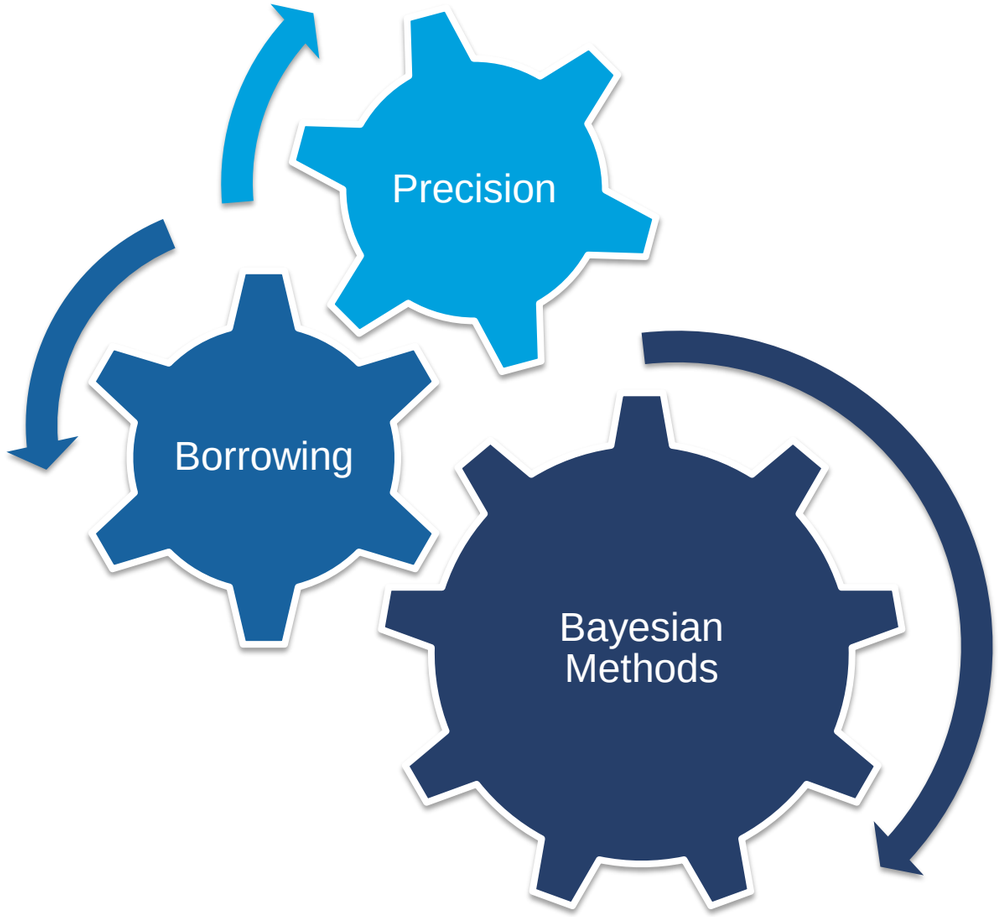
- Affects less than 50,000 Japanese people

One thing in common: low prevalence

Challenges Necessitate Innovation

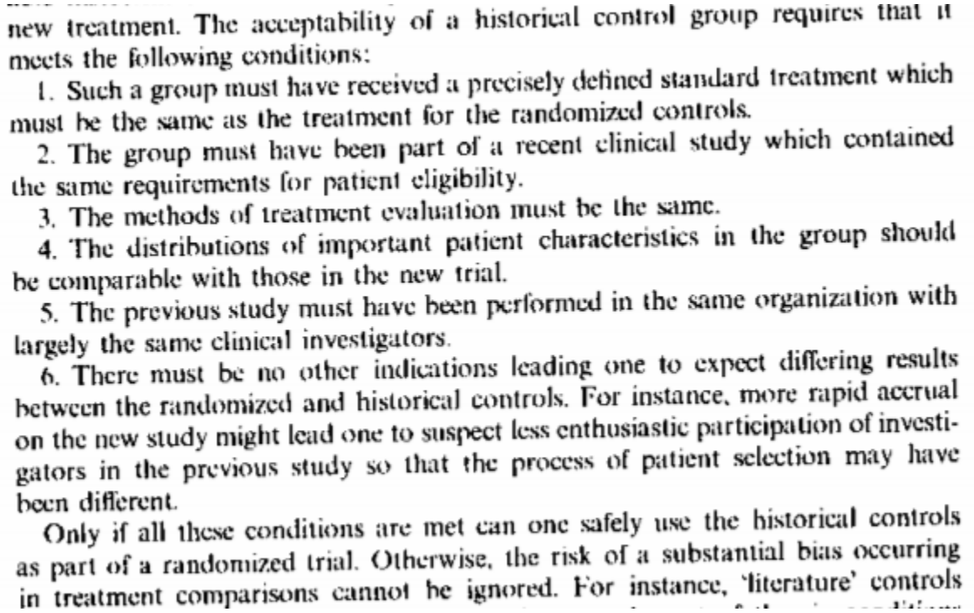






Borrowing in a Rare Disease Setting

- Pocock (1976) often cited when assessing appropriateness of borrowing
- Criteria set a gold standard for acceptability
- Attempts to mimic a RCT
- Some recommendations may be impractical or impossible in a rare disease setting
- Must be flexible

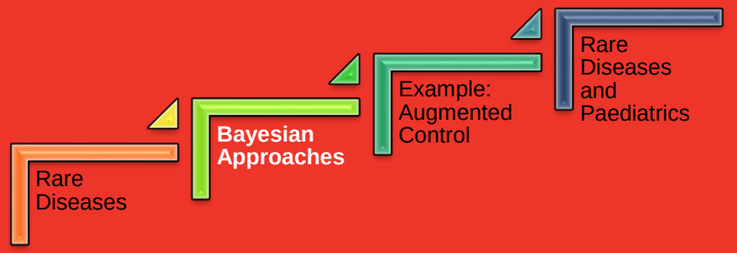


new treatment. The acceptability of a historical control group requires that it meets the following conditions:

1. Such a group must have received a precisely defined standard treatment which must be the same as the treatment for the randomized controls.
2. The group must have been part of a recent clinical study which contained the same requirements for patient eligibility.
3. The methods of treatment evaluation must be the same.
4. The distributions of important patient characteristics in the group should be comparable with those in the new trial.
5. The previous study must have been performed in the same organization with largely the same clinical investigators.
6. There must be no other indications leading one to expect differing results between the randomized and historical controls. For instance, more rapid accrual on the new study might lead one to suspect less enthusiastic participation of investigators in the previous study so that the process of patient selection may have been different.

Only if all these conditions are met can one safely use the historical controls as part of a randomized trial. Otherwise, the risk of a substantial bias occurring in treatment comparisons cannot be ignored. For instance, 'literature' controls

Two-Step Approach



1. Use Bayes rule to generate a posterior on parameter of interest using the historical data

2. Apply Bayes rule again to data from new trial

- Pooled analysis
- Discounting by increasing prior variance
- Power Priors
- Commensurate Priors
- Robust Mixture Priors

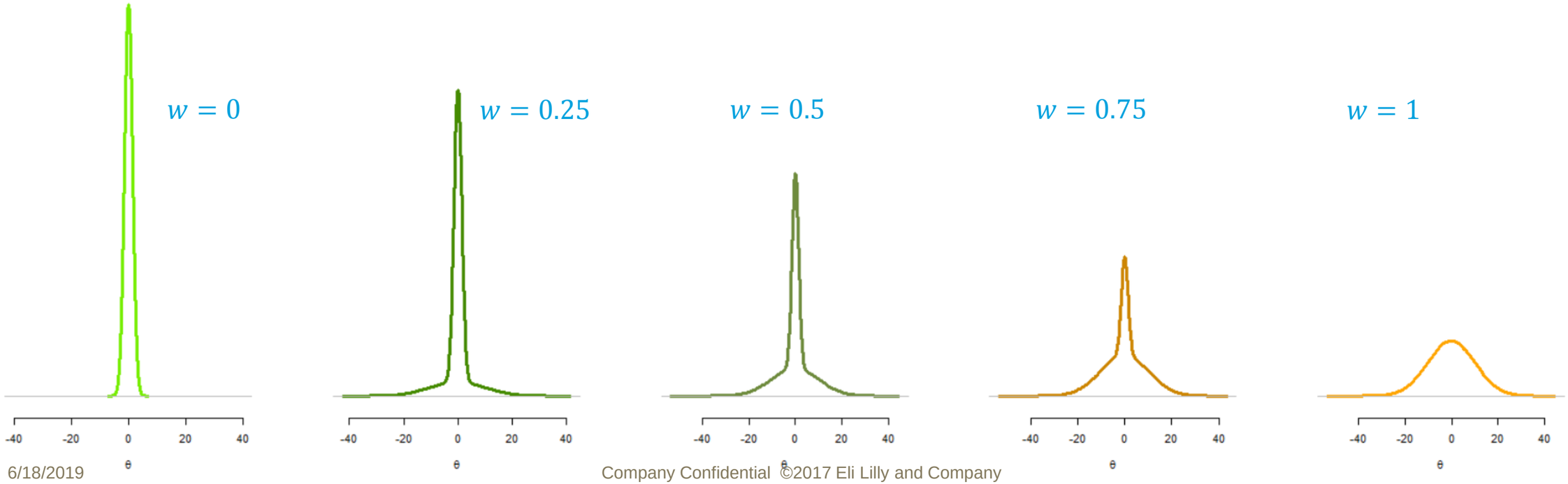
Robust Mixture

$$\pi_{RMP}(\theta, w \mid D_0) \propto (1-w)\,\pi(\theta \mid D_0) + w\,\pi_r(\theta)$$

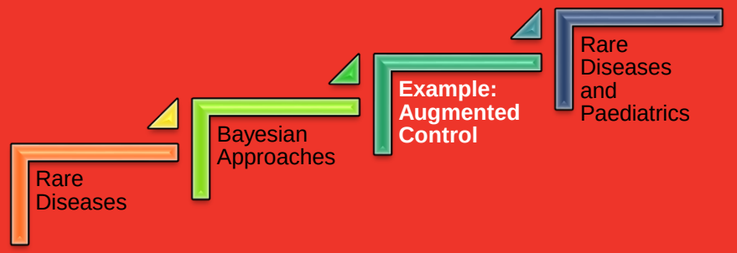
Historical data posterior

Mixture weight

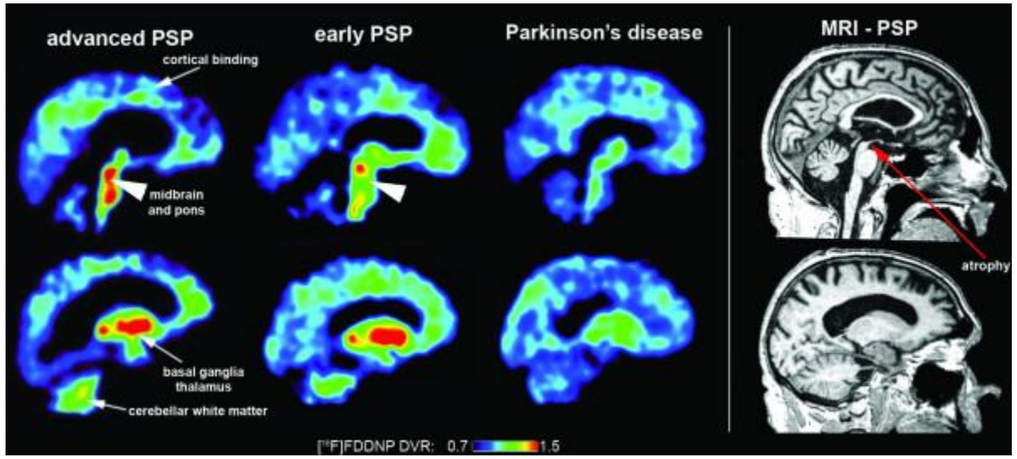
Robust (vague) prior



Progressive Supranuclear Palsy

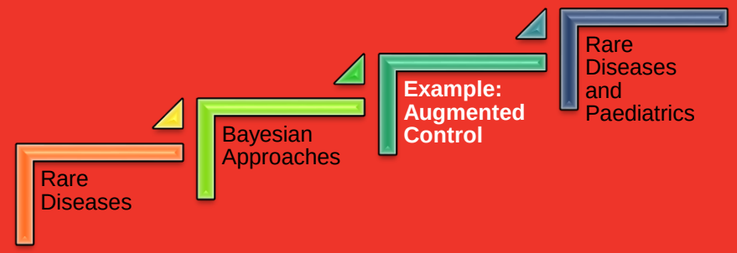


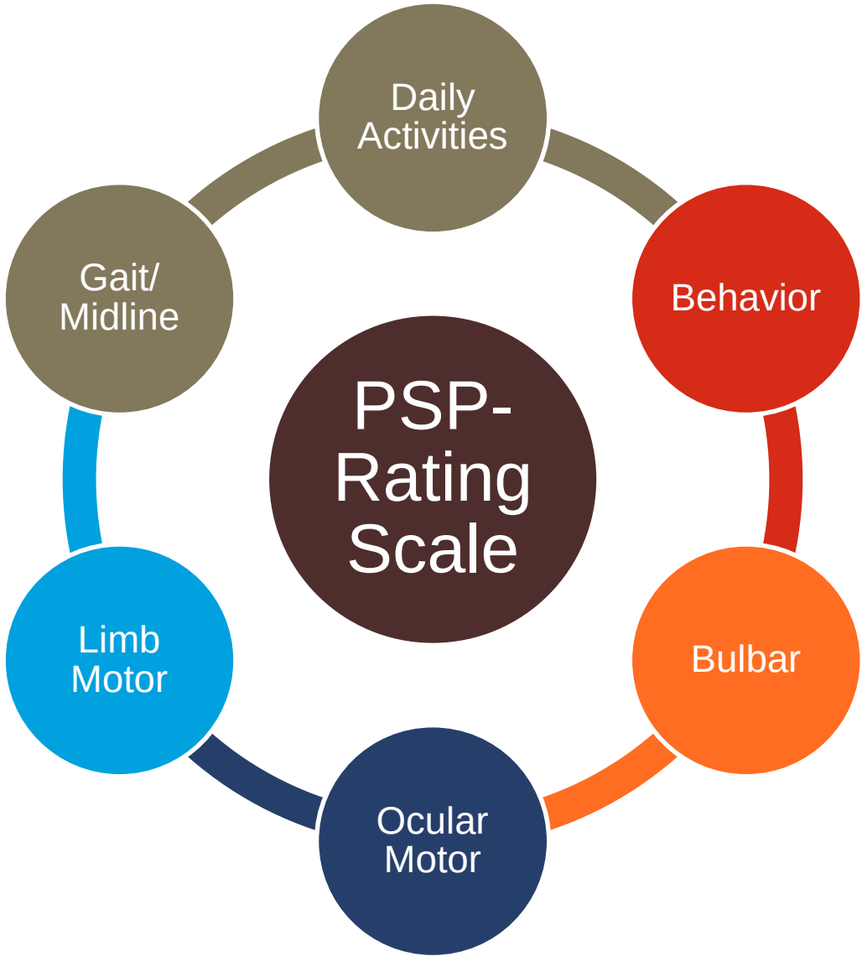
- PSP is a rare neurodegenerative disorder characterized by aggregates of tau protein in the brain
- Prevalence 1 in 16,600
- Several disease-modifying agents have been studied in PSP, but nothing has shown to be beneficial



We wish to leverage the information prom the previous studies, even though they were not able to meet their clinically meaningful endpoint.

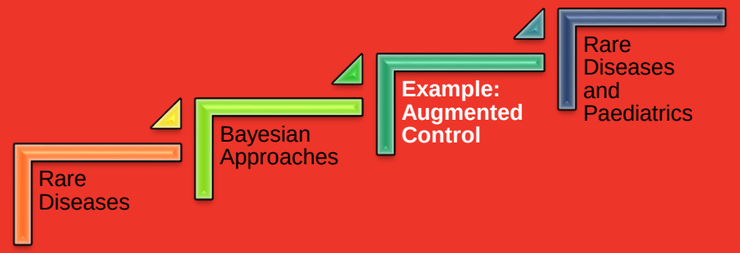
PSP: Historical Data





- 52-week endpoint
- PSPRS change from baseline assessed
- Two trials
  - Tideglusib vs. placebo
  - Davunetide vs. placebo
  - 144 placebo patients who completed treatment

Creating a RMP



Approximate historical control with normal distribution,

$$\theta \mid D_0 \sim N(\mu = 11.24, \sigma = 9.95/\sqrt{144})$$

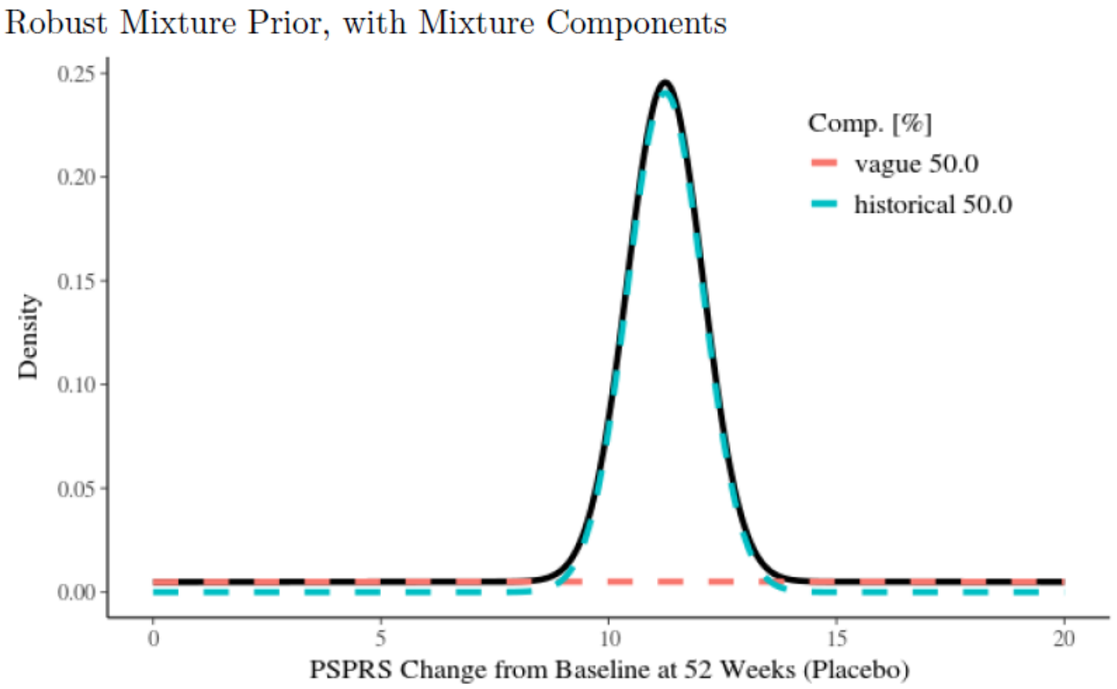
And select a robust prior which is centered at the observed historical effect, but with inflated variance,

$$\theta_{robust} \sim N(\mu = 11.24, \sigma = 40).$$

Using a mixing weight of 0.5, we get the RMP

$$0.5 \times N(11.24, 9.95/\sqrt{144}) + 0.5 \times N(11.24, 40)$$

Creating a RMP (cont'd)



- The mixture becomes a heavy-tailed version of the historical prior
- The mixture matches the robust distribution in the tails

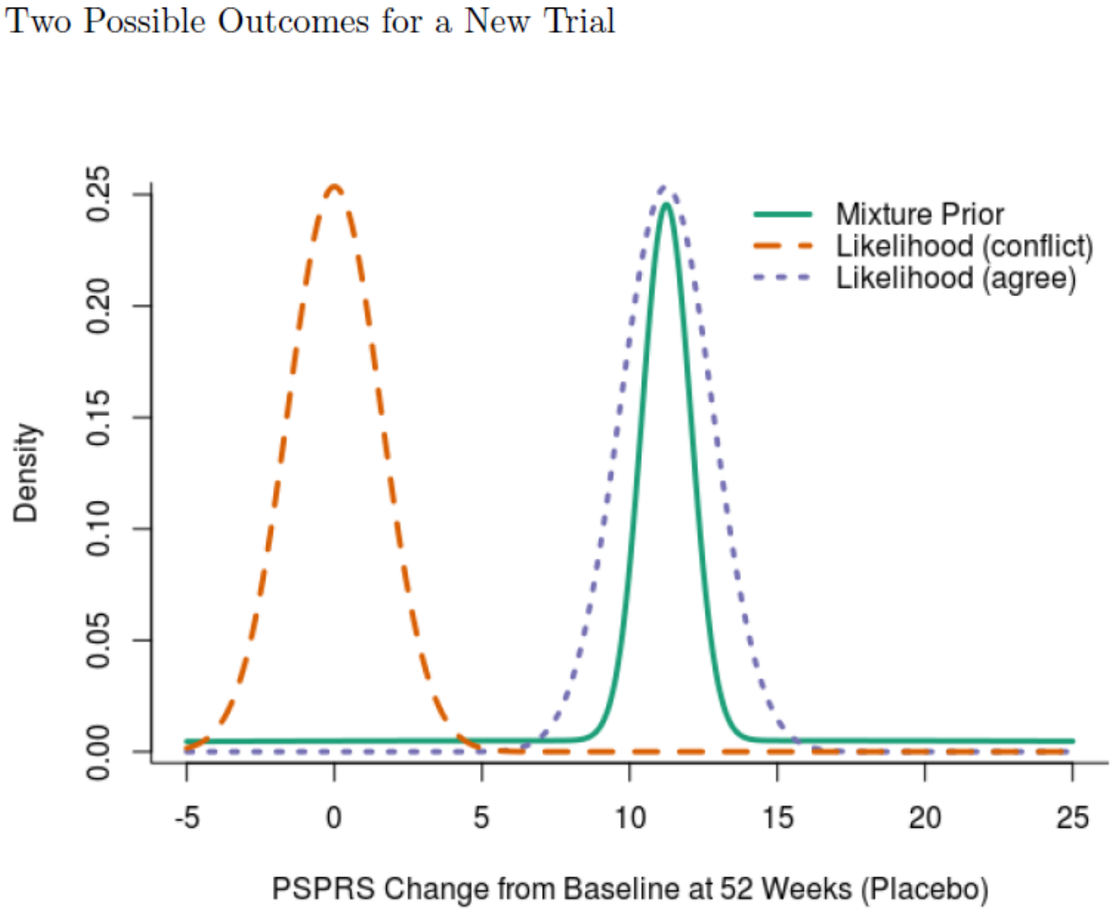
Note: the components are not plotted as densities, rather they integrate to their assigned weight (0.5 for each, in this case)

A New Trial

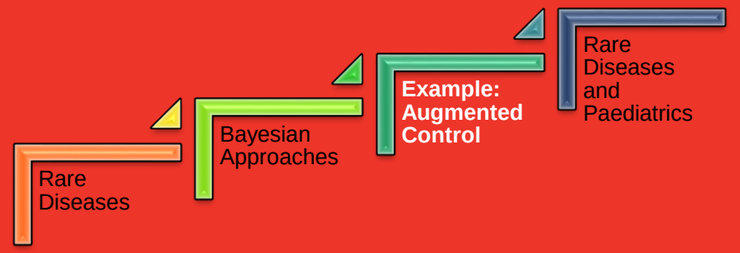
We plan to run a new trial in PSP, which randomly assigns 40 PSP patients to placebo.

Consider 2 extreme cases for the new trial:

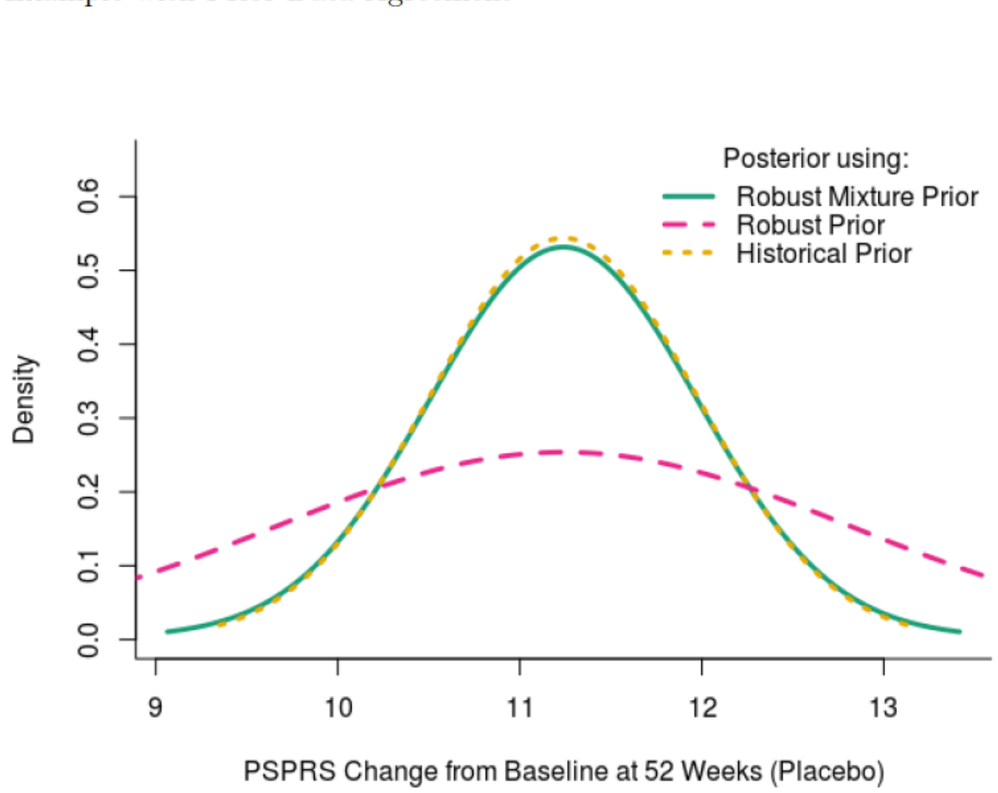
- Pbo response matches historical response
- Pbo response very different from historical meal (prior-data conflict)



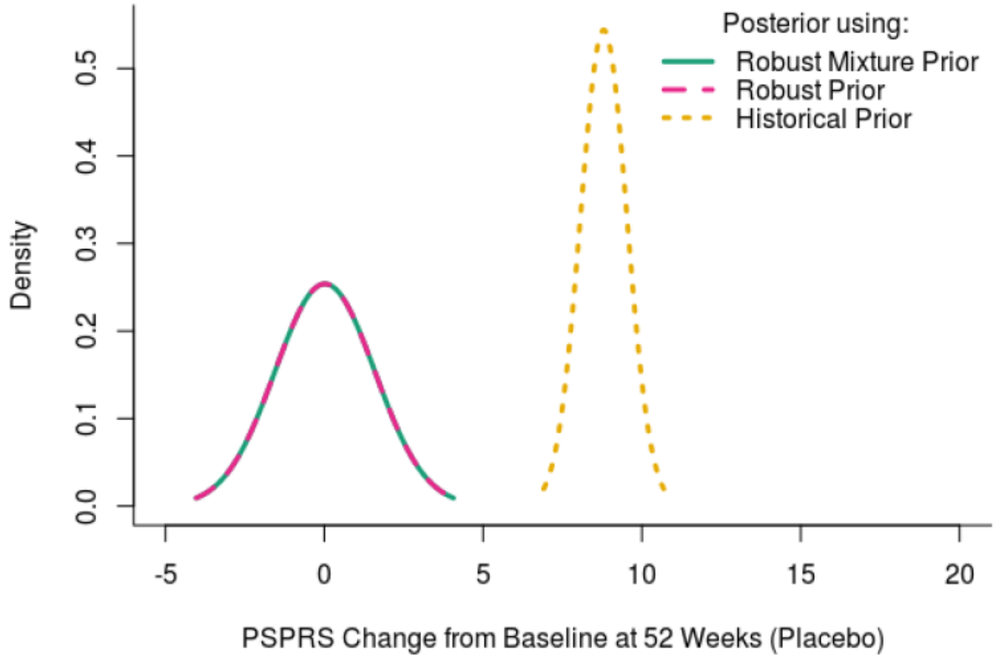
Impact on the Posterior



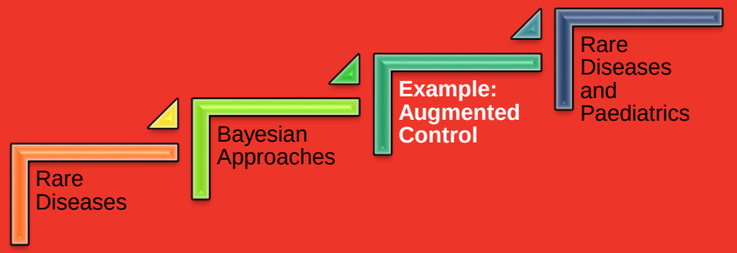
Scenario: No Conflict



Scenario: Conflict

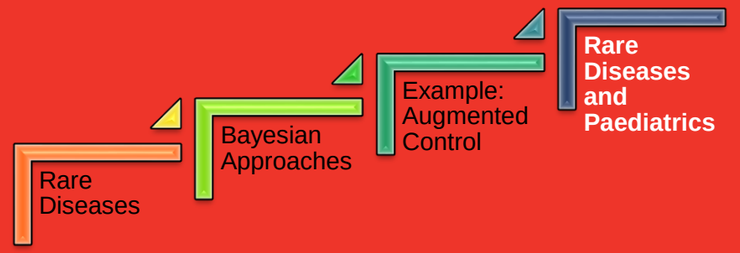


Multiple Historical Data Sources (if we're lucky!)



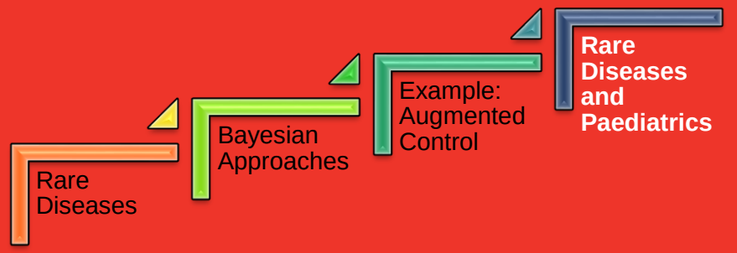
- When more than 1 historical data source is available, a meta-analytic predictive (MAP) prior may be constructed, then used as the historical component in the robust mixture
- Alternatively, a posterior could be derived on each historical trial and used in the mixture, allowing trials to be unequally informative in the analysis (borrow more only from trials which have less drift)

Rare Diseases in Children



- Rare diseases affect approximately 30 million Americans
  - 20 million of those are children
  - <1% of diseases have FDA approved treatment
  - Numbers are higher in Europe, with similar number of treatments available
- 50%-75% of all rare diseases begin in childhood

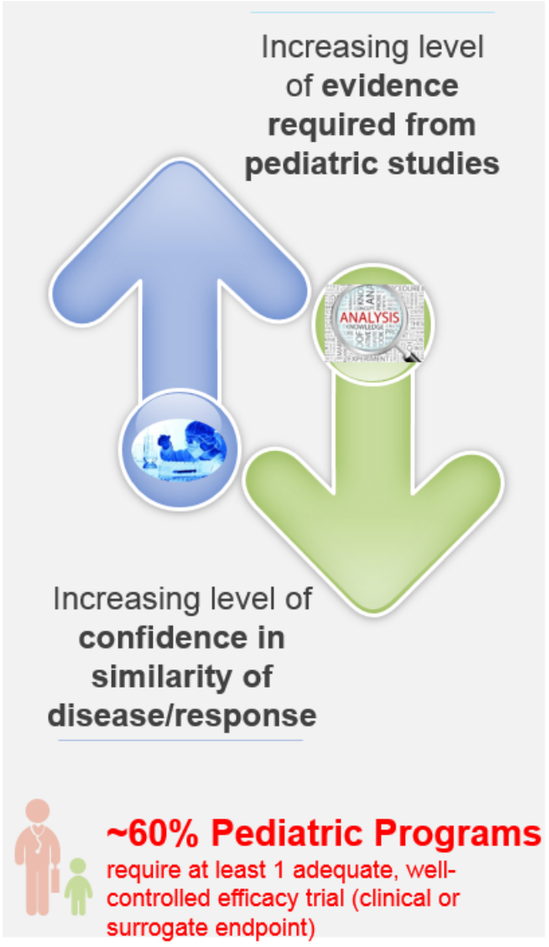
Extrapolation



Extrapolation. Extending information and conclusions from studies in a *source population* to make inferences for a *target population*, minimizing the need to generate additional information to reach conclusions for the target population.

While historical pediatric data may not exist, extrapolation allows us to use adult data as a source of information.

Bayesian methods particularly well-equipped to handle extrapolation, as it supposes existing information exists and may be applied as evidence to support effect in a new population.



1 or more adequate-well controlled studies powered on a clinically meaningful endpoint
Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, polyarticular JIA (pJIA), bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial seizures (<4 y/o), respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.

1 or more adequate-well controlled studies powered on a surrogate endpoint
Diabetes, anemia, idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.

Controlled study without formal statistical power
Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.

Descriptive efficacy study without concurrent control
Plaque psoriasis, Neurogenic detrusor over-activity, pJIA (NSAIDs), etc.

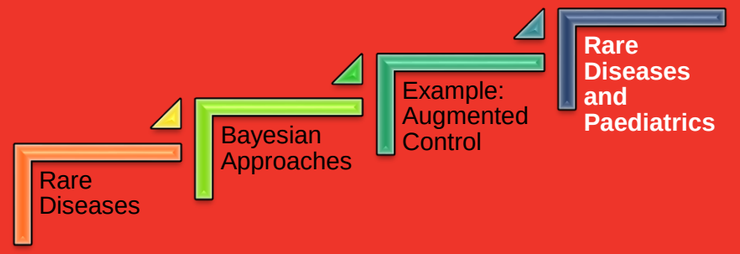
Small dose-ranging studies (randomization to multiple dose levels)
Sedation, ulcerative colitis, Crohn's, etc.

Small PK/PD studies (single dose level matching adult exposures)
HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension,

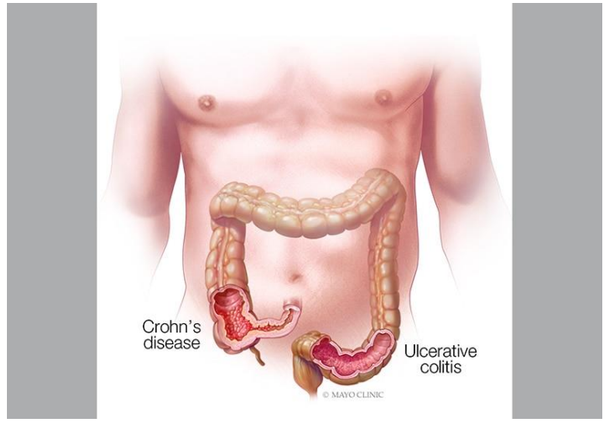
PK/safety only (single dose level matching adult exposures)
gastroesophageal reflux disease, bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

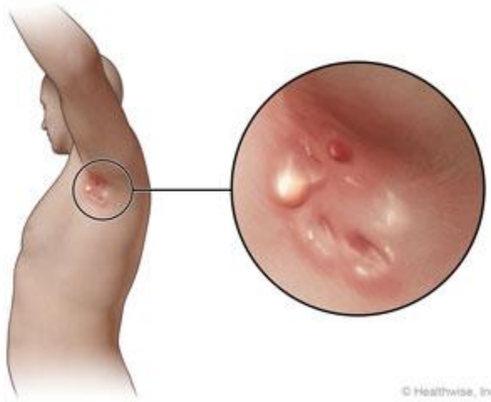
List partially adapted from Dunne et al. *Pediatrics* 2011

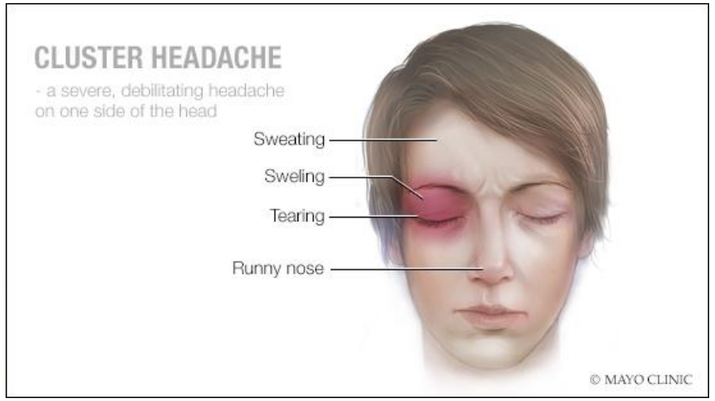
Changing landscape of pediatric orphan indications



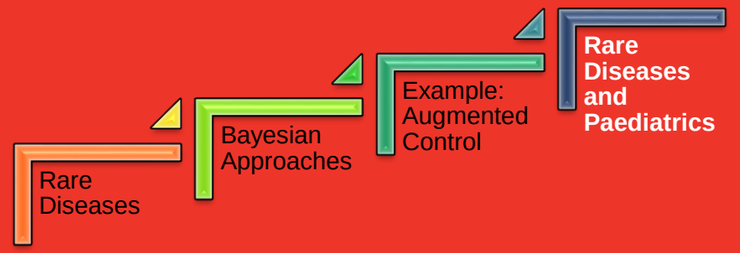
- Orphan product designation usually comes with incentives
- In the US, orphan indications were exempt from paediatric requirements
- Orphan designation no longer granted for sub-populations (FDA)
- Some indications which were granted orphan designation no longer qualify







Hidradenitis Suppurativa



- **Hidradenitis suppurativa** (HS) is a chronic skin disease which causes painful, boil-like lumps that form under the skin and often secrete pus and blood
- Earliest age of onset around 10 years
- No pediatric HS trials for efficacy
- 1 approved therapy in adolescents (based on PK data)
- HS would have been granted orphan designation 2 years ago, but now does not qualify in the US